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CONTENTS OF VOLUME 29

JANUARY, 1922. NUMBER 1

FEBRUARY, 1922. NUMBER 2

MARCH, 1922. NUMBER 3

APRIL, 1922. NUMBER 4

MAY, 1922. NUMBER 5

JUNE, 1922. NUMBER 6

JUNE, 1922—Continued

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MOTOR PHENOMENA OCCURRING IN NORMAL STOMACHS, IN THE PRESENCE OF PEPTIC ULCER AND ITS PAIN, AS OBSERVED FLUOROSCOPICALLY *

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This communication embodies the principal results of fluoroscopic observations of the stomachs of normal men and of patients with ulcer of the stomach or duodenum, after the feeding a meal composed of meat and barium, which we have recently made. The ulcer patients were studied in order to obtain detailed information regarding gastric motor phenomena occurring throughout the period in which the stomach was emptying itself and during the occurrence of pain due to the presence of the ulcer; and, also, to attempt to establish an objective method for determining the effects of therapeutic measures. The normal patients were studied to obtain further data as to normal motor activity. It may seem that there is no need for further roentgen-ray observations on the motor activities of the normal human stomach, for considerable data [1] are available describing such observations after the ingestion of various kinds of solid foods. But clinicians and physiologists do not always seem to be cognizant of this fact as judged from statements found in current textbooks of medicine. For example, a recent leading system of medicine contains the statement, "then by means of onward circular constriction the material is pressed toward the pylorus, but the pylorus opens only at intervals and not with every peristaltic wave. In fact, many peristaltic waves will frequently be seen before the pylorus relaxes." [2] While this statement holds true, accepting Cannon's [3] observations, for the stomach of the cat the work of Cole [4] and ourselves,[5] among others, shows that in normal man the pyloric sphincter

* From the Radiographic Department and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Carman, R. D., and Miller, A.: The Roentgen Diagnosis of Diseases of the Alimentary Canal, Philadelphia and London, 1920, p. 110.

2. Rehfuss, M. E.: Oxford Medicine, New York **3**:29, 1921.

3. Cannon, W. B.: Am. J. Physiol. **1**:359, 1898.

4. Cole, L. G.: J. A. M. A. **61**:762 (March 6) 1913; Am. J. Physiol. **43**: 618, 1917.

5. McClure, C. W.; Reynolds, L., and Schwartz, C. W.: Arch. Int. Med. **26**:410 (Oct.) 1920.

relaxes as each and every peristaltic wave approaches that orifice. This observation, alone, indicates the advisability of making more studies on the stomach of normal man.

For the purposes of the present investigation all subjects were fed one type of meal. The meal consisted of 160 gm. of finely ground, lean beef and 40 gm. barium sulphate baked in a loaf. Before feeding it, the loaf was ground up with sufficient water to make a thick mush, or was given in its dry state along with from 150 to 200 c. c. of water to drink, while to one subject it was given in the dry state without water to drink. The stomachs of the subjects were observed fluoroscopically immediately after the period of ingestion, a few minutes, then at fifteen minute intervals for one hour, and then at thirty minute intervals for two hours and then at hourly intervals until the stomach was nearly empty, when observations were made at more frequent intervals. Five normal subjects and sixteen patients with peptic ulcer were studied.

Immediately after the meal had been ingested by the subjects the stomach was seen to be about three-fourths filled, if observations were made with the patient in the erect posture. The air bubble in the fundus occupied the remaining fourth of the gastric cavity. As the stomach emptied, the upper level of the food gradually became lower until only the outline of the pyloric region was visible. While this was occurring that part of the outline of the stomach which was still visible was not modified appreciably in shape until but a small residue remained, which latter formed a hemispherical outline along the greater curvature just proximal to the pyloric sphincter. At this time, if the patient was standing, the sphincter was seen to occupy a position above the residue, the latter would roll back over advancing peristaltic waves and consequently would not be ejected through the sphincter into the duodenum. However, in the reclining position the residue lay up against the sphincter and each peristaltic wave forced a portion of it over into the duodenum, except when pylorospasm was present.

In the stomachs of the five normal subjects as soon as the pyloric region contained food, peristaltic waves were observed to eject barium containing chyme through the sphincter into the duodenum, as each wave approached that orifice, except in one subject. In the latter, gastric peristaltic waves were very shallow during the first twenty-five minutes after the meal was ingested, and no barium was seen to enter the duodenum; peristalsis then became active and the remaining phenomena corresponded to that seen in the other subjects. Peristaltic waves began as shallow indentations at about the junction of the upper and middle thirds of the stomach's outline and progressively deepened to about the midpyloric region, where the waves approximately half way bisected the stomach, while in the immediate neighborhood of the pyloric

sphincter the gastric outline was either almost or completely bisected. Waves began at regular intervals, roughly judged to be twenty seconds each, but accurate time measurements were not made. To the eye each peristaltic wave went through the same series of phenomena as it coursed along the stomach from its origin to the pyloric sphincter. The same peristaltic phenomena were observed in the subject who ate the meat and barium loaf in a dry state and without drinking water. In the stomach of this subject, during the first thirty minutes after ingesting the meal, the majority of the latter formed a globular mass below the air bubble in the fundus, while a smaller portion formed a long, narrow neck extending from the lower end of the globular mass to the pyloric sphincter, the whole appearing much like an inverted gourd. The outline of the stomach appeared very irregular due to the dry state of the contained food. Barium began to leave the stomach as soon as the meal was ingested, i. e., a few minutes. Within thirty to forty minutes after the ingestion of the meal this stomach had assumed the shape similar to that observed in the other four subjects and had, also, lost the irregularity of its outline.

Four of the normal subjects occupied the erect position throughout the period of observation. In three of these the stomach contained a small residue at the end of five hours. Peristalsis was active at this time in the stomachs of two of the subjects but was unable to eject barium into the duodenum for the reasons given. In the stomach of the third subject, peristalsis was no longer present. A medium sized residue remained in the stomach of the fourth subject at the end of seven hours. Peristalsis was active in the stomach of this subject for the first five hours after the meal was ingested, but during the sixth and seventh hours of the period of observation it was intermittent and feeble or absent. The stomach of the fifth normal subject, who was reclining throughout the entire period of observation, emptied itself in five hours.

In all the normal subjects the first portion of the duodenum filled out fairly well, but its outline was not as smooth nor its circumference as great as after the liquid meal ordinarily employed for diagnostic studies. Roentgenograms of the stomach and intestines of the normal subjects allowed the meat and barium meal to be followed through the small intestines and into the cecum. In about forty-five minutes the jejunum was seen to contain much barium. The ileum was reached by the barium in an hour to an hour and a half and the cecum in four to five hours. In one of the subjects the head of the barium column had reached the hepatic flexure at the end of five hours.

Gastric motor phenomena, as observed fluoroscopically, in the presence of ulcer in the stomach or duodenum showed in fourteen of the sixteen patients studied, either constantly or intermittently, devia-

tions from those observed in the absence of such a lesion. The abnormal motor phenomena were the same whether the ulcer was located in the stomach or in the duodenum, except that in gastric ulcer peristaltic waves did not course over the area of ulceration; this has been described in a previous communication.[6] Other than this, five types of abnormal gastric motor phenomena were observed, as follows: (1) exaggerated type of normal peristalsis; (2) irregular peristalsis; (3) antiperistalsis; (4) pylorospasm; and (5) the presence of an incisura in the greater curvature.

Exaggerated Type of Normal Peristalsis.—This type of peristalsis was observed in seven patients with ulceration of the first portion of the duodenum. It persisted throughout the emptying periods of the stomachs of four subjects and during a two hour period of observation of a fifth. In the sixth subject the exaggerated type of peristalsis was changed to the irregular type, described below, with the onset of pain, and in the seventh subject this change occurred without the onset of pain.

In the presence of exaggerated peristalsis the number of waves observed at any one time in a given stomach was constant, but the number of waves varied from one to three in the different individual stomachs. By the time a wave had progressed from its point of origin in the fundus to the beginning of the lower third of the stomach it either completely or almost completely bisected the stomach. These deep waves pushed a considerable amount of gastric contents before them, either filling the pyloric region of the stomach abnormally full and giving rise to the so-called "prepyloric bulge," or sending large amounts through the sphincter into the duodenum. Pylorospasm was discernible intermittently in five of these stomachs.

Irregular Peristalsis.—This type of peristalsis occurred in the stomachs of seven of the patients studied. It was characterized by marked variation in the time of appearance, duration and depth of the peristaltic waves. Beginning at the usual site a wave would course along the stomach distances varying from a few centimeters to as far as the plyoric sphincter. An occasional wave, reaching as far as the sphincter, would eject barium into the duodenum; this showed the absence of pylorospasm. More often, either the waves died out before reaching the pylorus or no peristalsis was visible. Under these circumtances the gastric peristalsis was not of such a character as to permit it to eject barium through the sphincter into the duodenum, and for this reason it was not always ascertained whether or not pylorospasm was present. However, certain of the peristaltic waves, which occasionally reached the pyloric sphincter, did not eject barium into the duodenum; at which times pylorospasm was considered to be present.

6. McClure, C. W., and Reynolds, L.: J. A. M. A. **74**:711 (March 13) 1920.

The irregular type of peristalsis persisted throughout the emptying period of the stomach in one patient and until after the cessation of pain in another. It began with the onset of pain in five patients; prior to the onset of pain peristalsis was of the normal type in three of these patients and of the exaggerated type in two. After the cessation of pain either through natural means or after the administration of sodium bicarbonate, peristalsis became of the normal or nearly normal type and the stomachs emptied rapidly.

Reversed Peristalsis.—In two patients the pyloric sphincter was found to be in a state of spasm during observations made over periods of about three and a half and six hours after the ingestion of the meal. During these periods antiperistaltic waves took origin at the pyloric sphincter and coursed back over the stomach a variable distance.

Pylorospasm.—Pylorospasm is defined as the failure of the pyloric sphincter to open or to open its normal width, as judged fluoroscopically, in relation to the advance of a gastric peristaltic wave; i. e., the sphincter opened partially, as judged by the small amount of barium seen to enter the first portion of the duodenum, or it remained closed, as judged by the failure to see barium enter the duodenum. Prolonged pylorospasm frequently accompanied the exaggerated type of gastric peristalsis, while it was observed in but one stomach in which the peristaltic waves were very shallow. The pylorospasm was usually intermittent.

Incisura.—In one patient a small penetrating ulcer occurred at about the midpoint of the outline of the lesser curvature of the stomach. Opposite the ulcer an incisura, invaginated from the greater curvature side, almost bisected the stomach, thereby dividing the latter into a lower and upper loculus. The patient's predominating symptoms were nausea and vomiting, unaccompanied by pain. She was unable to ingest more than a half of the usual meat meal because of the onset of nausea. On fluoroscopic examination it was found that the portion of the meal eaten completely filled the upper loculus of the stomach, and that very little of the food had entered the lower loculus. In spite of the complete filling of the upper loculus the patient did not experience a sensation of fulness. Within fifteen minutes after the ingestion of the meal eaten completely filled the upper loculus of the stomach, and that incisura was less deep. Active peristalsis was present in the pyloric region at this time and the sphincter was acting in a normal manner. Twenty minutes later the upper loculus of the stomach was found to be empty, and within a total period of three hours the stomach was found empty.

In four patients a small incisura developed in the greater curvature of the stomach coincidently with the onset of pain, which will be discussed later.

Pain.—During the period of observation twelve patients with peptic ulcer complained of epigastric pain. The character of the pain was severe in five, moderately severe in two, mild in two and mere discomfort in three. The pain developed between one hour and two and a half hours after the ingestion of the meal in all but one patient in whom discomfort developed thirty minutes after the meal. The onset of severe or moderately severe pain in four of the patients was preceded by milder pain over periods varying from five to thirty minutes. The onset of all types of pain was accompanied by distinct modifications in whatever type of motor activities the stomach had previously manifested, except in two patients who will be discussed later. If the peristalsis was of the exaggerated type with pylorospasm, the onset of pain was heralded by an increase in the depth of the waves or in the degree or duration of pylorospasm or both, except in one case in which the exaggerated peristalsis became the shallow type. If irregular peristalsis preceded the onset of pain, when the latter developed, the irregularity became more pronounced or peristalsis ceased altogether. If peristalsis had been normal before pain developed, it then ceased or became of the irregular type. In four cases with pain a small but definite incisura developed in the greater curvature, near the upper level of the barium shadow, with the onset of pain. In one of these the incisura accompanied mild pain a half hour before the severer pain occurred. In two of these the incisura was the only demonstrable abnormality developing coincidently with the onset of pain.

After cessation of pain peristalsis became normal, or nearly so, and the stomach rapidly emptied itself, except in two cases in which exaggerated peristalsis with intermittent pylorospasm remained. After the onset of severe pain in one patient and mild pain in two others, 3 gms. sodium bicarbonate or 2 gms. sodium bicarbonate with 1 gm. calcium carbonate suspended in 20 c. c. water were administered. Within from three to ten minutes after taking, the pain disappeared, and simultaneously the abnormal motor phenomena in the pyloric sphincter and stomach, including the incisura in one case, disappeared. In a fourth subject with the onset of moderate pain an incisura developed in the greater curvature of the stomach, while peristalsis and the behavior of the sphincter remained normal. The patient was given 20 c. c. tap water to drink, immediately after which peristaltic waves became deeper while the pain remained the same. Twenty-five minutes later 3 gms. sodium bicarbonate suspended in 20 c. c. tap water were taken. Ten minutes later all pain had ceased but gastric peristalsis remained unaffected and the incisura persisted. Just prior to the disappearance of pain after the administration of alkalis to these four patients it was noticed that the gas bubble in the fundus of the stomach was much increased in size.

Two patients, in whom ulcers were located in the first portion of the duodenum, were observed in whose stomachs no modifications of peristalsis occurred with the onset of pain. The type of peristalsis present in the stomach of one of these patients was the exaggerated type and in the other the waves were perhaps somewhat deeper than normal. Both subjects developed mild epigastric pain lasting fifteen and thirty minutes, respectively.

Four patients in whom active ulcers were located in the first portion of the duodenum were studied in whom no pain or discomfort developed during the period of observation after eating the meal. However, the ulcers present in these patients were of the acutely painful type and pain had been present up to the day of observations here reported. Two of the patients were observed over periods of two and three hours only, during which times the stomachs showed the exaggerated type of peristalsis; pylorospasm was present in one of these and but very little barium entered the intestines. The stomachs of the other two were observed throughout the period of emptying. One showed exaggerated peristalsis without pylorospasm and emptied in three hours and twenty minutes. The other showed a marked type of irregular peristalsis without pylorospasm and emptied in five hours.

Pain developed in eight of the patients at times when the amounts of food present in the stomachs varied from the quantity ingested to half that amount. The development of pain was delayed until the stomachs were nearly empty in four patients.

Emptying Time of the Stomach.—While the normal stomach was not quite empty at the end of five hours, in the presence of peptic ulcer the stomach was, with few exceptions, completely empty in three and one-half to four hours. The emptying time of the stomach of one patient was much delayed in the presence of prolonged pylorospasm. Delayed emptying time was not observed in any other condition. In one stomach in which the irregular type of peristalsis was present, there was an initial delay in emptying. This was evidently the result of the infrequency of peristalsis in the presphincteric region, since, whenever a peristaltic wave reached that region, barium was ejected into the duodenum. Nevertheless, this stomach emptied itself of barium in four hours. In another patient, with an ulcer in the first portion of the duodenum, the stomach emptied itself in three hours. Peristalsis was of the one wave type and during the first half hour after the ingestion of the meal peristaltic waves were regular in time but irregular in depth and almost complete pylorospasm was present. Peristalsis then became regular in the depth of the waves, spasm of the pylorus ceased and during the succeeding two and one-half hours the stomach emptied itself.

SUMMARY AND DISCUSSION

Fluoroscopic observations on the normal human stomach, after the ingestion of finely divided meat mixed with barium, show that it empties itself in a regularly progressive manner. Peristaltic waves begin high up in the gastric walls at uniform intervals of about twenty seconds and gradually deepening progress in an orderly manner to the region of the pyloric sphincter. As each wave approaches the sphincter the latter opens, allowing chyme to be ejected into the duodenum over a period of about ten seconds.[5] With the subject in the reclining position, one of the normal stomachs emptied itself in five hours. Three of the normal stomachs were almost empty in five hours; under the conditions of the observations here reported a very small residue remained along the greater curvature of these stomachs for a longer period. The stomach of the fifth subject contained a moderate sized residue at the end of seven hours.

Abnormal phenomena observed in the stomachs of patients with duodenal or gastric ulcer were modifications of the motor activities of the stomachs of healthy persons. The abnormalities noted were: (1) an exaggerated type of normal gastric peristalsis; (2) irregularity in the time of occurrence, depth and length of the course of peristaltic waves; (3) partial or complete intermittent spasm of the pyloric sphincter; (4) localized, permanent, stationary spasm of the gastric musculature causing the so-called incisura; (5) gastric antiperistalsis; (6) delayed emptying time of the stomach; and (7) very rapid emptying of the stomach. The onset of pain was accompanied by modifications in whatever type of motor activities the stomach had previously manifested, with two exceptions. The various abnormal motor phenomena were observed in the stomachs of peptic ulcer patients who did not develop pain during the period of observation.

The abnormal motor phenomena described are familiar to all clinical roentgenographers. But their relation to the pain of peptic ulcer as observed fluoroscopically has not been previously systematically studied. On the other hand, the relation of gastric motor phenomena to the pain of peptic ulcer has been studied by the well-known balloon method by Carlson,[7] Hardt,[8] Hamburger,[9] Homans,[10] and others. Carlson and Hardt state that the pain of ulcer is the result of contractions of the musculature of the stomach, pylorus (pyloric sphincter) or first portion of the duodenum. Their evidence that pain is accompanied by pyloro-

7. Carlson, A. J.: Am. J. Physiol. **45**:80, 1917.
8. Hardt, L. L. J.: J. A. M. A. **70**:837 (March 23) 1918.
9. Hamburger, W. W.; Tumpowsky, I., and Ginsburg, H.: J. A. M. A. **67**: 990 (Sept. 30) 1916.
10. Homans, J.: Am. J. M. Sc. **157**:74, 1919.

spasm or contraction of the duodenum is entirely indirect and consequently its existence in their experiments is problematical. Furthermore, Homans observed pain at a time when the balloon method failed to show the presence of peristalsis in the stomach. These contradictory findings are explained by our observations, since we found peristalsis might be either active or absent during the presence of pain.

While Carlson frequently did not observe modifications in gastric peristalsis in the patients with peptic ulcer which he studied, we observed them in fourteen of the sixteen patients which we studied. The frequent failure of Carlson to observe modifications of gastric motor phenomena during the presence of pain may be explained in two ways: (1) the balloon method permits recording of gastric peristalsis only, and by it small incisurae or pylorospasm are not ascertainable; and (2) as Luckhardt and Carlson [11] note, peristalsis as observed by the fluoroscope was not accurately recorded by the balloon method.

It has already been noted that we could not always determine the presence or absence of pylorospasm during the time of occurrence of pain. For this reason, and since the balloon method does not directly demonstrate pylorospasm, whether or not spasm of the pylorus always accompanies pain remains undetermined. However, we have made one observation which suggests that pylorospasm may be absent during the occurrence of pain. This observation was made on a subject with an active ulcer in the first portion of the duodenum. On one occasion the patient voluntarily complained of severe epigastric pain at a time when fluoroscopic observation showed barium to be passing through the pyloric sphincter in an apparently normal amount and manner. The next peristaltic wave, however, showed the presence of complete pylorospasm, although the pain had ceased.

The essence of our findings regarding the relation of peptic ulcer pain and motor phenomena of the stomach and pyloric sphincter is that during the presence of pain abnormalities of these motor phenomena are usually demonstrable. But merely because of this the conclusion reached by most observers, that motor phenomena are the cause of the pain of peptic ulcer, is not necessarily correct. Evidently these observers have as a basis for this conclusion the reasoning from the analogy that spasm of voluntary muscle can cause pain. But, on the other hand, spasm of voluntary muscle is also commonly a phenomenon protecting against the development of pain. Therefore, the mere association of the abnormal motor phenomena and pain, which we found in our observations, does not in itself determine the causal relation of the

11. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Am. J. Physiol. **50**:60, 1919.

two. However, it seems plausible to assume that muscular movements surrounding an ulcerated area in the stomach and duodenum could cause pain, provided pain nerves were present. But such an assumption does not explain why the pain does not usually persist throughout the entire emptying time of the stomach, nor why pain occurs early after food ingestion in some patients and late in others. The fact that pain did not always accompany abnormal gastric motor phenomena or pylorospasm could be explained on the theory that the degree of muscle spasm was not sufficient to produce pain. This theory could also explain the observation that pouring tenth normal hydrochloric acid onto a duodenal ulcer through a duodenal tube produced, without any subjective sensations, pylorospasm, cessation of gastric peristalsis and duodenal antiperistalsis in one patient which we studied. But it is to be emphasized that there is no means to prove such a theory. From this discussion it is evident that the fact that the two phenomena, normal or abnormal gastric or sphincteric motor phenomena and the pain of peptic ulcer, occur simultaneously does not conclusively demonstrate that motor phenomena cause the pain.

Hurst [12] and others have found that distention of the stomach or intestines by blowing them up with air to a sufficient pressure causes pain. Because of this finding Hurst proposed the theory that gastric or intestinal pain was the result of forceful distention of the gut wall due to violent contraction on material in the lumen of the gut of the section of the wall immediately above the distended region. Undoubtedly pain can be caused by the method employed by Hurst, but there is no experimental proof demonstrating that distention of the magnitude produced by it occurs as the result of the presence of peptic ulcer. Furthermore, we have observed, as has Homans, complete cessation of peristalsis in the stomach during the occurrence of pain; since under these circumstances no peristalsis occurred, there could not have been the distention produced as postulated in the theory proposed by Hurst.

This discussion shows that no motor phenomena are peculiar to the occurrence of the pain of peptic ulcer, that there is at present no accurate means available for measuring the degree of spasm of the gastric or sphincteric musculature, and that there is almost no support for the distention theory proposed by Hurst. In view of these facts it is evident that there is no incontrovertible proof that the pain of peptic ulcer is the result of motor disturbances in the stomach and pyloric sphincter. The most satisfactory evidence in support of the theory that such motor disturbances are the cause of the pain of peptic ulcer is that our observations show that gastric or sphincteric motor disturbances

12. Hurst, A. F.: Sensibility of the Alimentary Tract, London, 1911, p. 47.

are almost invariably associated with the pain. But our observations do not furnish conclusive proof of the truth of this theory, and for this reason it must be admitted that the causal relation of motor phenomena to the pain of peptic ulcer remains problematical.

From the clinical standpoint the most important feature of the work here presented is considered to be the fact that the usual disappearance of abnormal motor phenomena occurring simultaneously with the cessation of pain gives an objective means of judging the effects of therapeutic measures.

CLINICAL OBSERVATIONS ON THE CAPILLARY CIRCULATION *

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The direct observation of the capillary circulation in disease has long been the aim of many workers, interested in a variety of clinical and experimental problems. It is evident that the rest of the cardiovascular system exists only to regulate the blood flow through the capillaries, for here takes place the exchange of gases necessary for internal respiration and the exchange of materials necessary for metabolism. Any attempt to measure cardiovascular function is an indirect attempt to measure the efficiency of the capillary circulation. For example, blood pressure determinations are supposed to give some indication of the peripheral blood flow, but as will be seen later, blood pressure is often a poor index of the state of the capillary circulation. Much work has been done experimentally upon so called capillary poisons, such as arsenic, etc., stimulating a clinical interest in many of the acute intoxications, especially those accompanied by skin reactions, such as occur after arsphenamin injections, diphtheria antitoxin, also occasionally after the injection of foreign proteins. In acute infections, such as influenza, the sudden collapse is often attributed to a capillary intoxication. The disturbances of water balance in conditions like acute nephritis are by some supposed to be dependent upon an alteration of the permeability of capillary endothelium. In traumatic shock there may be stasis of blood in the capillaries, as Cannon [1] and his co-workers have shown. Disturbances of blood flow in arteriosclerosis, in gangrene of the extremities, in various functional nervous diseases, such as Raynaud's diseases, in fact, any condition altering the nutrition of a tissue must have some vital relation to the capillary circulation. It is thus evident that a direct view of the circulation in this most important part of the vascular system might be of some clinical value.

Experimentally, investigation on the capillary circulation began soon after the microscope came into use. Malpighi observed blood flow in the mesentery and bladder of the frog in 1686; Leeuwenhoek observed it in the tail of the fish and in the bat's wing; Cowper studied it in the mesentery of the rabbit. During the last century, investigation was centered particularly upon the contractility of capillaries and its control.

* This work was made possible by the clinical facilities offered by the Cleveland City Hospital.

1. Cannon, et al.: Nature of Wound Shock. Blood in Shock and Hemorrhage, J. A. M. A. **70**:526 (Feb. 23) 611 (March 2) 1918.

The names of Strickler, Golubew, Tarschanoff and the classical paper of Roy and Brown [2] in 1879 mark this period. Steinach and Kahn [3] in 1903, Krogh [4] in 1919, Hooker [5] in 1920 have contributed to this subject. An excellent review of the experimental work on capillaries was made recently by Hooker.[6]

Most of the animal observations have been made upon translucent tissues. The difficulties of similar observations in man are obvious. Ophthalmologists have carefully studied the condition of the vessels in the cornea and retina by means of various special microscopes. Augstein [7] observed in pannus the development of new corneal vessels by budding and branching, while Kraupa [8] observed the anastomosis of papillary veins, and also described the development of granular blood flow in arteriosclerosis and other conditions; and Streiff [9] saw changes in blood flow in vessels at the limbus due to nephritis and other conditions.

In 1874, Hueter,[10] by means of reflected light observed the vessels on the inner border of the lower lip, calling his method cheiloangioskopie. While he described stasis due to mechanical pressure, and experimented with the effects of applying various solutions, his results were indefinite.

Recently, Weiss,[11] standardized a method for the observation of the skin capillaries at the ends of the fingers and toes. Many years before, Spalteholz had shown that whole organs could be made translucent by reflected light, if they were immersed in a transparent oil. Lombard,[12] in 1912, working in Von Frey's laboratory applied this principle to the observation of capillaries at the fingertips in man, and made this obser-

2. Roy and Brown: Blood Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, J. Physiol. **2**:323, 1879.

3. Steinach and Kahn: Echte Kontractilität u. motorische Innervation der Haut-Kapillaren, Arch. f. d. ges Physiol. **97**:105, 1903.

4. Krogh: Studies on Capillariomotor Mechanism, J. Physiol. **53**:399, 1920; **52**:457, 1919.

5. Hooker: Functional Activity of Capillaries and Venules, Am. J. Physiol. **54**:30, 1920.

6. Hooker: Evidence of Functional Activity on the Part of Capillaries and Venules, Physiol. Rev. **1**:112, 1921.

7. Augstein: Gefäss-studien an der Hornhaut u. Iris, Ztschr. f. Augenh. **8**: 1902.

8. Kraupa: Die Anastomosen an Papillen u. Netzhautvenen, Arch. f. Augenh. **78**: 1915.

9. Streiff: Zur methodischen Untersuchund der Blutzirculation in der Nahe des Hornhautrandes, Klin. Monatsbl. f. Augenh., p. 395, 1914.

10. Hueter: Chielangioskopie, Zentralbl. f. d. med. Wissen., pp. 225, 241, 1879; Deutsch. Ztschr. f. Chir. **4**:105, 1874.

11. Weiss: Beobachtungen u. mikrophotographische Darstellung der Hautkapillaren der lebenden Menschen, Deutsch. Arch. f. klin. Med. **3**:119, 1916.

12. Lombard: Blood Pressure in the Arterioles, Capillaries and Smaller Veins of the Human Skin. Am. J. Physiol. **29**:355, 1912.

vation the basis of a method for measuring capillary pressure. Recently this method was modified by Hooker.[13] Weiss [14] together with Jürgensen [15] and other German workers have made numerous observations on the capillaries in a variety of clinical conditions. Niekau [16] by means of a special instrument extended the observations to other skin areas. Many records of the capillary picture were made in cardiovascular conditions, nephritis, diabetes, skin diseases, etc., and on this basis they have constructed tentatively rather definite capillary records corresponding to a variety of diseases. However, as Müller [14] states, it is too soon as yet to say what clinical value the method has. Normal standards for age, sex, climate, etc., have not been made. Many other difficulties will be pointed out later. A clinical method to be of value must be susceptible of wide use by a variety of observers under different conditions and with fairly constant results. It is with the hope of stimulating a trial of this method rather than of drawing any very definite conclusions that our observations are recorded.

Anatomic Basis.—Spalteholz [17] showed that the capillaries of skin are end capillaries, that is, they do not anastamose but form single terminal loops, each having a distinct arterial and a distinct venous limb. Each papilla of the skin is supplied by a single capillary loop which runs at right angles to the skin surface. However, as we approach areas where the skin ends, such as the base of the finger and toe nails, the long axis of the capillary tends to become more and more parallel with the skin, so that in cases with a well developed undisturbed cuticle, the loop runs in practically the same plane as the skin surface. Thus, looking down vertically upon the skin surface, at the junction of the cuticle and nail, we see the capillary loop in practically its entire length, while in other localities only the top of loop is seen. Figures 1 and 2, diagrams from Spalteholz, will make this clear.

The Method.—The finger, one with a well developed cuticle, is placed on the stage of an ordinary microscope, so that the junction of cuticle and nail is under the objective. This region of the finger is coated with any transparent oil (we have used liquid petrolatum). An electric light is then focused so as to strike the part observed at an angle of about 45 degrees. The light, a 50-100 watt, is enclosed in a conical hood with a convex lens inserted at the apex for condensing

13. Hooker and Danzer: Capillary Blood Pressure in Man, Am. J. Physiol. **52**:136, 1920.

14. Weiss and Müller: Ueber Beobachtung der Hautkapillaren u. ihre klinische Bedeutung, München. med. Wchnschr. **64**:609, 1917.

15. Jürgensen: Microscopic Study of the Capillary Circulation, Deutsch. Arch. f. klin. Med. **132**:140, 1920.

16. Niekau: Beobachtungen mit dem Hautkapillarmikroskop, Deutsch. Arch. f. klin. Med. **132**:301, 1920.

17. Spaltcholz: Handatlas der Anatomie des Menschen **3**.

the light. The hood is mounted on a ring stand. We used an ordinary Bausch and Lomb microscope with a 16 mm. objective and 5 × and 10 × oculars, giving a magnification of from fifty to one hundred times. Others have used lower magnification. The patient's arm can be put on pillows and braced by sandbags and to steady the observed finger, one can hold it lightly or have it inserted in a mould made of tin or a dental mould. Several minor precautions made the observation clearer, namely (1) the skin should be clean and dry, (2) it is best to observe a finger where the cuticle has not been recently cut or disturbed, (3) at times there are disturbing light reflexes from the

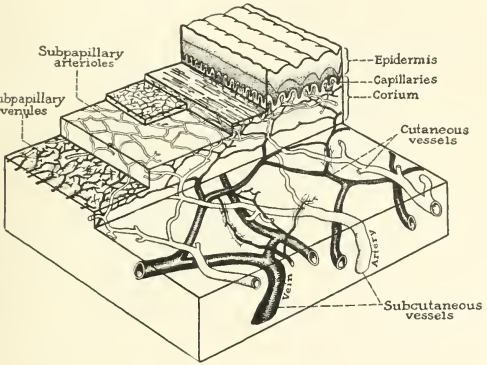

Fig. 1.—(After Spalteholz).

skin which can be diminished by changing the angle of the light or covering part of the convex lens in front of the light. One does not obtain a clear view in every case, for where the epidermis is thick and rough, and the cuticle is ragged, a good observation is impossible. Obviously it can not be used upon colored patients. Futhermore the patient must cooperate in holding his arm and fingers quiet, for much pressure upon the finger can not be used in restraint, because the blood flow will be altered.

Normal Appearance.—Wtih a clear view, just proximal to the junction of the cuticle and the nail, one sees a row of ten to twenty hairpin shaped loops, red upon a light orange background. Often more rows of capillaries are seen, running parallel to the first but with the indi-

vidual loops becoming shorter, that is, the more perpendicular to the skin, the more proximal the row. Observation should be focused on the most distal row of capillaries. It will be seen that each loop has a shorter, narrower limb (the arterial limb), and a thicker, longer limb (the venous limb), and that they are joined by a short connecting limb usually about the same thickness as the venous limb. Usually, no flow is at first visible but upon closer observation, in most cases, a rapid, steady, continuous stream will be seen going from the arterial to the venous side. The view is sometimes improved by the use of a green screen. Sometimes the individual blood cells are discernible, but more often not. In thin skinned individuals the subpapillary venules can be seen running at right angles to the loops, and occasionally the venous limbs can be traced down to this point. The subpapillary arterioles lie deeper, and are not visible except in infants. Normally, no pulsation of the field or the individual capillaries is

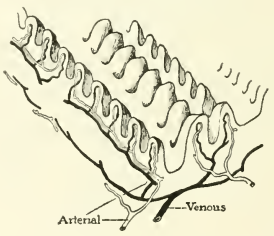

Fig. 2.—(After Spalteholz).

seen. The individual loops vary considerably in their contour. The arterial and venous limbs are fairly straight but in normal individuals they are often quite tortuous. Some may appear darker in color than others, probably due to differences in depth. There is also some variation in size.

For a systematic observation, the following points should be recorded:

1. The number of capillaries in the first row, increased or decreased over normal.
2. Color of background.
3. Size of capillaries, relative size and thickness of arterial limb, venous limb, and connecting limb.
4. Contour of capillaries.
5. Degree of capillary filling.

6. Presence of blood flow, speed and character of flow.
7. Pulsation of individual capillary or of field.

The interpretation of any single case may be wrought with many difficulties. No standards have been established for age, sex, race, climate, etc. It is a method not susceptible of accurate quantitative measurements, so that the personal equation of the observer enters into the conclusions very greatly. Furthermore, the observations are limited to skin capillaries, which are larger and because of their heat and water regulating function, capable of greater change due to external conditions than are capillaries elsewhere. We also know that

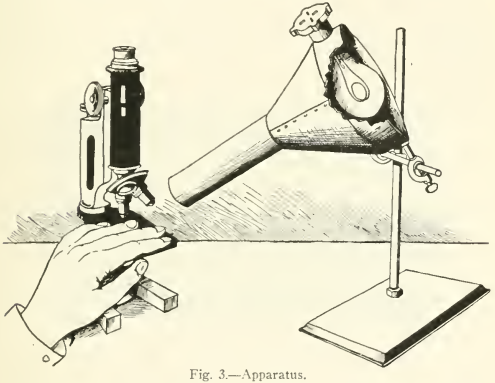

Fig. 3.—Apparatus.

capillary systems vary in form, depending upon function, thus differing in lung, intestine, pancreas, kidney, spleen, etc.[18] For these reasons, the skin capillary picture will never be a short cut diagnostic procedure, but may be at its best only of some diagnostic aid when taken with the rest of the clinical picture.

Variations Due to Age and Sex.—In observing over 200 cases, persons ranging in age from 1 day to 70 years, very few variations could be detected due to age alone. The skin vessels can be seen very clearly in young infants due to their thin epidermis. About half of the infants showed very small capillary loops with a diffuse

18. Nagel: Handbuch d. Physiologie **1**:760.

network of larger vessels, such as one sees in a frog's web, while in other cases there were long thin loops, rather widely separated, with arterial, venous and connecting limbs of the same caliber. The arterial and venous limbs were widely separated and very long and were traceable to the underlying subpapillary arterioles and venules. Occasionally, short buds were seen branching off of the limbs, suggesting the beginning of other loops. Probably, the large loops are not real capillaries, but only the subpapillary vessels. The blood flow in infants is steady and rapid. Why some infants show capillary loops and others do not is inexplicable to us. At the age of six months most of the cases observed showed very little difference from the adult condition. In older individuals there is a tendency for the capillaries to become more tortuous, but tortuosity is frequently seen in young people without any demonstrable cause. No differences attributable to sex were observed.

Fig. 4.—Normal.

Vasomotor Reactions.—It has long been a disputed point as to whether variations occur in the caliber of capillaries independent of changes in the arterioles and venules. An excellent review of the experimental work on this subject has recently been made by Hooker [6] and space will not permit us to repeat it here. Suffice it to say that overwhelming proof has not yet been assembled in favor of the independent contractility of capillaries. We have tried to observe the effects of mechanical stimulation as is done in the "tache" test of Marie, which was used clinically by Müller,[19] and Cotton, Slede and Lewis.[20] However, the field was so clouded by the stroke of the needle that no unequivocal observations could be made.

19. Müller: Deutsch. Ztschr. f. Nervenh. **48**:413, 1913.
20. Cotton, Slade, Lewis: Contractile Power of Capillaries, Heart **6**:227, 1915.

Weiss claims to have seen the arterial end of a capillary contract while observing a man with "vasomotor" spasm in the arm. He also quotes C. E. Weiss as having seen a spasm of the smaller retinal vessels (capillaries?) in a patient with a transient amaurosis.

Stewart,[21] by measuring the blood flow in the hand, showed that reflex stimuli such as heat and cold, when applied to the other hand, markedly altered the blood flow to the part, presumably by the reflex action causing constriction and dilatation of the arterioles. We have repeated these experiments by observing the capillaries of the finger in one hand while immersing the other hand in either cold or warm water. Cold caused a momentary increase in the velocity of the blood flow which gave way soon to a marked slowing, amounting sometimes to complete stasis. The capillaries appeared slightly wider and more full of blood. The appearance of increase in width was probably largely due to a slowing of the current, thus decreasing the axial stream, rather than to an active dilatation. This stasis was not permanent, but there was an intermittent alteration of the speed of the blood flow until gradually at the end of some minutes the flow became almost normal again. With heat the flow became much more rapid but the capillaries did not change in contour.

In explaining the reaction to cold one can conceive of the slow capillary flow being caused in any one of three ways. The velocity of the stream could be decreased by arterial constriction diminishing the intake; a contraction of the venules increasing the resistance to the outflow; and finally, a dilatation of the capillaries themselves. Arterial constriction by itself, however, could not cause the capillaries to be as full as they were in these cases; venous constriction alone could retard the flow, and in the absence of a decreased intake, as from arterial constriction, the venous pressure would not have to be very high in order to cause almost complete stasis. Briscoe,[22] investigated the capillary and venous pressures in patients with irritable hearts. Many of these patients habitually had cold cyanotic hands and others were very susceptible to cold, their hands becoming blue and cold upon short exposure. In the first group of cases it was found that the venous pressure was slightly raised, while the capillary pressure was markedly elevated. In the second group the vasomotor reflex experiments were tried and upon putting one hand in cold water while observing the other hand there was a marked rise in capillary pressure and a slight rise in venous pressure, and the venules on the back of the hand were observed to decrease in size. These phenomena were supposed to be

21. Stewart: Studies on the Circulation in Man, Heart **3**:76, 1912.

22. Briscoe: Observations on Capillary and Venous Pressure, Heart **7**:35, 1918.

due to simultaneous contraction of arterioles and venules. In our experiments capillary dilatation by itself could hardly be the cause of the slowed flow because the capillaries were only slightly dilated, but at the same time they were definitely redder, that is, more full of blood. Consequently, the most plausible explanation of reflex capillary stasis is a simultaneous contraction of arterioles and venules. The application of this to the cyanotic mucous membranes, ear tips, finger tips, etc., occurring upon exposure to cold is apparent, as it is also to the local asphyxia in Raynaud's disease.

Occasionally, as Jürgensen [23] stated, in the course of an observation some of the capillaries suddenly became obliterated and then a moment later filled up again while the other capillaries in the field did not change. Many explanations for this have been offered. Jürgensen thinks that there are precapillary arterial-venous anastomoses which are under control of the central nervous system and this sudden blotting out of the capillaries is due to the shuting off of the blood through these vessels which have been suddenly opened and closed by reflex action. We have no evidence which bears on this point. Variations in the rate of blood flow without any change in the capillary contour were observed in normal individuals, but were more frequent in patients with cardiovascular disease. These changes were probably dependent on a variation in tone of the supplying arterioles, because they appeared simultaneously in contiguous groups of capillaries, they were more frequent in cases with hypertonus, and they were not accompanied by any demonstrable change in the contour of the capillaries.

Shock and Hemorrhage.—It will be necessary to review a few of the recent experimental findings in shock in order to form a basis for the interpretation of the capillary observations. For a long time it has been assumed, and more recently it has been proven by Gasser and Erlanger [24] and also by Lee,[25] that there is a reduction in the effective blood volume in traumatic shock. The question of the "lost" blood or "exemia" has been vigorously investigated. Inasmuch as repeated experiments have eliminated the arteries and veins, attention was directed to the capillary area as the blood reservoir.

During the war, Cannon [1] and his co-workers showed that in patients with shock the red blood count of the capillary blood was much higher than that of the venous blood. Dale and Laidlaw [26] by the injec-

23. Jürgensen: Mikrokapillar Beobachtungen u. Puls der kleinsten Gefässe, Ztschr. f. klin. Med. **86**:410, 1918.

24. Gasser and Erlanger: Plasma Volume and Alkaline Reserve in Shock, Am. J. Physiol. **50**:104, 1919.

25. Lee: Field Observations on Blood Volume in Shock and Hemorrhage, Am. J. M. Sc. **158**:570, 1919.

26. Dale and Laidlaw: Histamin Shock, J. Physiol. **52**:355, 1918.

tion of histamin produced a condition very similar to traumatic shock, and by exhaustive experiments they seem to have proven that the important factor in this condition is an endothelial intoxication with capillary stasis and increased permeability, causing a marked exudation of fluid into the tissues. Following this work, Bayliss [27] and others have attempted to prove that shock is chemical in its nature, that is, that some product of traumatized or poorly metabolized tissue causes an endothelial intoxication with the production of a shock-like condition. Aub and Wu,[28] in a few experiments, by measuring the blood gas in arterial and venous bloods, tended to show that there is stasis in the peripheral circulation in cases of experimental shock produced by trauma. However, the result of all this work is difficult to evaluate, for although it is evident that there is a reduction in the effective blood volume, and capillary stasis, it has not been definitely proved that this is the initiating and not a secondary phenomenon. Much controversy has ranged over the condition of the vasomotor center in shock. Erlanger, Gesell and Gasser [29] in studies on secondary shock produced by exposure and manipulation of intestines, partial occlusion of the vena cava and partial occlusion of the thoracic aorta, showed that the vasomotor center retains its tone during the development of shock. At necropsy, there was intense capillary congestion, especially in the intestinal area. These authors [30] believed that the slow flow induced by the vasoconstriction caused a clumping of corpuscles in the capillaries and veneules, thus choking and dilating these vessels causing transudation into the tissues and the diminution of the effective blood volume. These phenomena could not be limited to the portal area because shock could be produced in eviscerated animals. Seelig and Joseph [31] also proved that the vasomotor center was tonic until late in shock. Gesell,[32] in experiments on volume flow through the submaxillary gland, showed that a relatively small reduction in blood volume, as by a small hemorrhage, caused a relatively large reduction in volume flow. This was due to vasoconstriction. A simultaneous constriction of arterioles and venules could cause a marked capillary stasis. It became

27. Bayliss: Intravenous Injection in Wound Shock, 1918.

28. Aub and Wu: Studies in Experimental Traumatic Shock, Am. J. Physiol. **54**:416, 1920.

29. Erlanger, Gesell and Gasser: Studies in Secondary Traumatic Shock, Am. J. Physiol. **49**:89, 1919.

30. Erlanger and Gasser: Treatment of Traumatic Shock, Ann. Surg. **68**: 389, 1919.

31. Seelig and Joseph: The Vasoconstrictor Center During the Development of Shock, J. Lab. & Clin. M. **1**:283, 1916.

32. Gesell: Factors Controlling Volume Flow of Blood, Am. J. Physiol. **47**:468, 1919.

33. Gesell: Studies in Secondary Traumatic Shock, Am. J. Physiol. **49**:90, 1920.

evident during the war that hemorrhage plays a part in producing traumatic shock, or in hastening it, and this may be due to the vaso-constriction induced.

Clinically, traumatic shock is recognized by the group of symptoms, consisting of low blood pressure—grayish pallor—mental stupor—rapid, small pulse—rapid, shallow respiration and usually subnormal temperature. During the war, Cowell [34] called shock primary, if these symptoms followed immediately on the trauma, and secondary, if they developed gradually, without primary shock, or if the primary shock were recovered from to some extent and then followed by the more permanent condition characterized by the symptoms.

REPORT OF CASES

These three cases would probably fall under the head of primary traumatic shock:

Case 1.—E. L., male, aged 23 years, admitted Jan. 8, 1921. About one hour before admission the patient had been struck by a train.

Physical Examination.—Temperature, 38 C.; pulse, 140, small volume; respiration, 30, shallow; blood pressure, systolic, 80; diastolic, not obtainable. Patient unconscious, grayish pallor. External wounds on scalp and body. Pupils: contracted, reacted slightly to light, other reflexes showed nothing abnormal. Capillary examination: (1) Increased in number; (2) capillaries full, and dark red in color; (3) contour—connecting and venous limbs relatively wide, as compared to arterial limb; (4) background, light orange; (5) blood flow—markedly slowed and stream somewhat segmented; (6) no pulsation of capillaries or of field.

Case 2.—J. C., aged 20 years, admitted April 15, 1921. Crushed between freight cars, about one-half hour before admission.

Physical Examination.—Temperature, 38 C.; pulse, 140, small volume; respiration, 38; blood pressure, systolic, 85; diastolic, 50. Patient conscious, pale. General rigidity and tenderness of abdomen, shifting dulness in flank, liver dulness not obliterated.

Operation revealed a rather large amount of blood in the peritoneal cavity, caused by the tearing of the mesentery for about six inches of the ileum. Resection of about one foot of the ileum, with lateral anastomosis. Patient died the next day.

Capillary examination: (1) Slight increase in number; (2) connecting and venous limbs relatively full; (3) capillaries, dark red; (4) field, light orange; (5) flow, slow; (6) no pulsation of capillaries or field.

These cases, clinically, are comparable to cases of primary traumatic shock. There was a definitely slowed capillary circulation and the capillaries appeared full. From the discussion in the previous section upon vaso-motor reactions, it is evident that the capillary stagnation could be due either to capillary dilatation or to a simultaneous contraction of arterioles and venules. Cardiac failure could hardly be a factor because there were no other signs of cardiac decompensation,

34. Cowell: Initiation of Wound Shock, J. A. M. A. **70**:607 (March 2) 1918.

such as distension of the jugular veins, enlargement of the liver, oedema, etc. Unfortunately, capillary and venous red blood counts were not made on these cases. The next case because of repeated observations may throw some light on the causative mechanism.

Case 3.—R. W., male, aged 43 years, admitted March 11, 1921. Patient had shot himself in the abdomen about fifteen minutes previous to admission.

Physical Examination.—Temperature, 37 C.; pulse, 100, small volume; respiration, 26; blood pressure, systolic, 100; diastolic, 70. Patient conscious, pale. Abdomen slightly rigid in epigastrium. Gunshot wound through epigastrium.

Capillary examination: (1) Number increased; (2) capillaries very red and full; (3) contour, nothing remarkable; (4) flow, very slow, almost complete stasis in some loops; (5) background, dark orange. Red blood counts of the capillary and venous bloods at this time showed: (1) Capillary red blood corpuscles, 6,200,000; (2) venous red blood corpuscles, 3,776,000. The examination was repeated forty-five minutes later, the patient having had morphin, ¼ grain, fifteen minutes before. Pulse, 80, larger volume than before; respiration, 26, unchanged; blood pressure, systolic, 110, diastolic, 70. Capillary examination: (1) Capillary number, same; (2) capillaries not so full or so dark in color; (3) contour about the same; (4) field lighter; (5) flow, faster than before. Blood counts at this time: capillary, 5,210,000; venous, 5,576,000.

Operation revealed a gunshot wound of the liver with moderate amount of hemorrhage. Patient seemed in good condition upon leaving operating room. This patient presented a picture of mild traumatic shock. There was marked retardation of capillary flow. Yet on the administration of morphin, and external heat, within forty-five minutes his systollic blood pressure had risen from 100 to 110, his pulse had become fuller and his capillary flow had become almost normal. The slowed peripheral circulation could hardly be due to an endothelial intoxication causing a capillary relaxation, because of the quick recovery, but was much more likely due to a vasoconstriction which was relaxed by morphin. However, we are aware of the fact, that we were only examining a small portion of the skin capillaries, and local effects due to external conditions, such as temperature have not been excluded. We can only say that in observing a great many cases, and without paying attention to external conditions, we have not seen such marked capillary stagnation except when due to some clearly assignable cause, such as seen in cardiac decompensation. These observations present no evidence as to the cause of the vasoconstriction. The low pressure in the presence of a sound heart and vasoconstriction could only be explained by a diminution in the effective blood volume due to a sequestration of the blood in some part of the circulatory system and a loss of plasma in transudation through the vessel walls.

The more permanent condition of secondary traumatic shock resembles clinically the so-called surgical shock. Without definite cause, symptoms appear with a more gradual onset and a tendency to progress to a fatal ending. It is this type of shock which was studied so extensively during the war. This corresponds also to experimental shock.

Case 4.—L. R., female, aged 30 years, admitted Nov. 18, 1920. About twelve hours prior to admission, patient was seized with a sharp pain in the epigastrium, shortly after which vomiting began, and continued at frequent intervals. Colicky pains had continued. No bowel movement for twenty-four hours.

Physical Examination.—Temperature, 38 C.; pulse, 84, slow, full. Patient somewhat pale, tongue dry. Abdomen slightly distended, no rigidity, tenderness on the left, above the umbilicus. No peristaltic waves visible, increased peristalsis audible, no evidence of free fluid in abdomen. Repeated enemas with no results. Laparotomy: left rectus incision revealed almost all of the small intestines strangulated through an opening in the transverse mesocolon. Small intestine gangrenous except for about six inches near cecum. Ends of small intestine were stitched to abdominal wall. Patient was returned to bed in a condition of shock with a grayish pallor, cold perspiration, pulse 144, small volume. Temperature, 38 C.; respiration, 44, shallow; blood pressure, systolic, 75; diastolic not obtainable.

Capillary examination: (1) Background, purplish hue; (2) increased number; (3) capillaries showed narrow arterial limbs with wide connecting limb; venous limbs slightly widened; (4) capillaries, bluish red; (5) complete stasis.

In this rather typical case of surgical shock, there was complete capillary stasis, the connecting limb appeared definitely widened in relation to rather short and small arterial and venous limbs, and the capillary blood appeared suboxygenated.

Thus, the evidence of capillary stasis was much more marked than in the preceding cases. Of course, the point of most interest is whether the capillary widening was primary or whether it was secondary to a capillary stasis due to vasoconstriction, and which being prolonged caused a deficient metabolism of the tissues with the piling up of carbon dioxid and other metabolites, and subsequent capillary dilatation. All that we can maintain in this case of shock is that by direct observation there was complete stasis in the skin capillaries and the connecting limb of the capillaries was widened. The globular massing of corpuscles mentioned by Erlanger was not seen in any of these cases of shock.

Collapse in Septicemia.—It is a rather frequent clinical observation that some patients suffering from a general setpicemia go rather suddenly into a shocklike condition several hours before death. We have had the opportunity of observing a number of these cases soon after the onset of collapse. They presented the general picture of shock, low blood pressure, grayish pallor, at times cyanotic, semiconscious, perspiration, skin cold and clammy, low temperature, small fast pulse, shallow respiration.

Case 5.—*Puerperal Septicemia, General Peritonitis After Abortion.*—E. B., aged 30 years. On admission: Temperature, 41 C.; pulse, 140; respiration, 32. About twelve hours afterward the patient suddenly went into collapse with the general picture as above except that cyanosis was rather marked. Temperature, 37.4 C.; pulse, 160; respiration, 40; blood pressure, systolic, 75; diastolic ?.

Capillaries: (1) Increased in number; (2) background, light; (3) capillaries full of blood, dark red; (4) venous and connecting limbs relatively wider

than arterial limb; (5) flow, very slow and intermittent with complete stasis in some capillaries. Venous red blood cells, 4,800,000; capillary red blood cells, 6,400,000. Capillary blood did not flow freely and was very dark in color. Patient died about three hours after this observation.

Case 6.—*Puerperal Septicemia, General Peritonitis Following Abortion.*—M. B., aged 22 years. General picture of collapse: Temperature, 37 C.; pulse, 132; blood pressure, systolic 75; diastolic, 50.

Capillaries: (1) Background, light; (2) about normal number; (3) contour, nothing remarkable; (4) filled, but in granular and segmented fashion, the cells being clumped together with clear spaces between; (5) absolute stasis. Venous red blood cells, 4,124,000; capillary red blood cells, 4,544,000.

These two cases of septicemia had capillary stasis, without showing other evidence of cardiac decompensation. There are so many factors to consider in these cases, that at this time we can only submit the observations without offering any theoretic basis for them.

Fig. 5.—Shock.

Several cases of uncomplicated hemorrhage have been observed, all of them being cases of incomplete abortion of which the following is typical:

Case 7.—S. S., aged 33 years, admitted April 29, 1921. The patient was about three months pregnant and several days previous to admission began to have vaginal bleeding. On the day of admission she had a severe hemorrhage and passed some clots.

Physical Examination.—Temperature, 38 C.; pulse, 128, small volume; respiration, 30, shallow. Blood pressure: systolic, 60; diastolic, 25. Patient was very pale, conscious and restless. Bleeding from vagina. Examination showed a partly retained placenta. Hemoglobin, 55 (Talquist); venous red blood cells, 1,840,000; capillary red blood cells, 2,108,000.

Capillary examination: (1) Decreased in number; (2) background very light, almost white; (3) capillaries poorly filled, appear granular due to clear spaces between blood cells. No dilatation; (4) capillary flow very slow and intermittent with varying speed.

The capillary was characterized by the granular appearance of the stream due to the anemia; and the slow capillary circulation was probably due to vaso-constriction resulting from the diminution in blood volume. The stasis, however, was not extreme as was evidenced by the red blood counts.

As was mentioned above, Gesell showed that a comparative small loss of blood volume as by hemorrhage could cause a large diminution in volume flow, because of vasoconstriction. Robertson and Bock,[35] in observation on the blood volume in soldiers who had had a hemorrhage, found that the diminution in blood volume was greater than the amount of the hemorrhage warranted. The red blood corpuscle count and hemoglobin determinations in capillary and venous blood showed that this was due to capillary stasis.

Cardiac Disturbances.—Decompensation: Weiss [14] and Jürgensen [15] made direct observations of the capillary circulation in many varieties of heart disease, and in all stages of decompensation. We have been able to confirm most of their findings. In well marked decompensation, the capillaries are increased in number, the arterial limb is small and narrow while the connecting limb and especially the venous limb are

Fig. 6.—Cardiac stasis.

wide and full. The flow is very slow. Sometimes there is complete stasis, and the blood flow is not steady, but the corpuscles appear rolled together, with clear spaces between. If the spaces are frequent, thus making the groups of cells small, the stream is called granular, and if the spaces are farther apart the stream is called segmented. Occasionally in complete stasis there is an intermittent retrograde movement from the venous toward the arterial limb. The background is very dark, probably due to stasis in the underlying venules. In mild cases of decompensation all that one may see are slightly widened venous and capillary limbs with slight slowing of the current and a granular or segmented stream. The German investigators claim that

35. Robertson and Bock: Blood Volume in Wounded Soldiers, J. Exper. M. **29**:136, 1919.

signs of stasis may be seen in the capillaries before other clinical signs are present, for example, after acute infections which are liable to produce cardiac complications, they claim that the capillary picture of decompensation may precede other symptoms. We have not observed any such cases. However, we have observed several cases of recovery from a cardiac breakdown, which clinically seemed to be compensated, but in which capillary circulation was slowed, the stream was granular or segmented, and the venous limb was full and wide. It appeared to us that the complete picture of stasis in mitral disease appeared earlier, was more marked, and persisted longer than in aortic disease. One of the most marked cases observed was a man with tuberculous pericarditis with a large effusion. A direct view of the capillaries has seemed useful to us in a few cardionephritics. Especially when they present the well developed picture of edema, shortness of breath, etc., it is often difficult to decide readily whether the kidney or the heart is more at fault. For example, one case was observed, that of a man about 50 years of age, who had general anasarca, ascites and hydrothorax and was markedly short of breath. The capillaries showed only a slight slowing and no marked fulness of the venous limb. It was apparent that this man's clinical picture could not be entirely due to cardiac failure. Weiss [36] thought that he could measure cardiac function by putting a blood-pressure cuff on the arm and then observing the capillaries. His method was to raise the pressure in the cuff until the flow stopped, then to lower the pressure, and observe the point at which the stream started. He claimed that in normal individuals the stream started at a point from 5 to 10 m. below the stytolic pressure, while in cases with diminished cardiac "power," the flow would not start until the pressure was much lower. As Jürgensen points out, this method as a test of cardiac function has very little basis theoretically, and we have found it of no practical value.

Capillary Pulse: It is well recognized that a capillary pulse is a constant finding in aortic insufficiency, and that it is frequently observed in aortitis, arteriosclerosis, exophthalmic goiter, febrile disturbances, etc. However, clinically, it has not been studied intensively. Herz [37] by means of onygraphic pressure records together with radial pulse records concluded that what was called a capillary pulse was really a pulsation of the smaller arterioles and could be changed or made to disappear in many cases by influences such as changes of temperature. However, Glässner,[38] using the same methods, concluded

36. Weiss: Eine neue Methode zur Sufficienz-prüfung des Kreislaufs, Ztschr. f. exper. Path. u. Therap. **19**: 1918.

37. Herz: Wien. Klin. **6**:165, 1896.

38. Glässner: Klinische Untersuchungen über Kapillarplus. Deutsch. Arch. f. klin. Med. **97**:83, 1909.

that a capillary pulse was either central or peripheral in origin, central in aortic insufficiency, but peripheral, due to vascular changes, in other cases, such as arterio-sclerosis, nephritis, exophthalmic goiter, etc. As Jürgensen points out, in observing the capillaries in aortic insufficiency, the whole field seems to move in two planes; one at right angles to the microscope and the other in the same plane as the microscope; that is, the field moves horizontally and vertically. In the few cases which we observed, it also appeared as if the flow in the capillaries was actually pulsatile, although, due to the vertical movement, it is difficult to observe the blood flow continuously. Observations were made on cases of exophthalmic goiter, arteriosclerosis and neurasthenia, in which a capillary pulse was present, but the pulsation was only in the horizontal plane, and the blood stream in the capillaries was not pulsatile. So

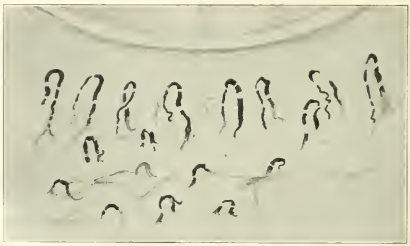

Fig. 7.—Anemia from hemorrhage.

this was definitely an arteriole pulsation and could be called a pseudo-capillary pulse. Jürgensen saw capillary pulsations in cases of syphilitic aortitis, but unfortunately all the patients with this disease, available to us, were colored.

Chronic Interstitial Nephritis and Hypertension.—Cases of hypertension, either with or without other signs of nephritis, are often puzzling because of the varying picture which they may present. Given two patients with the same blood pressure, one may be perfectly comfortable and the other may present all sorts of symptoms, such as aphasia, anaurosis, headaches, dizziness, etc. Various focal symptoms have been explained upon the basis of small hemorrhages, or arterial spasm. Again, in some cases, the blood pressure may be reduced without producing any symptoms, while in other cases a slight reduction in the pressure is attended by marked disturbances.

The capillary picture may possibly throw some light on these phenomena:

Case 8.—A. F., aged 41 years, female, admitted Feb. 14, 1921. For several months the patient had dizzy spells and headache, and black spots before the eyes. More recently she had frequent vomiting spells. For several days she had slight continuous vaginal bleeding. The day before admission she had a convulsion.

Physical Examination.—There was evidence of cardiac hypertrophy, but no edema. Pulse was 100 and small volume. The eye-grounds showed a marked albuminuric retinitis. Blood pressure: systolic, 240; diastolic, 160. Urine: albumin + + +, many casts.

Capillary examination: (1) Slight increase in number; (2) background, light; (3) capillaries poorly filled, appear granular. All limbs thin and of about the same width. Rather marked tortuosity; (4) flow, intermittent, stream being very swift for a moment, then it would suddenly stop completely.

When observed the next day the systolic blood pressure was 202, and the capillary picture was unchanged. An amylnitrite pearl was given and the systolic pressure dropped to 170, the capillary flow became steady, and there was a marked pseudo-capillary pulsation. However, in the course of five minutes the pressure was back to its previous level and the capillary flow resumed its original character.

It was seen that the capillaries were poorly filled and the flow was intermittent. This must have been due to arterial hypertonus, because first the capillaries were poorly filled, as one would expect with arteriole contraction, and second, the flow became better under amyl nitrite. In confirmation of this point, Kraus found a lowering of the capillary pressure along with a rise of the arterial pressure in many cases of hypertonus. Evidently, many of the patient's symptoms were due to poor capillary circulation, and in such a case reduction of the blood pressure would seem to be rational therapy. We have observed other cases of hypertension in which the flow was steady and continuous, and these patients had few symptoms.

In chronic interstitial nephritis the capillaries usually have long thin arterial and venous limbs with a slightly wider connecting limb. The flow depends on the degree of arterial tonus.

Arteriosclerosis.—In marked cases of arteriosclerosis the arterial and venous limbs are elongated, thin and tortuous and show a very characteristic formation of small loops off of the main limbs. These little loops look like buds and, by some, are supposed to represent an attempt at the formation of anastomosis or of new capillaries. Those loops do not appear in all cases of arteriosclerosis, and in our observations bear little relation to the amount of arteriosclerosis in the palpable arteries. The most marked cases of "budding" which we have seen, were in two cases of club fingers, with little demonstrable arteriosclerosis. However, other cases of club fingers did not show the "buds." Their significance is not clear to us.

Capillaritis.—The terms endothelial intoxication and capillary poison, have been used lately in relation to a variety of phenomena. Weiss [39] gives a rather definite picture for this capillary disturbance which he calls capillaritis. The capillary has short, narrow, arterial and venous limbs and a widely distended connecting limb. He described this in cases of acute nephritis, especially in children, in scarlet fever, occasionally before eruption. We have observed no cases of scarlet fever and only one case of acute nephritis, this in an adult whose capillaries showed no marked change. However, it was thought one should be able to obtain some evidence of capillary intoxication in cases of mercury and arsenic poisoning. In one case of fatal mercuric chlorid poisoning, with complete anuria, no capillary change was observed. Several cases were observed, showing salivation and gingivitis due to mercurial therapy, and with one exception there was nothing of note in the capillaries. This patient, age 20 years, had received a great deal

Fig. 8.—Arteriosclerosis.

of mercury by injection and inunction. He was markedly salivated and his gums were very swollen and sore. He also complained of anorexia and bachache. The capillaries appeared increased in number, very red, with short arterial and venous limbs, and relatively broad connecting limb. Blood flow was steady and moderately fast. Presumably, this is what Weiss describes as a capillaritis. However, the same picture was observed in three other cases, one, a patient with Banti's disease, and the others apparently normal individuals. Two cases of arsphenamin intoxication were observed, one an acute reaction with an eruption, fever, and edema; the other, a chronic case of jaundice, nausea and vomiting, and neither showed any capillary change.

39. Weiss: Beobachtung über Veränderung der Haut-kapillaren bei Exanthem, München. med. Wchnschr. **65**: 1918. Das Verhalten der Haut-kapillaren bei akuter Nephritis, München. med. Wchnschr. **63**:925, 1916.

Other Diseases.—Unfortunately, we have not had the opportunity of observing many conditions which might show something of interest; vasomotor disturbances, such as Raynaud's disease, erythromelalgia, disturbances in various kinds of paralysis, etc. Niekau,[16] by means of a special microscope designed by Müller observed the skin in locations other than the finger tips. He studied various skin diseases, such as psoriasis, also some of the acute exanthemata.

Some work has been done on capillary flow in diseases of infancy, such as exudative diathesis. Observations would be of interest in the acute intoxications in which Merriot [40] has shown by blood flow measurements that the peripheral circulation is slowed. Thus, there are many clinical branches in which a direct examination of the capillaries might be of interest.

CONCLUSION

While the observations in this series of cases might lead one to draw certain general conclusions as to circulatory condition in shock, in cardiac conditions, etc., one must be very careful in his deductions. The method is not a quantitative one, and only a few of the capillaries of a most labile part of the circulatory system are being observed. Consequently the reports of a large number of cases by different observers must be awaited before we can evaluate the method. However, because of the corroboration of the clinical picture and of certain experimental work, one has some faith in observations of a capillary stasis in shock, the capillary picture in cardiac decompensation, the poor capillary flow in some cases of hypertension, and the different pictures of a capillary pulse.

It is hoped that other workers will be interested in making similar observations.

SUMMARY

1. Observations on the capillary circulation in many clinical conditions were made by Lombard's method.

2. The effect of reflex vasomotor stimuli on the capillary circulation were observed, corroborating the blood flow experiments of Stewart.

3. In three cases of primary traumatic shock and one case of surgical shock, stasis was observed in the skin capillaries.

4. Capillary stasis was observed in several cases of septicemia, which had a sudden collapse.

5. Capillary stasis occurs in cardiac decompensation and may be of some value in differentiating the preponderant factor in cardiorenal diseases.

40. Merriot: Some Phases of the Pathology of Nutrition in Infancy, Am. J. Dis. Child. **20**:461 (Nov.) 1920.

6. In some cases of hypertension, there is a granular, intermittent capillary flow.

7. A true capillary pulse can be differentiated from a pseudocapillary pulse.

8. Observations may be of value in diseases where an endothelial intoxication or capillaritis is suspected, but no conclusive observations on such cases were made in this series.[41]

Our thanks are due to Dr. L. J. Karnosh for the drawings. The sketches are semi-diagrammatic camera lucida drawings with a magnification of approximately × 70. In some cases they represent the composite picture of several cases.

41. The attention of the authors has just been directed to the fact that a sort of polemic has been going on in the German and Austrian journals between Weiss and Schur[42] regarding priority in the application of Lombard's method to the clinical observation of capillaries. We know nothing of the merits of the controversy.

42. Schur: Ueber Kapillar-beobachtung, Wien. klin. Wchnschr. **33**:928, 1920.

THE PROTEIN REQUIREMENT IN TUBERCULOSIS *

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In a previous communication,[1] which was concerned chiefly with the total energy transformations in tuberculosis, a few experiments were given dealing with the nitrogen minimum in this disease. It was thought to be desirable to extend these observations so as to include data, not only regarding the minimal level of protein metabolism, but as far as possible to throw light on the optimal quantity with which to supply patients suffering from pulmonary tuberculosis.

Because of its intimate bearing on the problem of finding the optimal protein requirement for such patients, the knowledge acquired concerning the basal metabolism was supplemented by experiments on the effect of protein food upon the heat production. Further experiments were made[2] in which the action of all the foodstuffs was studied, not only on the metabolism, but on the pulmonary ventilation as well.

Studies of the protein metabolism in this disease, made up to 1903, have been compiled by Ott.[3] Up to that time no attempts seem to have been made to find the protein minimum in tuberculosis.

From 1888 to the present time there has been a great development of our knowledge of the size of the normal quota of protein for wear and tear. The general method for determining this has been to provide the experimental subject with a diet poor in protein (from 1 to 3 gm. nitrogen), but with an adequate supply of non-nitrogenous foods. Under these conditions, in normal men, the protein metabolism is reduced to the minimum which is necessary to cover the daily wear and tear of the protein containing organs and tissues. For ready reference the results of the more important of these experiments have been summarized in Table 8. More recently investigations of a similar character have been made to determine to

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical (Cornell) Division of Bellevue Hospital, New York, and from the Pathological Department, Bellevue Hospital.

1. McCann, W. S., and Barr, D. P.: The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.

2. McCann, W. S.: The Effect of the Ingestion of Foodstuffs on the Respiratory Exchange in Pulmonary Tuberculosis, Arch. Int. Med. To be published.

3. Ott, A.: Die chemische Pathologie der Tuberculose. Berlin, 1903.

what extent this wear and tear quota is affected in various diseases. A number of these have been summarized in Table 9.

Considerable discussion has arisen in the literature as to the existence or nonexistence of a "toxic destruction" of protein. For instance, if the size of the wear and tear quota is found to be increased some authors maintain that the increase is due to the action of toxins in disease. Others hold that the protein metabolism is increased as part of a generally increased metabolism, and that in spite of this nitrogen equilibrium may be established if an adequate diet is given. Reference to the experiments of Kocher [4] will show that the wear and tear quota in typhoid is much increased. However, the experiments of Schaffer and Coleman [5] show beautifully that if adequate amounts of carbohydrate, especially, and fat are given in typhoid fever the body may be protected from protein loss. This question has been well reviewed by Rolland,[6] who finds that there is no toxic destruction of protein in the sense that the body can not be protected from protein loss if an adequate diet be given, although she admits the possibility that it may occur to a slight degree in cases with temperature about 40 C. Rolland studied four cases of tuberculosis, one of whom she was able to keep in nitrogen balance with a diet furnishing 47 calories per kilogram and 10.7 gm. nitrogen. In another case 1.6 gm. nitrogen were added to the body daily with 49 calories per kilogram and 9.6 gm. nitrogen in the diet. Two of her patients were in negative nitrogen balance, but in one of these an adequate number of calories was furnished. Kocher [4] also studied some patients with tuberculosis in two and three day experiments, of which the data are too meager to justify any conclusions.

A great deal of attention has been directed towards elevation of body temperature as a possible factor in the increased protein metabolism of acute infections. May [7] has shown that the carbohydrate metabolism is greatly increased in fever. A deficiency of glycogen rapidly occurs, and the body proteins are called upon to take a large share in the increased energy production. That this state of febrile inanition plays a great part in the increased protein destruction has been shown by the results of Schaffer and Coleman,[5] to which reference has already been made. Bearing on the influence of body tempera-

4. Kocher, R. A.: Ueber die Grösse des Eiweisszerfalls bei Fieber und bei Arbeitsleitstung. Deutsch. Arch. f. klin. Med. **115**:82, 1914.

5. Schaffer, P., and Coleman, W.: Protein Metabolism in Typhoid Fever, Arch. Int. Med. **4**:538 (Nov.) 1909.

6. Rolland, A.: Zur Frage des toxogenen Eiweisszerfalls im Fieber des Menchen, Deutsch. Arch. f. klin. Med. **107**:440, 1912.

7. May, R.: cit. v. Noorden's Handb. d. Path. d. Stoffwechsels. Berlin, p. 591, 1906.

ture upon the protein metabolism are the valuable experiments of Graham and Poulton,[8] who elevated body temperature artificially by means of baths. These authors found that a rise of body temperature to 104.3 F., (40.2 C.) does not by itself cause any breakdown of the protein of the body. If a diet of very high caloric value is taken, containing a large excess of carbohydrate but a minimal quantity of protein, nonnitrogenous substances supply the whole of the increased energy production set up by the high temperature.

For the best recent summaries of our present knowledge of the protein metabolism reference may be made to those of Lusk,[9] Cathcart [10] and Van Slyke.[11]

TECHNIC

The technic of the management of the metabolism ward, in which the patients were kept, has been described in a paper by Gephart and DuBois.[12] In regard to the manner of weighing food, recording it, calculating its composition and caloric value, and the collection of the excreta the plan of Gephart and DuBois has been strictly followed.

The preparation of diets which could be completely taken and retained by sick patients, especially the tuberculous, required the greatest skill and painstaking care, for which we are greatly indebted to the chief nurse, Miss Estelle Magill, and her three assistants, Miss Elsa Forter, Miss Doris Cutler, and Miss Florine Nelson.

The data regarding diets given in Tables 1 to 4 represent only food which was actually ingested by the patients. The chief source of error which may exist is in the loss of food in the vomitus. A note has been made in each case in which this occurred.

In determinations of the respiratory metabolism made on our patients the apparatus used was a Tissot spirometer, in which expired air was collected and measured, and from which samples were taken for analysis. The analyses were done with a modified Henderson-Haldane apparatus. The exact technic of these determinations is given in a previous communication.[2] The first four subjects, in Table 7, were studied in the respiration calorimeter.[1] The basal

8. Graham and Poulton: Influence of Temperature Upon Protein Metabolism, Quart. J. M. **6**:82, 1912.

9. Lusk, G.: The Science of Nutrition, Ed. 3, W. B. Saunders Company, Philadelphia, 1917. Especially Chapter XII, pp. 334-361.

10. Cathcart, E. P.: The Physiology of Protein Metabolism. Monographs on Biochemistry. Longmans, Green and Co., London, 1921.

11. Van Slyke, Donald D.: The Chemistry of the Proteins and their Relation to Disease, Oxford Medicine, Vol. I. Oxford Press, 1920.

12. Gephart, F. C., and DuBois, E. F.: The Organization of a Small Metabolism ward. Clinical Calorimetry, Third Paper, Arch. Int. Med. **15**:829 (July) 1915.

requirement of energy for each patient was calculated from the data of the metabolism observations, adding 10 per cent. to the observed heat production to cover the effect of the specific dynamic action of foodstuffs.

In separation of the feces carmine was given in perforated capsules. The separations were all made satisfactorily for periods varying from three to eight days, generally five days. The stools were preserved with formalin in a refrigerator until the period was complete. They were then mixed and sent to the laboratory where they were rubbed to homogeneity with alcohol containing 1 per cent. sulphuric acid. After drying on a water bath the dry weight was taken, and the stools ground to a fine powder and preserved in a tightly stoppered bottle. Nitrogen in the urine and stools was determined by the Kjeldahl method. These analyses were made by Miss Frances D. Rule.

CASE HISTORIES

CASE 1.—*Early Apical Tuberculosis with Hemorrhage.*—Hubert W., a negro aged 28 years, was admitted Nov. 3, 1920, on account of blood spitting. He had "felt fine" in the morning of day of admission and had gone to work as usual. A few minutes after starting work he had a severe fit of coughing lasting ten minutes, during which he spat up one half cupful of frothy blood. Coughing thereafter at frequent intervals produced more hemoptysis. With the cough there was a dull sense of soreness over sternum and precordium.

Up to this time his health had been excellent. While in Central America in 1911 he had malaria. Cardiorespiratory history was negative, except for the fact that he was subject to frequent colds, with headaches and neuralgic pains about the eyes. For this he habitually took "headache powders." Weight was constant at its maximum of 135 pounds up to admission, though one week after admission it was found to be 120 pounds.

On admission, examination of the patient was limited to the front of the chest, in which the findings were only those of dulness, bronchovesicular breathing over the left upper lobe. His hemoglobin was 85 per cent.; red blood corpuscles, 5,152,000; leukocytes 6,400 with a normal differential count. The urine was normal, except for an occasional hyalin cast. Blood Wassermann reaction was negative. Temperature range, from 98 to 100 F.; pulse, from 60 to 90; respirations, from 20 to 30. Hemoptysis continued until November 10. Several sputum examinations were made, but no tubercle bacilli could be demonstrated.

November 10, physical examination was negative except for the chest. Patient was well developed and well nourished. The chest was large and well formed. There was distinct limitation of motion on the left side. There was normal resonance, except over the left upper lobe from the third rib in front to the mid-scapula behind. Over the dull area breathing ranged from bronchovesicular to bronchial in quality. Fine râles were heard over a small area below the outer third of the clavicle. The heart was normal in size and position. There were no murmurs. The rate and rhythm were regular. Blood pressure, systolic, 122 mm., diastolic 100 mm.

Roentgenograms Nos. 80,942 and 80,943 showed evidence of thickening of the pleura of the left lung, with infiltration of the extreme left apex, with hypervascularization of the right upper lobe. Heart shadow normal. Tuberculosis.

Patient was observed in the metabolism ward from November 10 to November 24. Dietary measurements and excreta analyses are tabulated in Table 1 (See also Fig. 1).

Nov. 27, 1920: Basal metabolism determination. Tissot spirometer. Age, 28; height, 166.5 cm.; weight, 55.1 kg.; surface area, 1.60 sq. m.; temperature, 98.2 F.; pulse, 80; respirations, 20. Expired volume, liters per hour, S. T. P. D. = 57.95. Gas analysis—O_2 per cent. 18.54, 18.58, CO_2 per cent. 2.30, 2.33. R. Q. 0.94, calories per hour = 67.9. Metabolism, 107.5 per cent. average normal. Twenty-four hour heat production estimated $68 \times 24 = 1{,}632$ calories, basal energy requirement, $1{,}632 + 163 = 1{,}795$ calories.

TABLE 1.—CASE OF HUBERT W. (CASE 1)

Date, Nov. 1920	Calories per 24 Hrs.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Weight, Kg.	Calories in Excess of Basal Requirement	Creatin per 24 Hrs. Mg.	Creatinin per 24 Hrs. Mg.
10	1,977	62.0	89.1	218.4	9.9	16.92	2.39	19.31	−9.4	55.51	182	119	1,836
11	1,950	63.5	90.6	206.5	10.2	8.40	2.39	10.79	−0.6	.....	155		
12	1,751	62.2	90.8	207.7	10.0	10.12	2.39	12.51	−2.5	55.19	(−44)	48	1,520
13	2,538	36.1	121.5	307.2	5.8	6.20	2.30*	8.50	−2.7	.....	743	31†	1,473
14	2,507	37.1	120.9	300.2	5.9	6.20	2.30	8.50	−2.6	.....	712	12†	1,495
15	1,293	19.3	57.0	166.9	3.1	6.20	2.30	8.50	−5.4	55.16	(−502)	10†	1,445
16	2,290	37.7	112.4	300.2	4.4	6.20	2.30	8.50	−4.1	.....	595	8†	1,258
17	2,290	37.7	112.4	300.2	4.4	6.20	2.30	8.50	−4.1	55.29	595	†	1,400
18	2,509	24.3	109.3	327.6	5.5	4.77	2.30*	7.07	−1.6	.....	705		
19	2,601	38.6	110.0	331.3	6.2	5.20	2.30	7.50	−1.3	.....	806		
20	2,508	35.6	110.0	326.3	5.7	4.50	2.30	7.80	−2.1	56.41	713		
21	2,508	35.6	109.5	326.3	5.7	5.07	2.30	7.37	−1.7	.....	713		
22	2,390	27.7	112.4	300.2	4.4	4.11	2.30	6.41	−2.0	.....	595		
23	2,312	26.6	105.2	298.7	4.3	3.78	2.30	6.08	−1.8	.....	517		
24	2,469	27.7	120.9	300.2	4.4	3.96	2.30	6.26	−1.9	55.11	674		

* Fecal nitrogen estimated. Analyses made in Periods 1 and IV.
† Creatin-free diet.

Comment.—Examination of the data in Table 1 shows that the urinary nitrogen excretion did not fall as promptly in response to the reduction in food nitrogen as it did in the subsequent cases. The cause of the lag is not at once apparent. There was practically no fever (from 98 to 100 F.) during the two weeks of observation. There was no evidence of toxicity. The patient felt quite well. It it not unlikely that the source of the extra nitrogen was clotted blood retained in the lung and undergoing slow absorption.

The nitrogen loss in the feces was quite large throughout. There was no diarrhea. The diet was not of a bulky nature such as would ordinarily lead to poor utilization.

At the end of the period of observation the area of dulness over the left upper lobe was somewhat diminished below the clavicle. Breath sounds had a slightly higher pitch than normal and a somewhat prolonged expiration. No râles were heard.

Case 2.—*Acute Pneumonic Phthisis.*—Abraham M., an Arab, aged 21 years, was admitted Nov. 29, 1920, complaining of cough and pain in the chest. His illness began two months before admission with a severe "cold," cough persisted with expectoration. For two weeks prior to admission he had been expectorating blood.

His previous health was good, except for an attack of pneumonia (date not given), and an ischiorectal abscess, which he had before coming to America in 1920. He also had measles and typhoid fever (dates not given). He had an operation for hemorrhoids in 1917. His appetite was always poor, but he had no digestive disturbances until present illness. Venereal disease was denied. He smoked cigarettes excessively. Weight before present illness was 130 pounds. Four of his brothers died of tuberculosis.

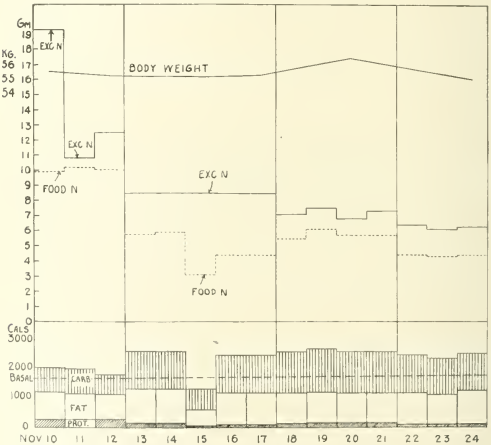

Fig. 1.—Hubert W.

From November 20 to 26 he was on the service of Dr. James Alexander Miller, on which the following examination was made:

General appearance: Poorly developed and poorly nourished colored Arabian male lying quietly in bed with rapid respirations and productive cough. The skin is hot, dry and shiny, with no visible cyanosis or rashes. Glands are not enlarged. Extremities show no edema, clubbing, but marked wasting. Reflexes: Knee jerks sluggish, Oppenheim and Babinski not obtained. The head is of normal contour. Hair, thick and curly. Eyes: Pupils dilated, react normally to light and accommodation. There is no nystagmus, strabismus or ptosis. Ears: No discharge or mastoid tenderness. Mouth: Teeth fairly good. Tongue coated. Pharynx injected. Neck: No rigidity, no thyroid enlargement. Thorax: Long and narrow. Retraction of both supraclavicular fossae. Expansion is

limited throughout the left side. Fremitus poor throughout and marked dulness and bronchovesicular breathing above the left second rib and angle of scapula. Below these there is bronchial breathing and pectoriloquy. There are numerous fine and moist râles throughout the left side. The right side is resonant with harsh breathing and increased whispered voice above the spine of the scapula. No definite râles were heard. Heart: Apex impulse in fifth left intercostal space. No enlargement, no thrills or murmurs. The pulmonary second sound is accentuated. Rate rapid, rhythm regular. Abdomen: Scaphoid, no areas of tenderness or rigidity. Liver and spleen not palpable.

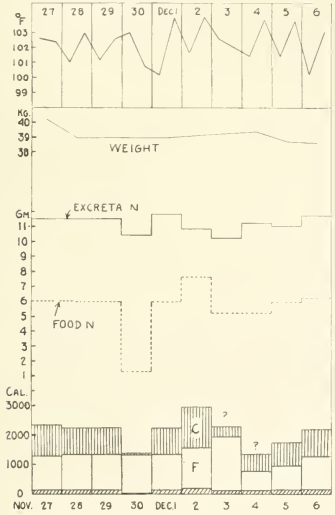

Fig. 2.—Ab. M.

A provisional diagnosis of acute pneumonic phthisis was made. Many tubercle bacilli were found in the sputum. Urine normal. Temperature: High with remissions, from 104 to 100 F. Pulse, from 100 to 120. Wassermann reaction negative.

November 26: Admitted to metabolism ward (See Table 2 for data regarding diet and excreta) (Fig. 2).

December 1: Passed *ascaris lumbricoides* in stool. Examination shows no other ova present than those of ascaris.

December 3: Leukocyte count, 15,800; eosinophils, 5 per cent.; lymphocytes, 3 per cent.; large mononuclears, 13 per cent.; transitionals, 1 per cent., polymorphonuclears, 78 per cent.

November 29: Basal metabolism determined. Height, 168 cm. Weight, 40 kg. Body surface area, 1.42 sq. meters. Temperature, 101.6 F. Volume expired. S. T. P. D.—57.85 liters. Gas analysis: CO_2 per cent. 2.17, 2.20. O_2 per cent. 18.42, 18.40. R. Q. = 0.824, calories per hour, 72.74. Metabolism 130 per cent. of average normal. Daily heat production (average temperature 101 F.) = 1,744 calories. Estimated basal requirement = 1,744 + 174 = 1,921 calories per diem.

The patient was observed in the metabolism ward from November 27 to December 6 inclusive. During this time he was extremely ill. It was with the greatest difficulty that he could be persuaded to take food. On three days vomiting occurred so that an unknown quantity of food was lost.

TABLE 2.—ABRAHAM M. (CASE 2.)

Date, Nov.-Dec., 1920	Total Calories per 24 Hours	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Food Calories ÷ Basal Requirement	Body Weight, Kg.	Creatin, Mg. per Diem	Creatinin, Mg. per Diem	Remarks
27	2,360	37.3	123.8	257.6	6.0	10.83	0.70	11.53	−5.5	+440†	.....	71*	962	Period I
28	2,497	36.8	128.7	280.4	5.9	10.83	0.70	11.53	−5.6	+577	40.25	71*	962	
29	2,497	36.8	128.7	280.4	5.9	10.83	0.70	11.53	−5.6	+577	.....	71*	962	
30	1,375	8.4	140.0	9.6	1.3	9.72	0.70	10.42	−9.1	−545	.....	211*	987	Vomited
1	2,497	36.8	128.7	280.4	5.9	11.13	0.70	11.83	−5.9	+577	38.99	227*	997	
2	2,947	47.2	148.9	333.9	7.6	9.97	0.80	10.77	−3.2	+1,027	35.15	....	...	Period II
3	2,360	32.4	196.0	83.9	5.2	9.43	0.80	10.23	−5.0	+380	.....	....	...	Vomited
4	1,360	32.6	70.7	138.6	5.2	10.40	0.80	11.20	−6.0	−560	39.39	....	...	Vomited
5	1,758	36.8	87.1	189.4	5.9	10.20	0.80	11.00	−5.1	−182	38.70			
6	2,184	39.0	119.1	223.4	6.2	10.86	0.80	11.66	−5.5	+264	38.61			

* Creatin-free diet.
† Basal requirement estimated at 1,920 calories per diem.

The data regarding diet measurements and excreta analyses are shown in Table 2, and graphically in Figure 2. It will be seen that the urinary nitrogen figure at its lowest was almost double the food nitrogen, in spite of the fact that on all but three days the energy value of the food was in excess of the estimated basal requirement.

Of the ten cases in which the nitrogen metabolism has been studied by us, this one shows the highest protein metabolism. It is unique in our series, resembling much more closely the patient with croupous pneumonia studied by Kocher[4] (Table 9). This patient had the physical signs of a pneumonic consolidation, with tubercle bacilli in the sputum. It is not known to what extent other organisms entered into the production of the pneumonia.

This patient was the subject of an experiment to determine the specific dynamic action of fat, and its effect upon the pulmonary ventilation. The data of this experiment are to be found in a previous paper.[2]

CASE 3.—*Massive Bilateral Infiltration of Lungs with Multiple Excavations.*—Fred R., a porter, aged 41 years, was admitted Nov. 23, 1921, complaining that for three years he had had a chronic cough with progressive loss of weight and strength. He had never enjoyed good health. In 1917 he began to have a cough with a little sputum. He felt badly but continued to work fourteen hours a day up to February, 1920, when he was obliged to quit work because of weakness and shortness of breath. He then had three hemoptyses. He was admitted

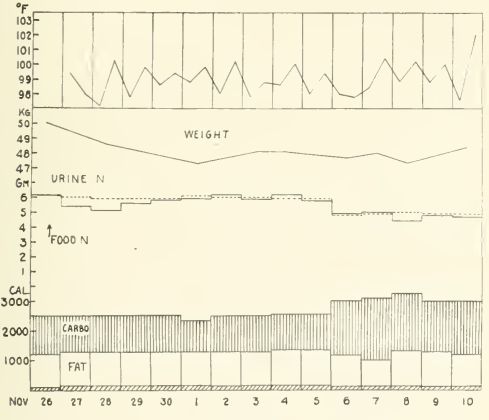

Fig. 3.—Fred R.

to the Seaview Hospital in April, 1920, and remained there until September, 1920. After his discharge he went to the country where he stayed until Nov. 15, 1920. Since his return to New York he has had attacks of "heart standing still," which brought him into the hospital. The past history is chiefly irrelevant. His best weight was 145 pounds, present weight 105 pounds. Two of his brothers are known to have tuberculosis.

Physical Examination.—Height, 167 cm., weight, 47 kg. Fairly well developed, emaciated, lips slightly cyanotic, respirations rapid but with no subjective distress. The head, eyes, ears, nose, mouth, throat and neck were normal.

Chest: There was marked emaciation with myoidema. There was marked limitation of the respiratory excursion on the right side, with supraclavicular retractions and of the lower right intercostal spaces. Both upper lobes were

dull, especially the right. The whole right chest was dull, front and back. The left lower chest was resonant, almost tympanitic. Over the whole chest numerous fine and coarse râles and rubs were heard. The breath sounds over the left upper lobe were harsh with prolonged expiration. Over the right upper lobe there were areas of amphoric breathing, elsewhere bronchial, and over the right lower lobe there was distant bronchial breathing.

Heart: Apex impulse was in the fifth intercostal space 11 cm. to the left of the midline. Rhythm regular. No murmurs heard. The pulmonary second sound was accentuated. Pulses synchronous, soft, and rapid. The vessels were not sclerosed. Blood pressure, systolic 85 mm. The abdomen was normal, except that the soft smooth liver edge was felt just below the costal margin.

TABLE 3.—Fred R.

Date, Nov.-Dec., 1920	Total Calories per Diem	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Calories ± Basal Requirement*	Creatin per 24 Hrs. Mg.	Creatinin per 24 Hrs. Mg.	Body Weight, Kg.	Remarks
26	2,524	26.1	120.0	317.2	4.2	6.14	1.12	7.26	−3.1	+454	0	956	50.00	Period I
27	2,524	37.2	128.8	286.2	6.0	5.37	1.12	6.49	−0.5	+454	3	982	.....	Creatin-free
28	2,497	36.8	128.7	280.4	5.9	5.09	1.12	6.21	−0.3	+427	0	957	48.56	diet
29	2,497	36.8	128.7	280.4	5.9	5.57	1.12	6.69	−0.8	+427	12	959		
30	2,497	36.8	128.7	280.4	5.9	5.79	1.12	6.91	−1.0	+427	20	885	.....	No urine le st
1	2,344	38.1	113.6	276.0	6.1	5.87	0.96	6.83	−0.7	+274	0	950	47.29	Period II
2	2,491	37.2	112.3	315.7	6.0	6.13	0.96	7.09	−1.1	+421				
3	2,502	37.4	112.4	318.2	6.0	5.86	0.96	6.82	−0.8	+432	..	...	48.08	
4	2,537	36.8	127.7	292.3	5.9	6.18	0.96	7.14	−1.2	+467	..	...	48.04	
5	2,537	36.8	127.7	292.3	5.9	5.83	0.96	6.79	−0.9	+467				
6	3,004	29.7	114.4	443.4	4.8	4.88	1.32	6.20	−1.4	+934	..	...	47.65	Period III
7	3,134	30.4	105.6	493.8	4.9	4.95	1.32	6.27	−1.4	+1,061	..	...	48 03	
8	3,277	31.0	129.1	475.5	5.0	4.40	1.32	5.72	−0.7	+1,207	..	...	47.30	
9	2,595	30.5	122.4	422.4	4.9	4.85	1.32	6.15	−1.3	+925	..	...	48.0	
10	2,955	30.5	118.1	422.4	4.9	4.70	1.32	6.02	−1.3	+885	..	...	48.35	
11	2,647	91.4	144.8	225.6	14.6	9.26	....	....	.....	.....	..	...	47.46	Period IV
12	(2,748)	70.8	148.1	263.6	11.3	9.09	....	....	.....	.....	..	...	47.96	Vomited
13	(3,239)	93.0	183.0	282.0	14.9	8.00	....	....	.....	.....	..	...	48.71	Vomited
14	(986)	34.4	50.4	91.8	5.5	....	....	....	.....	.....	..	...	48.83	Died

* Basal requirement 2,070 per diem.

Reflexes: All deep reflexes were exaggerated. There was an exhaustable bilateral patellar and ankle clonus. Plantar reflexes were normal. The neck was not stiff, and Kernig's sign was not elicited. Further examination showed no abnormalities.

The urine was normal. Many tubercle bacilli were found in the sputum. He was transferred to the metabolism ward November 26 and remained there until his death on December 14. His diet and excreta are shown in Table 3 and graphically in Figure 3.

His basal metabolism was determined December 2 and 11, using the Tissot spirometer. The effect of ingestion of protein food on the heat production and pulmonary ventilation was studied. These experiments are to be found in a previous paper.[2]

The basal metabolism was 12 per cent. above the average normal when the temperature was 98 F. It was 28 per cent. above normal when the temperature was 100 F., being 65.5 and 75.0 calories per hour, respectively. The elevation

of metabolism is believed to be due largely to the dyspnea. The basal heat production is estimated to be between 1,620 and 1,880 calories per diem., and the basal requirement 2,068 calories.

Referring to the data in Table 3 it will be seen that, while the urinary nitrogen fell practically to the level of ingested protein, there was a persistent loss of nitrogen amounting to about 1 gm. per diem. Assuming muscle to be about one fifth protein, this nitrogen loss would represent the equivalent of about 30 gm. muscle per diem or about 1 kg. per month.

On the afternoon of the last day of period 3 the temperature rose to 102 F. On the following day it was planned to raise the food intake to the equivalent of 4,000 calories, with 90 gm. protein. The patient was unable to take the entire amount. On the following day vomiting occurred, and the temperature continued to rise, with a marked increase in the pulse and respirations. The patient continued to grow worse. Late in the afternoon of December 14 the patient became very dyspneic, respirations from 50 to 60 per minute, pulse from 130 to 140. Death ensued on the night of December 14.

Necropsy showed massive infiltration of the right lung, with huge cavities but no erosion of vessels. The left lung showed extensive infiltration, with small cavities, but still contained considerable air. There was no gross evidence of a superimposed pneumonia.

Case 4.—*Infiltration of Both Upper Lobes.*—John O'C., a porter, aged 49 years, admitted Dec. 3, 1920, complaining of pain in the right chest and lumbar region, cough and expectoration. His mother died of tuberculosis. He had been married twenty years, having five children living and well. He had been well until 1889, when he had some pulmonary trouble for which he was confined to bed for three months. After that he had a persistent cough. His general condition remained fairly good up to 1910 when he began to work at night. His weight which had been 170 pounds dropped to 150 pounds. In 1917 he developed a migratory arthritis which involved many joints, for which he was twice admitted to Bellevue Hospital. He had had a nystagmus all his life. He had many attacks of quinsy sore throat. He had had a persistent cough since 1889, with occasional streaks of blood in the sputum. No history of dyspnea, edema or night sweats until present illness. He had had frequent attacks of alcoholic gastritis. Appetite habitually good. Bowels constipated. Until present illness patient had nocturia, no dysuria or other urinary symptoms. Venereal disease was denied. Habits alcoholic. Weight: best, 170 pounds; 150 pounds in 1910; 133 pounds in 1917; present weight 110 pounds.

Present Illness.—Began in the middle of November, 1920, with pain over the whole front of the right chest and in the right lumbar region. There was considerable cough and some expectoration. The pain was increased by deep breathing. He remained at work one week in this condition and then was forced to spend the afternoons in bed. Growing worse he came to the hospital for admission.

Physical Examination.—Height, 174.3 cm., weight, 49.7 kg. Patient was a thin pale man appearing quite ill, lying flat in bed, very emaciated. There were dilated venules on the nose. The lips and finger tips were quite cyanotic. Respirations accelerated but not labored. Head: normal. Eyes: extraocular movements well performed. Patient unable to fix gaze because of a slight nystagmus, which is brought out strongly by looking to the left but not to the right, with the slow component to the left. Pupils equal and regular, react to light and accommodation. Ears and nose normal. Mouth: Teeth carious.

with many missing in the upper jaw. There was some pyorrhea. Tongue coated and tremulous. Pharynx congested. Tonsils normal. Larynx not examined, though voice was husky. Neck: Normal except for spasm of the right sternocleidomastoid muscle.

Thorax: of the long type with prominent sternum. There were marked supraclavicular retractions. Respiratory movements were shallow with greater restriction on the right side.

Lungs: both upper lobes were dull front and back. The left lower lobe showed little impairment of resonance. The right lower lobe was dull to

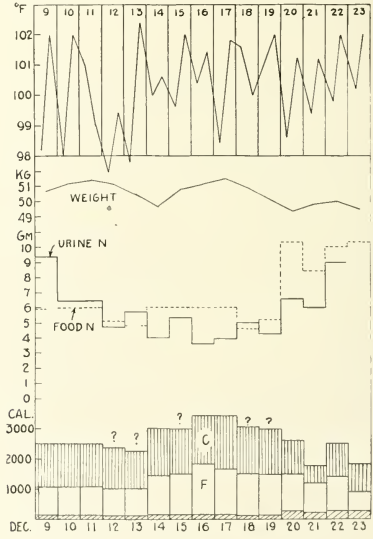

Fig. 4.—J. O'C. Question mark indicates an unknown amount of food lost in vomitus.

flat behind, extending almost to midline in front. Over this area there was diminished fremitus. Breath sounds over both upper lobes were bronchial, with clicking râles heard during quiet breathing and showers of fine râles during inspiration after coughing. At the right base the breath sounds are diminished or absent behind, with distant bronchovesicular breathing laterally. At the left base there was prolonged low pitched expiration of the emphysematous type.

Heart: Apex beat not seen and hardly felt. Apex dulness in the fifth intercostal space 8 cm. to the left of midline. The right border was 7.5 cm. to

the right in the third intercostal space. The rhythm is irregular (extrasystoles), rate rapid (90). No murmurs were heard. The arteries are somewhat thickened. The pulses equal and synchronous. Blood pressure: systolic, 128; diastolic, 100 mm.

Abdomen: Flat, rather rigid in the right upper quadrant. Liver and spleen were not felt. No tenderness or masses felt. Further examination revealed no abnormalities.

On admission the temperature was 101 F., and during the next five days it rose gradually to 102 F., in the afternoon. The urine was normal. The sputum contained many tubercle bacilli. Leukocytes, 9,800, with a normal differential count. Roentgen-ray examination (No. 84,275), December 14, showed evidence of narrowing of the intercostal spaces on the right side with marked thickening of the pleura of the right lung. There was peribronchial infiltration and agglutination of the foci in the upper parts of both pulmonic fields. The heart was slightly retracted to the right. A small effusion in the right costophrenic sinus could not be ruled out.

TABLE 4.—JOHN O'C

Date, Dec. 1909	Total Calories Food	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Body Weight, Kg.	Remarks Calories ± Basal Requirement †
9	2,505	37.1	100.3	346.4	5.9	9.40	0.65	10.05	−4.2	50.71	+ 895 calories
10	2,503	37.3	100.9	343.3	6.0	6.44	0.65	7.09	−1.1	51.23	+ 893 calories
11	2,515	37.3	100.9	347.3	6.0	6.44	0.65	7.09	−1.1	51.41	+ 905 calories
12	2,271	31.8	94.6	351.9	5.1	4.71	0.65	5.36	−0.3	51.06	Vomited part of food
13	2,257	30.2	97.5	299.0	4.8	5.69	0.65	6.34	−1.5	50.50	Vomited part of food
14	3,004	37.2	139.2	381.9	6.0	4.00	0.53	4.53	+1.5	49.73	+ 1,394 calories
15	2,982	37.2	143.1	365.4	6.0	5.33	0.53	5.86	+0.1	50.89	Vomited at 11 p. m.
16	3,422	37.8	179.7	389.2	6.0	3.64	0.53	4.17	+1.8	51.10	+ 1,812 calories
17	3,427	37.6	161.4	432.3	6.0	3.94	0.53	4.47	+1.5	51.54	+ 1,817 calories
18	3,046	28.7	149.7	374.6	4.6	5.02	0.53	5.55	−1.0	50.89	Vomited part of food
19	2,984	32.3	143.7	369.7	5.2	4.26	0.53	4.79	+0.4	.....	Vomited part of food
20	2,601	64.4	132.1	270.2	10.3	6.58	1.0*	7.6	+2.7	49.33	
21	1,776	52.4	105.5	141.4	8.4	6.01	0.8*	6.8	+1.6	49.75	
22	2,503	62.7	123.6	267.6	10.0	8.95	1.0*	10.0	0	50.00	
23	1,823	64.3	63.6	236.1	10.3	....	....	.....	.....	49.50	

* Estimated at 10 per cent. of intake.
† Basal requirement estimated at 1,610 calories per diem.

Comment.—The patient was in the metabolism ward from December 9 to 20. The data regarding his diet and analyses of excreta are given in Table 4, and shown graphically with the temperature chart in Figure 4.

His basal metabolism was determined on two occasions, using the Tissot spirometer. December 14, with a temperature of 100.8 F., his metabolism was 3 per cent. above the average normal. December 23, it was exactly normal with a temperature of 100.6 F. The heat production was 62 and 61 calories per hour, respectively, on the two occasions. The basal heat production for twenty-four hours is 1,464 calories. Adding 10 per cent. for the specific dynamic action of food the basal requirement is estimated at 1,610 calories.

An experiment was done to study the effect of a small protein meal on the heat production and pulmonary ventilation. The experimental data of this and of the basal determinations are given in the preceding communication.[2]

Referring to the data in Table 4 it will be seen that the lowest urinary nitrogen excretion was reached December 16. This low figure was not obtained by reduction of the nitrogen intake to an extremely

low level, but rather by the ingestion of a large quantity of carbohydrate and fat. In spite of considerable fever, it was possible to achieve positive nitrogen balance by the ingestion of from 37 to 38 gm. protein when the total caloric value of the food was more than twice the estimated basal requirement of energy. The patient, however showed a marked tendency to digestive disturbances, and vomiting resulted frequently when attempts were made to increase the diet. The diet was much better taken when 60 or 65 gm. protein were given, and it will be seen that in this case nitrogen balance could be achieved by the ingestion of much less nonprotein food.

CASE 5.—*Infiltration, Right Upper and Middle Lobes, with Cavitation.*—Frank D., a plumber's helper, aged 17 years, was admitted Jan. 30, 1921, complaining of cough and weakness. Family history rather indefinite. Patient was raised in an orphanage. He had had measles, chickenpox and mumps. Each year he had attacks of severe sore throat. After a severe illness he was treated for one year for "heart trouble." He never had arthritis. He gave no history of any cardiorespiratory symptoms prior to present illness. Gastro-intestinal, urinary, and venereal history were negative. After leaving the orphanage he was employed at night doing very heavy work for two months. He became very much "run down." His weight fell from 125 to 97 pounds. He was out of work for a month, after which he found that he was too weak to work. He was then supported by another boy from the orphanage, who could allow him only $0.40 a day for food. For two months before admission he coughed, at first slightly, later severely with yellowish sputum. Three weeks before admission he had become so weak he remained in bed. Two weeks later he coughed up about one and one half ounces of blood.

Physical Examination.—Height, 165.5 cm., weight, 43 kg. A thin pale weak looking boy lying quietly in bed without respiratory embarrassment. No abnormalities were found other than those in the thorax.

Thorax: The clavicles were prominent, supraclavicular fossae well marked, especially of the right side. Respiratory excursion more limited on the right side.

Lungs: Both apices were dull, on the right side from the second rib to midscapula, on the left above the clavicle and spine of scapula. Over both dull areas the breath sounds were modified, bronchovesicular to bronchial, with many crepitant and subcrepitant râles. Resonance and breath sounds over the lower lobes were normal.

Heart: Apex beat, somewhat diffuse, was seen in the fifth intercostal space inside the nipple line. The area of dulness extends to the left 7.5 cm. in the fifth space and to the right 2.5 cm. in the third space. No murmurs were heard. The rate was rapid. There was a respiratory arrhythmia. The pulmonary second sound was accentuated. Pulses soft, rapid, equal and synchronous. Blood pressure, systolic 98 mm., and diastolic 70 mm.

On admission the temperature was 101 F.; pulse, 100; respirations, 24. The urine was normal. Tubercle bacilli were present in the sputum. Blood examination showed: hemoglobin, 79 per cent.; red blood cells, 4,320,000; leukocytes, 10,700 with 31 per cent. lymphocytes.

Roentgen-ray examination (No. 89,021) showed a localized area of peribronchial infiltration at the right upper lobe. There was considerable production of fibrous tissue with the presence of a cavity between the first and second ribs. There were also several foci of peribronchial infiltration in the middle lobe of the right lung.

The basal metabolism was determined with the Tissot apparatus Feb. 4, 1921. Height, 165.5 cm., weight, 43.24 kg. Volume expired, S. T. P. D., 363.1 liters per hour. Gas analysis: CO_2 per cent. 3.10; 3.11; O_2 per cent. 17.69, 17.72. R. Q. =

0.945. Calories per hour = 58.6. Calories per twenty-four hours = 1,406. The metabolism was 5 per cent. below the average normal for his age. The basal requirement, allowing 10 per cent. for specific dynamic action, was 1,547 calories per diem. The subject was not very suitable for respiration experi-

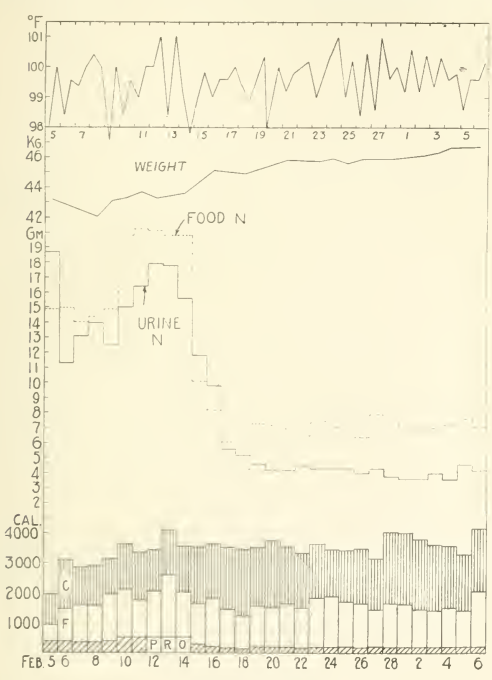

Fig. 5.—Frank D.

ments because of a persistent tendency to overventilate, which produced "Auspumpung" of carbon dioxid.

March 5 the metabolism was again determined. The weight was greater, 46.7 kg. Calories per hour 61.0 The metabolism was 4 per cent. below the average normal. Basal requirement = 1,610 calories.

He was observed in the metabolism ward from February 5 to March 7, 1921. The data regarding his diet and analyses of excreta are shown in Table 5, and graphically in Figure 5.

TABLE 5.—FRANK D.

Date, Feb.-March, 1921	Total Calories Food	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Calories ± Basal Requirement*	Body Weight, Kg.
5	1,969	93.0	59.4	252.6	14.9	18.65	1.32	19.97	−5.1	+422†	43.2
6	3,101	93.8	116.2	398.7	15.0	11.31	1.32	12.63	+2.4	+1,554	
7	2,863	87.4	133.1	309.1	14.0	13.06	1.32	14.38	−0.4	+1,316	42.4
8	2,906	89.9	129.8	324.4	14.4	13.95	1.32	15.27	−0.9	+1,359	42.08
9	3,141	93.0	168.9	289.9	14.9	12.45	1.32	13.77	+1.1	+1,594	43.06
10	3,640	123.8	172.5	372.8	19.8	15.04	1.94	16.98	+2.8	+2,093†	43.28
11	3,377	126.2	133.3	395.2	20.2	16.43	1.94	18.37	−1.8	+1,830	43.77
12	3,455	125.7	166.9	338.5	20.1	17.86	1.94	19.80	+0.3	+1,908	43.33
13	4,115	124.0	255.0	369.2	19.8	17.77	1.94	19.71	+0.1	+2,568	
14	3,573	123.7	163.6	376.9	19.8	15.62	1.94	17.56	+2.2	+2,026	43.6
15	3,564	63.4	149.0	467.8	10.1	11.76	....	.....	.....	.....	44.39
16	3,634	51.1	171.9	445.1	8.2	9.81					
17	3,334	38.2	149.3	485.1	6.1	5.59					
18	3,470	26.6	121.4	519.9	4.3	5.93	....	.....	.....	.....	44.88
19	3,544	45.7	149.4	480.0	7.3	4.63	....	.....	.....	.....	45.17
20	3,783	44.8	143.8	551.7	7.2	4.22					
21	3,598	43.8	156.9	470.5	7.0	4.20	....	.....	.....	.....	45.8
22	3,344	40.4	143.0	450.8	6.5	4.52					
23	3,654	45.9	176.6	444.9	7.4	4.28	1.25	5.53	+1.9	+2,044*	45.69
24	3,466	44.1	181.9	387.0	7.1	4.31	1.25	5.56	+1.5	+1,850	45.89
25	3,454	51.0	159.4	425.1	8.2	4.28	1.25	5.53	+2.7	+1,824	45.65
26	3,489	39.8	159.8	448.8	6.4	3.98	1.25	5.23	+1.2	+1,879	45.85
27	3,196	49.1	134.7	415.2	7.9	4.37	1.25	5.62	+2.3	+1,546	
28	4,044	45.4	168.0	560.0	7.3	3.75	1.82	5.57	+1.7	+2,434*	45.85
1	4,008	45.0	155.3	580.6	7.2	3.57	1.82	5.39	+1.8	+2,398	
2	3,894	43.4	153.4	577.4	6.9	3.60	1.82	5.42	+1.5	+2,194	46.12
3	3,599	44.0	133.2	531.6	7.0	4.00	1.82	5.82	+1.2	+1,989	46.33
4	3,574	44.9	140.7	507.9	7.2	3.59	1.82	5.41	+1.8	+1,964	46.66
5	3,272	47.3	122.0	451.1	7.6	4.63	1.82	6.45	+1.1	+1,662	
6	4,150	44.6	202.3	508.7	7.1	4.22					

* Basal requirement estimated at 1,610 calories per diem.
† Basal requirement estimated at 1,547 calories per diem.

The observations were divided into five periods, in four of which the feces were separated and analyzed. In the first two periods the protein ingested was about 90 and 125 gm. per diem, respectively, with enough nonprotein calories to greatly exceed the requirement.

Period	Average Total Food Calories	Average Protein Daily, Gm.	Average Positive Nitrogen Balance
1 (last 4 days)	3,008	91	0.55
2	3,632	124.7	1.44
4	3,439	46	1.9
6	3,717	45	1.5

In period three the average daily calories ingested was 3,430. The food nitrogen was rapidly reduced to 4.3 gm., the urine nitrogen output falling gradually to 5.2 gm. At this point the food nitrogen intake was again raised to about 7 gm., (period 4), the urine nitrogen continuing to diminish.

Case 6.—*Infiltration of Left Apex and Right Hilum, with Large Cavities.*—George R., a truck driver, aged 35 years, was admitted Jan. 4, 1921, complaining of fistula in ano, cough, loss of weight, and night sweats. Family history negative.

Past History.—General health not impaired until two months before admission. He had had fistula in ano for three years. In childhood he had measles only. No history of other infections, operations or injuries. He had never had a cough before July, 1920, and had never had dyspnea or edema. His appetite was always good and his bowels regular. There was never any pain on

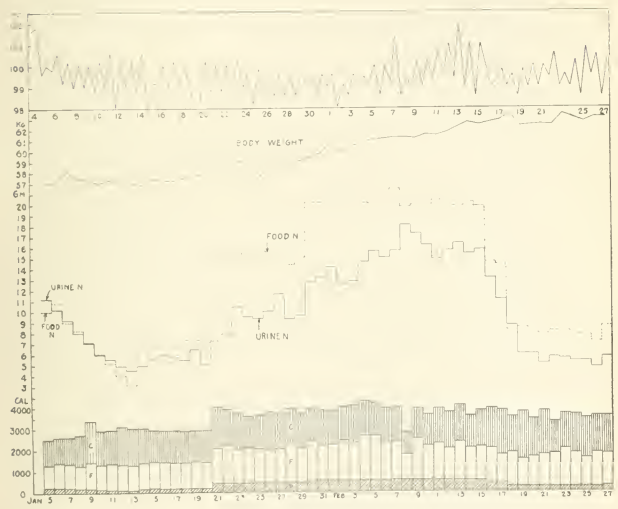

Fig. 6.—George R.

defecation though for three years he had had a fistula discharging pus. In January, 1920, a second fistula appeared, and in December, 1920, a third. He had never had any urinary symptoms. In 1908, he had a chancroid infection in the left inguinal glands. He had recently become a heavy drinker in spite of prohibition. His weight rose from 150 to 172 pounds in 1918, but fell again during the summer of 1920 to 144 pounds. Present weight 126 pounds.

Present Illness.—He began to cough in July, 1920. At first the cough was dry, later productive. In December, 1920, he began to notice small clots of blood in the sputum. He was never aware of afternoon fever, but about

TABLE 6.—GEORGE R. (CASE 6)

Date, Jan.-Feb. 1921	Total Calories Food	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Calories ± Basal Requirement†	Body Weight, Kg
5	2,508	62.6	112.5	294.0	10.0	11.20	.....	...	.....	+724	57.1
6	2,597	67.8	122.2	288.6	10.8	10.22	...	....	.....	+813	57.1
7	2,583	56.1	120.5	300.0	9.0	9.16	.....	....	.....	+797	58.1
8	2,760	51.3	111.3	369.6	8.2	8.00	.....	....	.....	+976	57.4
9	3,375	44.4	134.9	472.7	7.1	7.08	.....	....	.....	+1,591	
10	2,910	37.6	126.5	385.4	6.0	6.02	.....	....	.....	+1,126	57.0
11	2,968	31.6	131.3	394.5	5.1	5.54	.....	....	.....	+1,184	57.3
12	3,094	25.2	139.8	435.1	4.0	4.88	.....	....	.....	+1,310	57.1
13	3,012	19.6	128.6	423.4	3.1	4.48	.....	....	.....	+1,228	57.1
14	3,033	42.4	129.9	403.8	6.8	4 86	0.84	5.70	+1.1	+1,254	56.8
15	2,922	46.3	135.4	359.3	7.4	5.57	0.84	6.41	+1.0	+1,138	57.4
16	2,928	40.8	131.7	374.6	6.5	5.89	0.84	6.73	—0.2	+1,144	
17	2,919	41.5	129.1	377.6	6.6	5.69	0.84	6.53	+0.1	+1,133	57.2
18	2,877	45.5	129.5	362.7	7.3	5.42	0.84	6.26	+1.0	+1,093	57.5
19	2,906	45.7	134.2	358.8	7.3	6.35	0.84	7.19	+0.1	+1,122	57.6
20	2,933	44.6	128.4	379.5	7.1	5.05	0.84	5.89	+1.2	+1,149	57.9
21	4,013	94.8	180.1	475.3	15.2	7.24	*	8.8	+6.4	+2,229	
22	3,916	94.4	168.6	470.2	15.1	7.85	*	9.4	+5.7	+2,132	59.8
23	3,695	92.2	173.8	413.2	15.0	10.37	*	11.9	+3.1	+1,911	
24	3,556	96.0	179.0	365.3	15.4	9.50	*	11.0	+4.4	+1,772	58.7
25	3,631	94.2	174.3	396.0	15.1	9.27	*	10.8	+4.3	+1,847	57.4
26	3,744	96.7	166.0	439.2	15.5	10.05	*	11.6	+3.9	+1,960	58.1
27	3,674	93.7	177.6	399.5	15.0	11.61	*	13.1	+1.9	+1,890	59.5
28	3,918	89.5	208.0	394.3	14.3	9.26	*	10.7	+3.6	+2 134	58.6
29	3,659	94.0	189.3	389.6	15.0	9.59	*	11.1	+3.9	+1 875	
30	3,935	125.6	201.6	376.8	20.1	12.74	*	14.7	+5.4	+2,151	
31	3,824	125.4	179.5	400.2	20.1	13.05	*	15.1	+5.0	+2,040	59.8
1	3,795	127.1	182.2	385.4	20.3	14.08	*	16.1	+4.2	+2,011	60.6
2	3,976	123.8	204.1	383.0	19.8	12.53	*	14.5	+5.3	+2,192	59.9
3	4,062	125.7	189.8	429.8	20.1	12.73	*	14.7	+5.4	+2,258	60.4
4	4,249	125.6	223.7	403.3	20.1	14.56	*	16.6	+3.5	+2,465	60.8
5	4,160	125.2	227.3	376.0	20.0	15.56	*	17.6	+2.4	+2,385	61.0
6	3,897	124.3	191.5	391.8	20.0	15.03	*	17.0	+3.0	+2,113	
7	3,934	131.6	191.5	393.4	21.4	15.57	*	17.7	+3.7	+2,150	61.2
8	3,775	123.4	191.5	355.1	19.7	18.01	*	20.0	—0.3	+1 991	61.8
9	3,892	124.4	212.6	342.7	19.9	17.16	*	19.2	+0.7	+2,108	61.1
10	3,603	124.5	175.6	356.2	19.9	16.06	*	18.1	+1.8	+1 819	61.5
11	3,901	127.1	184.6	405.5	20.3	14.77	*	16.8	+3.5	+2,117	61.4
12	3,714	125.4	161.9	413.1	20.1	15.58	*	17.6	+2.5	+1,930	61.7
13	4,043	123.5	196.7	401.5	19.8	16.32	*	18.3	+1.5	+2,259	
14	3,567	125.9	162.9	374.2	20.1	15.30	*	17.3	+2.8	+1,783	62.6
15	3,781	123.8	168.2	416.8	19.7	15.69	*	17.7	+2.0	+1,997	62.4
16	3,896	90.6	174.6	463.7	14.5	13.00	*	14.5	0	+2,112	
17	3,818	89.1	145.0	513.1	14.3	10.98	*	12.4	+1.9	+2,034	62.8
18	3,511	90.4	173.6	412.2	14.1	8.58	*	9.4	+4.3	+1,727	63.4
19	3,729	82.4	137.3	545.5	8.4	5.93	*	6.8	+1.6	+1,945	62.8
20	3,399	49.5	151.2	436.7	7.9	5.90	*	6.7	+1.2	+1,615	
21	3,780	48.9	160.7	508.6	7.8	4.58	*	5.8	+2.0	+1,996	62.4
22	3,268	49.7	166.1	370.4	8.0	5.59	*	6.4	+1.6	+1,484	
23	3,626	49.0	192.4	398.0	8.0	5.45	*	6.3	+1.7	+1,842	63.4
24	3,489	48.0	169.1	443.6	7.7	5.23	*	6.0	+1.7	+1,825	63.1
25	3,428	47.7	146.1	456.8	7.6	5.22	*	6.0	+1.6	+1,644	62.7
26	3,595	43.6	175.9	417.1	7.0	4.56	*	5.3	+1.7	+1,741	63.1
27	3,957	53.1	164.1	454.8	8.5	5.60	*	6.5	+2.0	+1,743	

† Basal requirement estimated at 1,784 calories per diem.
* Fecal nitrogen estimated as 10 per cent. of food nitrogen.

July, 1920, night sweats began and had persisted. Appetite was still good, but patient was weak and short of breath on exertion.

Physical Examination.—Height, 163.5 cm.; weight, 57 kg. Patient was a young man with a full red face, sitting in bed, coughing occasionally, not acutely ill. He was fairly well nourished, with a rather flabby panniculus adiposus.

Head: Eyes, ears, and nose were normal. Mouth: Most of teeth present, moderate pyorrhea and dental caries. Pharynx and tonsils were normal. Neck normal. Thorax: Well formed and symmetrical. Respiratory excursions were equally limited.

Lungs: Both upper lobes were dull above the clavicles and behind as far as the midscapula. Anteriorly resonance was fairly good. Breath sounds were modified in the right axilla and along the border of the pectoral muscles there was bronchovesicular breathing and fine râles, and over the rest of the front there were moist and sonorous râles. Over both apices behind fine râles were heard on quiet breathing, chiefly on the left side. These râles were exaggerated by coughing. At the left apex just below the tip a squeaking post-tussive sound was heard. Breath sounds were bronchial or bronchovesicular with showers of fine râles.

Heart: Apex in fifth intercostal space 10 cm. to left of midline. Cardiac dulness extended to the left 11 cm. in the fifth space, and to the right 3 cm. in the third space. The sounds were of good quality, with no murmurs. Rhythm regular and rate slow. The pulmonary second sound was accentuated. Pulses soft and synchronous. Arteries normal. Blood pressure: systolic, 98; diastolic, 60.

Further examination revealed no other abnormalities, with the exception of the three fistulas which were situated close to the anus.

The sputum contained many tubercle bacilli. The *urine* was normal. Fluoroscopic examination showed pulmonary fields of equal size, diminished in illumination of both upper halves. There was a dense area running out from the hilus on the right side to the ribs. Above this area there was an intensely illuminated circular area which was thought not to be an antrum because lung markings could be seen through it. At the left apex there was seen to be an antrum, which was brought out by coughing, which was undoubtedly the source of the post-tussive sound heard in that region.

January 12: leukocyte count 10,000 with normal differential count.

January 18: leukocytes 15,000 with normal differential count; red blood cells, 4,200,000; hemoglobin, 75 per cent.

The patient was in the metabolism ward from January 5 to February 28. The diet record and the analyses of excreta are given in Table 6 and shown graphically in Figure 6.

The basal metabolism was determined January 26, and it was found to be 6 per cent. above the average normal, with a heat production of 67.6 calories per hour. The twenty-four hour basal heat production is estimated, therefore, to be 1,622 calories. If one adds 10 per cent. to this to allow for the specific dynamic of food the basal requirement equals 1,784 calories per diem.

An experiment was done to determine the effect of ingesting 350 gm. meat. The data for these observations is contained in a previous communication.[3]

Comment.—The data in Table 6 show that from January 5 to 13 the food nitrogen was reduced about 1 gm. daily, while during the same period the total caloric value of the diet was increased from 2,500 to about 3,000 calories. Under these circumstances the urine nitrogen decreased parallel with the food nitrogen until the latter reached 6.0 gm. per diem. After this point was reached the urinary nitrogen decreased more slowly until with a minimum ingestion of 3.1 gm. food nitrogen the urinary nitrogen was 4.48 gm.

For the remaining periods of observation the following summary is given:

Periods, Dates inclusive	Average Daily Calories in Food	Average Daily Protein in Food, Gm.	Average Daily Nitrogen Balance, Gm.
Jan. 14-20	2,932	43.8	+ 0.67
Jan. 21-29	3,756	94.1	+ 4.13
Jan. 30-Feb. 15	3,859	125.4	+ 3.1
Feb. 19-27	3,541	49.2	+ 1.67

It will be seen, therefore, that 43.8 gm. protein may be fairly taken as the minimum for this patient if a total of 2,600 calories per diem are ingested. It is quite clear that in this case there was no advantage to be had in giving more than 94 gm. protein per diem. Also in order to make large gains in nitrogen it was necessary to give a diet of which the energy value was about twice the basal energy requirement.

Entirely satisfactory gains in nitrogen and weight occurred during the last period, February 19 to 27. In this period 192 gm. was the maximum fat ingested, so that it was necessary to give between 370 and 545 gm. carbohydrate. From the standpoint of sparing the ventilation of the lungs this diet would not be satisfactory, because the increased breathing volume after taking this amount of carbohydrate would be greater than the effect of a diet containing more protein and less carbohydrate.

At the end of the period of observation the patient was transferred to the tuberculosis service. He had gained 14.8 kg. in weight, but in spite of the improved nutrition no improvement could be noted in his clinical condition.

DISCUSSION OF RESULTS

The Nitrogen Minimum.—Table 7 is a summary in which are arranged the data for each subject for the day on which the lowest urinary nitrogen excretion was noted. The first four subjects were studied in 1919-1920, and the complete data regarding them are to be found in the previous communication of McCann and Barr.[1] The total length of the observation in days is given. The number of the day selected for Table 7 is given for easier reference to the original data in preceding tables.

TABLE 7.—SUMMARY OF NITROGEN MINIMUM EXPERIMENTS IN TUBERCULOSIS

Name of Subject	Length of Experiment, Days	Day of Experiment	Total Calories in Food	Calories per Kg. Body Weight	Body Weight, Kg.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	Nitrogen Balance, Gm.	Food N per Kg., Gm.	Urine N per Kg., Gm.	Per Cent. Calories from Carbohydrate	Ratio of Total Calories to Basal Requirement
Charles G.*	24	16	2,091	40.1	52.2	2.8	4.3	(1.0)	(5.3)	(—2.5)	0.054	0.083	43	1.1
George F.*	12	10	2,380	41.0	58.1	2.9	3.9	(1.0)	(4.9)	(—2.0)	0.050	0.067	70	1.2
John H.*	25	24	1,914	43.2	44.3	3.0	3.1	(1.0)	(4.1)	(—1.1)	0.068	0.070	39	1.2
Joseph R.*	16	14	2,493	41.4	60.4	3.3	2.5	(1.0)	(3.5)	(—0.2)	0.055	0.041	54	1.3
		16	2,466	42.0	59.4	3.3	3.9	(1.0)	(4.9)	(—1.6)	0.056	0.066	54	1.3
Hubert W.	14	13	2,312	41.0	56.4	4.3	3.8	2.3	6.1	—1.8	0.076	0.067	70	1.3
Fred R.	18	13	3,277	69.3	47.3	5.0	4.4	1.3	5.7	—0.7	0.106	0.093	59	1.6
John O'C.	15	8	3,422	66.0	51.3	6.0	3.6	0.53	4.2	+1.8	0.117	0.071	47	2.1
Ab. M.	10	7	2,990	65.3	35.2	5.2	9.4	0.8	10.2	—5.0	0.148	0.267	15	1.2
Frank D.	30	26	3,804	82.5	46.1	6.9	3.6	1.8	5.4	+1.5	0.150	0.078	62	2.4
		28	3,574	76.5	46.7	7.2	3.6	1.8	5.4	+1.8	0.154	0.077	58	2.2
George R.	54	9	3,012	52.7	57.1	3.1	4.5	0.9	5.4	—2.3	0.054	0.079	58	1.7

* Cases of McCann and Barr, 1920.

In the first five cases and in the last case shown in Table 7 the nitrogen minimum was attained by reducing the nitrogen intake to a low level (from 2.8 to 4.3 gm. N), at the same time giving a diet, of which the caloric value varied from 1.1 to 1.7 times the basal requirement of the patient. When these six cases are compared with the experiments on normals, which are compiled in Table 8, it will be seen that the urinary nitrogen excretion, in terms of grams per diem, fell to approximately the same level as in most of the normal subjects. A diminution of urinary nitrogen elimination occurred with about the same promptness in both series, following a reduction in food nitrogen. This can best be seen by consulting the graphic figures.

While in grams per diem the urinary nitrogen excretion of the tuberculous patients approaches closely that of normals, when one estimates the amount excreted per kilogram of body weight it is seen to be much higher for the tuberculous series. However, it was not to be expected that the wear and tear quota should vary directly with total body mass. It is rather more probable that it varies with the total metabolism.

In the remaining four cases shown in Table 7 the protein in the diet was only moderately reduced (to the equivalent of 5 or 7 gm. nitrogen daily). The attempt was made rather to determine to what extent the nitrogen excretion could be reduced by the protein sparing action of a diet rich in nonnitrogenous foodstuffs. Positive nitrogen balance was achieved in two of these cases by the ingestion of 6.0 and 6.9 gm. nitrogen, respectively (from 37.5 to 43.1 gm. protein), when the diet furnished from 2.1 to 2.4 times the basal requirement of energy. It will be noted that in the case of George R. (Table 6), that with a diet furnishing 2,932 calories and 43.8 gm. protein an average of 0.67 gm. nitrogen was added to the body daily for a seven day period. Subject Ab. M. showed persistent large losses of nitrogen. It was impossible to give him adequate amounts of food because of digestive disturbances. He had physical signs of a pneumonic consolidation, and it is not known to what extent organisms other than the tubercle bacillus had entered into the production of the pneumonia.

There is evidence that the quality of the protein supplied is an important factor in determining the amount which will cover a given wear and tear quota. Thomas [21] studied the biologic value of various proteins. First, he reached his nitrogen minimum by taking a nitrogen-poor diet. He then found the relative amounts of various proteins

21. Thomas, K.: Ueber die biologische Werthigkeit der Stickstoffsubstancen in Verschiedenen Nährungsmitteln, Arch. f. Physiol, 219, 1909.

required to cover this known wear and tear quota. A few of Thomas' results are given for purposes of illustration. Each 100 gm. of the following proteins will cover the equivalent of the following number of grams of flesh:

Ox-flesh	104.74 gm.
Milk	99.71 gm.
Fish	94.46 gm.
Potato	78.89 gm.
Flour	39.56 gm.
Maize	29.52 gm.

In our three cases in which positive nitrogen balance was obtained with a low protein diet the source of animal protein was chiefly from milk, lean beef, and chicken, with occasionally a little cheese and eggs. In the case of John O'C., 52 per cent. of the protein was from animal sources; with Frank D., 42 per cent.; and with George R., 47 per cent.

In Tables 7 and 8 the percentage of total calories in the form of carbohydrate is given. In the tuberculous series this varies from 15 to 70 per cent., while in the normal series it varies from 38 to 100 per cent. of the total calories. In the case of Ab. M., who showed the greatest nitrogen excretion, only 15 per cent. of the calories were from carbohydrate. In this instance the table may be misleading, for if one refers to Table 2 it is apparent that the nitrogen loss was greater on several days on which a much higher percentage of carbohydrate calories was taken.

There has been a great deal of work done to determine the relative efficiency of carbohydrate and fat as protein sparers. Kayser [22] found that he could not replace carbohydrate in a diet with an isodynamic amount of fat without a rise in the output of nitrogen. Voit and Korkunoff [23] showed that when protein is fed with fat the fall in protein catabolism, although it reaches a level well below that for protein alone, is not so marked as in the case of protein plus carbohydrate. However, Tallquist [24] in Rubner's laboratory found that, keeping the same carbon: nitrogen ratio, the relative proportions of fat and carbohydrate in the diet could undergo considerable variation without disturbing the nitrogen balance greatly. Landergren [25] made a clear demonstration of the difference in sparing action

22. Kayser: Ueber die Eiweissparende Kraft des Fettes vergleichen mit derjenigen des Kohlenhydrats. DuBois-Reymond Arch. f. Physiol., 371, 1893.

23. Voit, E., and Korkunoff: Ueber die geringste zur Erhaltung des Stickstoffgleichgewichtes noethige Menge von Eiweiss, Ztschr. f. Biol. **32**:58, 1895.

24. Tallquist: Arch. f. Hyg. **41**:177, 1902.

25. Landergren: Ueber die Eiweissumsetzung des Menschen, Skand. Arch. f. Physiol. **14**:112, 1903.

of the two foodstuffs. There was a steady fall in the nitrogen output on an exclusively carbohydrate diet, and when the diet was changed to one exclusively of fat there was a steady and progressive rise. Finally Zeller [26] fed both dogs and men with varying quantities of fat and carbohydrate. He came to the conclusion that from 70 to 90 per cent. of the carbohydrate in a diet could be replaced by an isodynamic amount of fat without the nitrogen minimum, reached by exclusive carbohydrate feeding, being materially affected. The gen-

TABLE 8.—Summary of Nitrogen Minimum Experiments on Normals

Author and Subject	Length of Experimental Days	Day of Experiment	Total Calories in Food	Calories per Kg. Body Weight	Body Weight, Kg.	Food N. Gm.	Urine N. Gm.	Fecal N. Gm.	Total N. Gm.	Nitrogen Balance, Gm.	Food N per Kg., Gm.	Urine N per Kg., Gm.	Per Cent. Calories from Carbohydrate	Reference Number
Hirschfeld														
II 1888	8	6-8	3,462	47.0	73.0	7.46	5.76	1.65	7.41	+0.05	0.102	0.079	..	(13)
Klemperer														
II 1889	8	6-8	5,020	77.0	65.3	5.28	2.51	1.02	3.53	+1.75	0.081	0.038	38	(14)
Sivén 1898	43	42	2,441	42.0	58.9	2.43	1.78	1.33	3.17	−0.74	0.041	0.030	67	(15)
Landergren														
1903 II	4	4	3,374	45.2	73.4	0.82	3.76	0.75	4.51	−3.69	0.011	0.051	95	(16)
III	4	4	3,163	37.8	79.1	2.5	3.95	1.47	5.42	−2.92	0.032	0.050	52	
IV	4	4	2,920	45.0	62.4	2.05	3.04	1.02	4.06	−2.01	0.033	0.049	44	
V	4	4	3,089	38.4	77.2	2.4	4.20	1.33	5.53	−2.13	0.031	0.054	43	
VI	4	4	2,745	36.1	73.4	2.2	4.95	1.28	6.23	−4.03	0.030	0.067	53	
Hindhede (Madsen)		Av.												
VII–15	19	per.	3,796	53.0	71.5	3.62*	3.41	....	....	+0.21	0.051	0.048	61	(17)
Kocher														
R. A. K.	10	5	5,089	64.0	79.2	1.01	2.92	1.16	4.08	−3.07	0.013	0.037	100	
J. G. F.	10	4	5,089	72.0	70.4	1.01	2.89	1.13	4.02	−3.01	0.014	0.041	100	(4)

* Utilizable nitrogen = food N − fecal N.
13. Hirschfeld: Virch. Arch. **114**: 301, 1888.
14. Klemperer: Zeitschr. f. klin. Med. **16**: 550, 1889.
15. Sivén: Skand. Arch. f. Physiol. **10**: 128, 1900.
16. Landergren: Skand. Arch. f. Physiol. **14**: 240, 1903.
17. Hindhede: Skand. Arch. f. Physiol. **30**: 97, 1913.

eral correctness of Zeller's conclusions seems to be borne out by the results in Table 7 and by the experiments of Landergren shown in Table 8.

Attention should next be turned to the observations carried out on Frank D., and George R. during periods of forced feeding. In the case of Frank D. a very striking result was obtained, which was summarized under the case history. The gain of the body in nitrogen was greater on the low protein diets of periods 4 and 5. This was not due to any apparent diminution in the activity of the tuberculous

26. Zeller: Einfluss von Fett und Kohlenhydrat bei Eiweisshunger auf die Stickstoffausscheidung, Arch. f. Physiol. **2**: 3, 1914.

process during the latter periods, as evidenced by the physical signs or by the temperature record (Fig. 6). It should be pointed out that the subject was only 17 years old, incompletely developed, and that he had suffered from inanition before coming under observation. However, the periods of high protein feeding preceded the low periods, so that the body had the greater opportunity to store nitrogen first. Recently, von Hoesslin [27] in Germany has studied groups of individuals who were suffering from severe inanition. He noted an abnormally high nitrogen retention during periods of relatively low protein and caloric intake, and that this retention was but little influenced by the caloric value of the food.

In the case of George R., who had been better nourished previously, it was seen that although a slight gain in nitrogen was made when 43.8 gm. protein were ingested, the retained nitrogen increased as the protein ingestion increased. The maximum retention was noted when there was 90 gm. protein in the diet. Less nitrogen was stored when the protein intake was increased to 125 gm. daily.

Extensive and very valuable studies have been made by Bardswell and Goodbody [28] on the effect of large diets on patients with pulmonary tuberculosis. Some of their patients received 270 gm. protein with about 5,000 calories, others more moderate diets with 160 gm. protein and 3,400 calories. The clinical results with the more moderate diet were satisfactory, in fact "the patients made much less satisfactory all-round progress on the very large diets. . . ." Failure of appetite, marked digestive and intestinal derangements were noted. "When the amount of proteid in the diet was much increased, it resulted in an increased excretion of nitrogen out of all proportion to the increased amount retained in the body." The percentage of nitrogen excreted as urea fell. There was an increase in the amounts of aromatic sulphates excreted. Generally the large gains in weight were not permanent, but disappeared on return to a normal diet. Dyspnea was frequently complained of by patients undergoing forced feeding. This we know [2] is the direct result of the effect of the ingestion of food on the respiratory exchange.

In determining, therefore, the optimal quantity of protein for tuberculous patients one must strike a balance somewhere between the two extremes. While some patients can be made to gain nitrogen and weight on diets containing from 37.5 to 45 gm. protein this requires a large allowance of nonprotein food, especially of carbohydrate, in

27. Von Hoesslin, H.: Klinische Eigentümlichkeiten und Ernährung bei schwerer Inanition, Arch. f. Hyg. **88**:147, 1918.

28. Bardswell, Noel, and Chapman, J. E.: In "Diets in Tuberculosis," they give a complete summary of this work, Oxford Press, 1908.

amounts sufficient to bring the total calories up to from 3,500 to 4,000 per diem. When one compares the effect on the pulmonary ventilation produced by the amount of protein, which might be fed at one meal in an ordinary diet (from 30 to 40 gm.), with the effect of the amount of carbohydrate to be fed at one meal with a forced diet, the effect of the ordinary amount of protein becomes insignificant. Our results have shown that nitrogen balance may be established at from 10 to 15 gm. nitrogen (62 to 93 gm. protein), with a rather moderate number of

TABLE 9.—SUMMARY OF NITROGEN MINIMUM EXPERIMENTS IN VARIOUS DISEASES

Author; Subject; Disease	Length of Experiment, Days	Day of Experiment	Total Calories in Food	Calories per Kg. Body Weight	Body Weight, Kg.	Food N, Gm.	Urine N, Gm.	Feral N, Gm.	Total N, Gm.	Nitrogen Balance, Gm.	Food N per Kg., Gm.	Urine N per Kg., Gm.	Reference Number
Psoriasis *													
8 VI	7	..	1,866	32.0	58.4	4.39	1.88	1.97	3.85	+0.54	0.075	0.032	(18)
9 III	7	..	1,355	28.5	54.6	4.29	2.99	1.93	4.92	−0.62	0.079	0.055	
9 IV	7	..	1,666	....	54.5	5.16	2.47	1.89	4.36	+0.80	0.095	0.045	
Kocher Paratyphoid													(4)
T., 38.5 C.	16	7	3,213	56.0	....	2.2	14.52	0.88	15.40	−13.2	0.038	0.250	
T., 38.1 C.	16	10	4,666	78.0	....	3.5	5.82	0.88	6.70	−3.2	0.058	0.097	
T., normal	16	16	4,666	78.0	....	3.5	4.79	0.76	5.55	−2.05	0.058	0.080	
Erysipelas													
J. S., T., 39.5 C.	10	4	4,255	74.5	55.8	1.82	13.34	1.03	14.37	−12.55	0.033	0.240	
J. S., T., 38 C.	10	9	4,250	75.0	53.8	1.88	11.52	1.03	13.55	−11.67	0.035	0.210	
E. M., T., 39.6 C.	6	6	3,360	73.0	46.0	2.02	16.02	....	.....	.....	0 044	0.350	
R. M., T., 39-40 C.	6	2	4,050	....	61.0	2.01	9.35	0.94	10.29	−8.28	0.033	0.156	
R. M., T., normal	..	6	4,230	....	60.0	1.05	4.04	0.94	4.98	−3.93	0.018	0.067	
Lobar pneumonia	8	8	3,960	63.0	62.9	1.84	13.40	1.20	14.60	−12.76	0.029	0.213	
Acute polyarthritis													
E. S., T., 40 C.	11	7	2,600	....	33.5	1.12	11.48	0.92	12.40	−11.28	0.033	0.342	
E. S., T., normal	..	11	2,840	....	33.5	1.12	3.55	0.92	4.44	−3.32	0.033	0.105	
Basedow's disease													
J. A. D.	16	14	2,480	....	50.7	3.13	3.19	1.15	4.34	−1.21	0.062	0.063	(19)
Syphilis, secondary—111a	8	5	2,408	43.0	56.0	1.6	3.6	0.9	4.5	−2.9	0.029	0.064	(20)

18. Schamberg, Kolmer, Ringer and Raiziss: Jour. Cut. Dis., Oct., Nov., 1913.
19. Rudinger: Wein. klin. Wchnschr. **21**: 1581, 1908.
20. Cederkreutz, A.: Beitrage zur Kenntnis des Stickstoffwechsels in der Frühperiode der Syphilis. Breslau, 1902.

calories in the diet (2,500). We have no evidence of any advantage of ingesting an excess over 90 gm. protein. If a maximum of 90 gm. per diem were given the stimulating effect of the protein taken at any one meal would be negligible. It should be possible to give most patients at least 150 gm. fat, which would require only 150 gm. carbohydrate to bring the total energy value up to 2,500 calories. Such a diet could be taken at the least expense of respiratory function.

SUMMARY AND CONCLUSIONS

1. In nine of the ten tuberculous patients studied the minimal urinary nitrogen excretion observed was between 2.5 and 4.5 gm. per diem, and between 0.041 and 0.093 gm. per kilogram per diem. In one case the lowest excretion of urinary nitrogen was 9.4 gm. per diem, or 0.267 gm. per kilogram. In the nine cases with a minimal nitrogen excretion the diet given had an energy value from 1.1 to 2.4 times the basal energy requirements of the subjects, and furnished 39 to 70 per cent. of the calories in the form of carbohydrate.

2. In some cases it is possible to maintain nitrogen balance, and even to retain nitrogen, when from 37 to 44 gm. protein are ingested, of which about one half is from animal sources. The attainment of nitrogen equilibrium with such a small amount of protein is dependent upon the ingestion of large amounts of carbohydrate and fat, sufficient to make the total caloric value of the diet from 1.7 to 2.4 times the basal energy requirement.

It is probable that the failure to establish nitrogen balance on such low protein diets is due to failure or inability of the subject to ingest sufficiently large quantities of carbohydrate and fat, rather than that it is due to an inherently large wear and tear quota in tuberculosis.

3. Positive nitrogen balance in bed patients may be attained by the ingestion of from 60 to 90 gm. protein when the diet contains carbohydrate and fat, with a total caloric value of less than 1.7 times the basal requirement. The evidence indicates that the optimal quantity of protein for patients who are confined to bed with pulmonary tuberculosis, lies between the limits of 60 to 90 gm. per diem, when the caloric value of the diet is about 2,500 calories. Additional carbohydrate and fat calories must be furnished when patients are allowed to exercise.

OBSERVATIONS ON THE USE OF QUINIDIN IN AURICULAR FIBRILLATION *

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A great deal of interest has been aroused by the recent reports on the favorable action of quinidin in auricular fibrillation. Since Frey's [1] first publication in 1918, the results from the treatment of over one hundred cases have appeared, nearly half of which have been reported by Frey.[2] The literature is given in the recent article by Levy,[3] who also reports the results on four cases. The purpose of this report is to record the experience in the use of this drug in two cases selected from a number under observation in this clinic. The first of these cases is reported to bring out a point which in our opinion has not been emphasized sufficiently, namely, the danger in the use of this drug in certain cases. The other case illustrates the strikingly favorable action of quinidin in the rather rare condition in which auricular fibrillation is uncomplicated by advanced valvular or myocardial damage and in which no serious break in compensation has occurred.

ABSTRACT OF CASE REPORTS

CASE 1.—Mrs. P. F. S., aged 47, white, admitted to hospital, April 5, 1921, complaining of shortness of breath and palpitation. From the history, it was evident that from moderate to severe cardiac decompensation with irregular pulse had been present for the preceding seven months. Previous to this time there had been no serious decompensation. The diagnosis was chronic endocarditis, mitral incompetence, cardiac decompensation, auricular fibrillation. Examination revealed cyanosis, dyspnea, hydrothorax, ascites and edema of the extremities. On admission the ventricular rate was 124; radial rate, 110. Venous pressure was 23 cm. of water. Urine output in the first twenty-four hours was 7 ounces. As a result of rest and treatment all symptoms improved, the ventricular rate and pulse deficit decreased, the venous pressure fell and urine output increased.

April 19, the apical rate was 80; radial, 76; venous pressure, 8 cm. Urine output was 36 ounces. Cardiac area as determined by the teleroentgenogram showed definite reduction over that present on admission. The condition continued to improve, and by May 7, ascites, hydrothorax and nearly all trace of peripheral edema had disappeared. The patient was up in a chair for several hours daily and was allowed moderate exercise. Auricular fibrillation persisted, however, and numerous electrocardiograms taken during residence in the hospital failed to reveal a normal cardiac rhythm at any time.

* From the Bradley Memorial Hospital, Department of Clinical Medicine of the University of Wisconsin.

1. Frey, W.: Ueber Vorhofflimmern beim Menschen und seine Beseitungung durch Chinidin, Berl. klin. Wchnschr. **55**:417, 1918.

2. Frey, W.: Chinidin zur Bekämpfung der absoluten Herzunregelmässigkeit. Deutsch. Arch. f. klin. Med. **136**:70, 1921.

3. Levy, R. L.: Restoration of the Normal Cardiac Mechanism in Auricular Fibrillation by Quinidin, Arch. Int. Med. **76**:1289 (May 7) 1921.

May 17, quinidin sulphate was given in doses of 0.25 gm. every fourth hour for four doses. After three doses (0.75 gm.) auricular tachycardia developed with a rate of 180. After an hour or so, periods of auricular fibrillation alternated with the periods of rapid regular heart action. Palpitation, dyspnea and cyanosis developed. Venous pressure rose to 12 cm. Urine fell to 26 ounces. During the night, a few hours after the last dose of quinidin, heart action became more stable. On the following morning, quinidin administration was begun again with the same dosage as on the previous day. Palpitation, cyanosis and dyspnea again appeared. The urine was 21 ounces, the venous pressure 11 cm. Electrocardiograms showed periods of tachycardia interspersed with periods of auricular fibrillation. The symptoms again subsided with the cessation of quinidin administration the following night. The following morning (May 19) quinidin administration with the same dosage was begun again. A short time after the first dose, extreme distress developed. There was dyspnea (respiratory rate 36), marked cyanosis, palpitation, pain in side and cough with expectoration of blood streaked sputum. Examination revealed right sided hydrothorax, pulmonary edema, ascites, tympanites, and slight edema of the extremities. Venous pressure rose to 18 cm. Electrocardiograms revealed the same type of rhythm as on the two previous days. The cardiac area was increased (teleroentgenogram). Due to the critical condition of the patient and the absence of any favorable action on the cardiac rhythm, quinidin administration was stopped after the third dose on this day, and digitalization with general treatment for cardiac decompensation established. A total of 2.75 gm. quinidin sulphate had been administered. On the following two days the condition was critical. The venous pressure had risen to 21 cm., the urine had fallen to 6 ounces in twenty-four hours. Continuous auricular fibrillation persisted with an average apical rate of 136 and radial of 82. By the next day (May 22) the general condition had begun to improve. Venous pressure had fallen to 16 cm. and urine increased to 16 ounces. Steady improvement continued and June 3, the patient was discharged from the hospital free from any symptoms or signs of decompensation. Auricular fibrillation, however, was still present, with an apical rate of 72 and with a very small pulse deficit. On discharge the venous pressure averaged 7 cm. and the urine was approximately equal to the fluid intake.

Case 2.—L. J. R., white, male, university student, aged 23, came under observation for the first time Aug. 7, 1919, complaining of shortness of breath, palpitation and irregular heart action. This condition developed on the third day of a rather severe influenzal attack in November, 1918. No heart irregularity or palpitation was noted previous to this time. Following recovery from the attack of influenza, the cardiac irregularity persisted. Shortness of breath was present on very slight exertion and at times paroxysms of dyspnea with severe cardiac palpitation occurred, even when the patient was at rest. Examination revealed marked irregularity of the heart with considerable pulse deficiency. There was, however, no evidence of venous stasis in lungs, liver or other organs, and no adventitious heart sounds were heard. The cardiac area (roentgenogram) was increased approximately 25 per cent. The enlargement was symmetrical. Electrocardiograms revealed auricular fibrillation. The past medical history was unimportant and furnished no evidence of cardiac involvement previous to the attack of influenza.

Under restricted activity and dietetic control, the condition improved somewhat. The patient was again examined Jan. 29, 1920. General health had been fair for the past few months, and he had been able to pursue his university work on a restricted schedule. There had been no symptoms of severe cardiac incompetence. Moderate exercise could be taken without extreme shortness of breath. Examination revealed a cardiac area somewhat smaller than previously observed (approximately 20 per cent. above normal), totally irregular cardiac rhythm, no adventitious sounds and no evidence of venous stasis.

The patient entered the hospital June 28, 1921, for treatment with quinidin. The irregular heart action had persisted without apparent interruption from its initiation thirty-one months previously. For the past year he has had to give up practically all work, due to frequent periods of shortness of breath and general weakness. Rather severe attacks of palpitation and dyspnea, lasting from fifteen to twenty minutes, have occurred every few days and have increased in frequency recently. There has been, however, no serious cardiac incompetence at any time. For the past eighteen months he has had abdominal symptoms which were stated by the physician in attendance to be due to spastic colitis.

Examination revealed practically the same condition as found at the two previous examinations, thirty-one and eighteen months ago. The cardiac area was found to be less than 15 per cent. above normal. No adventitious heart sounds were heard. The patient was kept at rest in bed for five days without medication. Repeated electrocardiograms were made during this time, all showing uninterrupted auricular fibrillation. The apical rate averaged 115, the radial 94. Venous pressure varied between 8 and 9 cm. of water in the dorsal prone position. Urine output was normal.

July 4, the patient was given a single dose of 0.25 gm. quinidin sulphate by mouth. About two hours later an electrocardiogram revealed periods of tachycardia interspersed with periods of fibrillation. On the next day (July 5), he was given 4 doses of 0.25 gm. quinidin at three hour intervals. There developed brief periods of rapid regular heart action with moderate distress (palpitation and shortness of breath). No other signs of circulatory deficiency were present. The apical rate averaged 120, the radial 110. Venous pressure was unchanged. Urine output was normal.

July 6, six doses of 0.25 gm. quinidin at two hour intervals were ordered. Before the first dose, rather frequent series of rapid regular beats were present, interspersed with periods of fibrillation. At 4 p. m., following the fourth dose of quinidin, the patient became uncomfortable, due to palpitation and shortness of breath. The pulse became exceedingly irregular in force and rhythm. Electrocardiograms made at this time showed continuous fibrillation with a ventricular rate of 120. The subjective distress increased somewhat until about 6 p. m., when the patient fell asleep. On awakening in about half an hour, all distress had disappeared and cardiac action was found to be entirely regular in force and rhythm. Electrocardiograms revealed a normal sino-auricular rhythm with a rate of 66, with normal P-R interval and without evidence of preponderance of either ventricle.

The patient was discharged from the hospital July 14. Subsequent to its initiation, eight days previously, normal heart action had persisted without interruption. For the first two days following the return of normal rhythm, a single dose of 0.25 gm. quinidin sulphate was given daily, subsequently a single dose every other day, to be continued after leaving the hospital. All symptoms disappeared and examination failed to reveal any abnormality with the exception of slight symmetrical cardiac hypertrophy (15 per cent.). The pulse rate averaged approximately 60 during this period. The venous pressure (dorsal prone position) fell to 5 cm. shortly after the establishment of normal cardiac rhythm and remained at this point.

COMMENT

No one who has carefully followed the action of quinidin on the heart in auricular fibrillation can be but impressed with the powerful action of this drug on the cardiac mechanism in this condition. Clinical experience has shown that its action is sufficient to restore the normal mechanism at least temporarily, in approximately half of the cases of auricular fibrillation in man. Much of this experience is too recent,

however, to state in how large a percentage permanent success can be obtained. Since in most cases conditions tending to produce auricular fibrillation are probably still present even after the normal rhythm is restored, subsequent administration of the drug may be necessary to avoid recurrence. Additional experience will be necessary before the details of this will be clear. In most cases, perhaps in all, disturbances of rhythm occur during the transition stage between auricular fibrillation and sino-auricular rhythm. The most characteristic and frequent of these transition rhythms is rapid regular heart action (auricular tachycardia, "auricular flutter") occurring either alone or in periods interspersed with periods of fibrillation. These intermediary stages may occur even when the normal rhythm is not subsequently restored, as in the first case presented here. It is apparently the result of these stages of transition in which the dangers of the treatment lie. While acutely developing auricular fibrillation undoubtedly causes considerable mechanical deficiency of the heart (Eyster and Swarthout [4]) and is probably not infrequently the immediate cause of cardiac decompensation, the heart may compensate for this as it does for valve injury, particularly when it is assisted by the protective influence on ventricular stimulation of digitalization. That the removal of this compensated auricular fibrillation under the action of quinidin in producing transition rhythm may destroy clinical cardiac compensation, is illustrated by the first case reported. Possibly also the contractility of the ventricular muscle is reduced by the drug. The case again becomes critically ill, and if restoration of the normal sino-auricular rhythm fails, as it apparently so frequently does in the older and more severe forms of chronic heart disease, the best that can be hoped for is a tedious restoration of compensation with another period of cardiac failure with its attendant permanent damage to be charged to the quinidin treatment. On the other hand, when auricular fibrillation is unassociated with valvular or severe myocardial damage and with no history of severe circulatory failure, the cardiac reserve is able to carry the circulation through the periods of "transition rhythm" with only transitory circulatory deficiency.

With a therapeutic agent as definite in its action as quinidin of use in a clinical condition as common and important as auricular fibrillation, it is inevitable that great interest in and widespread use of the remedy will follow. We have attempted to point out a definite danger in its use and the necessity of the utmost care in its administration to at least the more severe forms of chronic heart disease. In such cases it should be used only, first (as has been pointed out by Frey) after compensa-

4. Eyster, J. A. E., and Swarthout, E.: Experimental Determination of the Influence of Abnormal Cardiac Rhythms on the Mechanical Efficiency of the Heart, Arch. Int. Med. **25**:317 (March) 1920.

tion is as thoroughly established as possible; and second, only when the patient can be under almost continuous observation, when frequent electrocardiograms are obtained, and when repeated physical examinations are made for signs of breaking compensation. For the present, and until more experience is gained as to the mode of action, contraindications, the size of dose and the frequency of administration for the best results, the treatment of the more severe cases should be carried out only in a hospital under strict regulation and observation. The patient should be prepared for a break in compensation by rest in bed and limitation of food and liquids during the period of administration.

TUBERCULOSIS OF THE HEART

WITH THE REPORT OF TWO CASES *

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In a study of 7,219 necropsies Norris [1] found 1,780 tuberculous cases and among these eighty-two cases of tuberculous pericarditis. In five cases the heart muscle was involved. This indicates the relative infrequency of the conditions being reported. A point of added interest is the unusual degree of involvement in the first case.

REPORT OF CASES

CASE 1.—*History.*—The patient, a colored male, aged 25, was admitted to the Jefferson Hospital, on the service of Dr. H. A. Hare, Dec. 27, 1920, complaining of pain in the upper half of the abdomen and chest. His family history was negative for tuberculosis. He had gonorrhea in 1909 and syphilis in 1913, for which he received no treatment. In October, 1918, he had an attack of influenza and since then a persistent cough at night. In July, 1920, he developed abdominal pain which grew progressively worse and about December, 1920, his abdomen began to enlarge. His cough became more severe; he was dyspneic and complained of pain in his chest. He stated that he had lost 40 pounds in the past year.

Examination.—On examination there were evidences of a pleural effusion at the right base and immense enlargement of the heart—both confirmed by roentgen ray. His abdomen was slightly distended and tender and the liver could be palpated at the level of the umbilicus in the right midclavicular line. There was some fluid in the left tunica vaginalis. Blood count showed a leukopenia and moderate secondary anemia; his blood Wassermann was positive; his sputum was negative for tubercle bacilli. He died Feb. 21, 1921, and necropsy was performed the same day.

Necropsy Report.—The body was that of an adult colored male, weighing about 170 pounds. The heart and pericardium were immensely enlarged, weighing 1,580 gm., the pericardial cavity being obliterated by large, dense, yellowish nodules which invaded the heart muscle, auricles and ventricles to a similar degree. The nodules were continuous with the mediastinal and peribronchial lymph nodes which were also large, yellowish and firm. No tuberculosis of the lungs could be established but the pleurae averaged about 0.4 cm. in thickness and this thickening was especially marked at the right base which contained an encapsulated effusion of about 700 c.c. of brownish-red serum. The spleen, right suprarenal, kidneys and liver showed a number of firm, yellowish nodules scattered throughout. At the juncture of the ileum and cecum was a large ulcer, 2.5 cm. in diameter, with base of reddish granulations and firm, undermined edges. This, with the large, firm and yellowish mesenteric and retroperitoneal nodes aided in the gross diagnosis of tuberculosis.

The microscopic study revealed a fibrocaseous tuberculosis of the following organs and tissues: pericardium and myocardium, pleurae, spleen, right adrenal, kidneys, liver, mediastinal, mesenteric and retroperitoneal lymph nodes.

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* Read before the Pathological Section of the National Tuberculosis Association, New York City, June 16, 1921.

* From the Department of Pathology, Jefferson Medical College.

1. Norris, G. W.: Tuberculous Pericarditis Based on a Study of 7,219 Autopsies in Philadelphia Hospitals, Univ. Penn. M. Bull. **17**:155, 1904.

No typical tubercles were seen and very few giant cells. Smears from the fresh material and stained sections of pericardium, pleura and retroperitoneal nodes were studied for tubercle bacilli but failed to reveal the organism. Guinea-pig inoculation, however, produced a diffuse tuberculous lymphadenitis and tuberculosis of the spleen. Smears from the caseous nodes showed many tubercle bacilli but attempts to culture the organism failed.

Case 2.—S. W., a colored male, aged 25, dishwasher by occupation, was admitted to the Department for Diseases of the Chest of the Jefferson Hospital, March 15, 1921.[2] He complained of a dull pain in the back and sternal region and of a moderate cough productive of a large amount of mucoid sputum which was occasionally blood-streaked.

Family History.—Negative for tuberculosis.

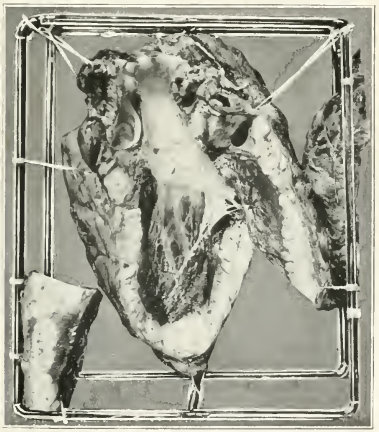

Fig. 1.—Case 1. Tuberculous pericarditis and myocarditis. Note the invasion of heart muscle by the immense, tuberculous nodules of the pericardium, shown best by insert in left hand corner.

Personal History.—He had a chancre in 1913 and gonorrhea in 1914. He stated that he had been in poor health ever since his discharge from the army in 1918. At that time he noticed a cough. Shortly after the onset he became short of breath on slight exertion and felt weak. From time to time he had a vague pain in the front of the chest. Increasing disability caused him to give up his work in the latter part of January, 1921. He entered a Philadelphia hospital and was later transferred to the Jefferson Chest Hospital.

2. I am indebted to Dr. E. H. Funk for the clinical notes of this case.

Physical Examination.—This showed an emaciated, colored, adult male. His pupils reacted normally. Throat was red, tonsils swollen. The cervical lymph nodes were distinctly palpable with a small mass of enlarged glands above the clavicle on the left side. Chest was long, narrow and flat. Expansion was generally limited. Vocal fremitus was increased throughout the right side of the chest and the percussion note was generally impaired. Breath sounds were distinctly audible with a blowing characteristic over the entire chest except the right base posteriorly where the intensity was diminished. Many squeaking sounds were heard with numerous crackling râles throughout, especially

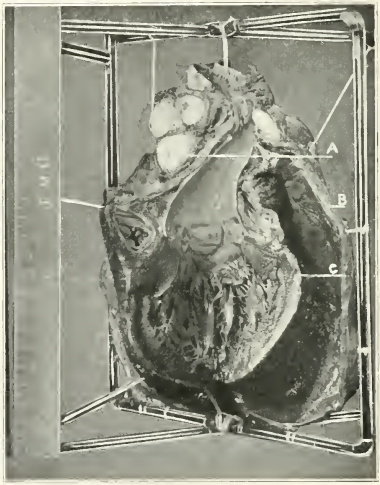

Fig. 2. Case 2. Tuberculous pericarditis, showing (a) enlarged, tuberculous nodes at the base of the heart; (b) thickened, parietal pericardium, and (c) tuberculous nodules of visceral pericardium.

on the right side. Whispering pectoriloquy was noted in the third interspace on the right side, anteriorly.

Heart: There was marked precordial pulsation with an increase to the left in the lateral diameter of cardiac dulness. Heart action was rapid but regular; heart sounds were distinctly heard; no murmurs were present. Sputum examinations were repeatedly negative for tubercle bacilli. Urine contained a trace of albumin and an occasional hyaline cast. Temperature, 102 F.; pulse, 130; respirations, 40. Patient died, April 25, 1921, and a necropsy was made the following day.

Necropsy Report.—The important findings were as follows: The anterior cervical lymph nodes were distinctly palpable and those on the left side just above the clavicle were especially enlarged. There were several enlarged, firm, yellowish nodes adherent to the posterior surface of the sternum. All of the mediastinal nodes were similarly enlarged, clustered about and pressing on the trachea and larger bronchi. These nodes varied in size from less than 1 cm. to 3 or 4 cm. in diameter. Some had caseous centers.

The pericardial cavity was distended with about 700 c.c. of blood-tinged serous fluid. There was likewise a dense, yellowish, fibrinous exudate present.

Fig. 3.—Case 2. Tuberculosis of peribronchial lymph nodes with practically no lung involvement.

The visceral pericardium of the left ventricle was distinctly thickened, measuring about 0.3 cm., and consisted of a zone of dense, yellowish tissue made up of conglomerate nodules which grew larger near the base of the ventricle at the reflection of the pericardium. These nodules, unlike those of the first case, showed no tendency to invade the heart muscle. The lymph nodes at the base of the heart were of the same type as the mediastinal nodes and were continuous with them, pressing on the great vessels. These nodes were likewise firmly adherent to the pericardium.

Left Lung: The left pleural cavity contained about 500 c.c. blood-tinged serous fluid and the lung was compressed. On section the pulmonary tissue was dark red in color and only partially crepitant. About 6 cm. from the apex, on the anterolateral surface of the lung, was a conglomerate caseous tubercle, a little less than a centimeter in diameter. There was no further evidence of tuberculosis in the lung structure; the nodes at the hilus, however, were greatly enlarged, similar to and continuous with the mediastinal nodes.

Right Lung: It was more voluminous than the left but on section presented nearly the same appearance. Near the hilus, a little area of pulmonary tissue, about 2 cm. in diameter, adjacent to an enlarged and caseous lymph node, showed tuberculous infiltration.

None of the other organs showed any evidence of tuberculosis but the mesenteric and retroperitoneal lymph nodes were moderately enlarged, firm and yellowish.

A few tubercle bacilli were found in smears from the caseous mediastinal nodes.

Microscopic study revealed a typical caseous tuberculosis of the structures mentioned. The pericardium showed the lesion especially well; unlike the first case, there were many typical tubercles present with caseous centers and numerous giant cells. The tuberculous process, as mentioned in the gross description, exhibited no tendency to invade the myocardium.

Guinea-pigs were inoculated with emulsified caseous nodules from the base of the heart. The animals, killed six weeks later, showed tuberculosis of the abdominal lymph nodes and spleen. A number of tubercle bacilli were recovered in smears but cultures both on Petroff's and Dorset's mediums failed to develop the organism.

COMMENT

In 1902 Anders[3] summarized seventy-one cases of tuberculosis of the myocardium and added a case of his own. He classified the condition as occurring in three forms: (1) large tubercles; (2) miliary tubercles (less common) and (3) diffuse form or tuberculous infiltratiton (rare). He stated that cardiac tuberculosis was most frequent in early life, 40 per cent. of his cases occurring under 15 years. In a large proportion of cases, the lungs and bronchial glands were tuberculous. In twenty-nine out of thirty-one cases in which the glandular condition was noted, tuberculosis was present and this he believed to be the seat of the disease. This extended from the bronchial to the mediastinal nodes and thence directly to the heart or quite commonly by way of the pericardium.

Cases very similar to the present ones have been reported by Ellis,[4] Raviart and Caudron,[5] Benda and Geissler,[6] Toldt,[7] Passamonti,[8]

3. Anders, J. M.: Tuberculosis of the Myocardium, J. A. M. A. **39**:1081 (Nov. 1) 1902.

4. Ellis, A. G.: Heart Showing Chronic Tuberculosis of the Pericardium, with Involvement of the Myocardium, Proc. Path. Soc., Phila., June, 1903.

5. Raviart and Caudron: A Case of Tuberculosis of the Myocardium, Echo méd. du Nord **8**:529, 1904.

6. Benda, C., and Geissler: New Cases of Tuberculosis of the Heart and Blood Vessels, Deutsch. med. Wchnschr. **31**:1169 (July 20) 1905.

7. Toldt, G.: A Case of Tuberculosis of the Myocardium, Rev. de méd. **26**:101, 1906.

8. Passamonti, M.: A Case of Tuberculosis of the Myocardium, Policlinico, Rome **14**:88, 1907.

Beifeld,[9] Fraga,[10] and more recently by Adamson,[11] Doermer,[12] and Binder.[13]

Ellis' case presented, in addition to tuberculous pericarditis and myocarditis, tuberculosis of the mediastinal nodes and lungs and a miliary tuberculosis of liver, spleen, pancreas and kidneys. Only after a study of many blocks from the heart were a few tubercle bacilli seen in one section. Beifeld's case showed a tuberculous scar at the apex of the left lung and a caseous tuberculosis of the mediastinal, tracheal, bronchial and left lower cervical nodes. There was a tuberculous pericarditis with total obliteration of the pericardial sac. The liver and spleen contained conglomerate tubercles. Microscopic examination demonstrated typical tuberculous tissue but up to the time of his report search for tubercle bacilli in the tissues was unsuccessful. He concluded that infection traveled from the left apex to the mediastinal nodes and then by contiguity or lymphatic extension or both, to the pericardium and by contact infection to the heart muscle. In Adamson's case no evidence of tuberculosis was found in the lungs or bronchial lymph nodes but he felt that the process probably started in the nodes at the base of the heart.

It is generally conceded that the mediastinal nodes act as the focus of infection for the pericardium and myocardium in this condition. Toldt however, reports a case of tuberculosis of the heart (limited to the right auricle) with no sign of pericardial involvement. He found but little evidence of tuberculosis disease in the tracheobronchial nodes but did note a healed lesion at the apices of both lungs. In commenting on the condition he mentions that Fuchs in a report of fifty-three cases of tuberculosis of the myocardium, found twelve cases of isolated auricular tuberculosis. Of these the right auricle alone was affected in nine; both auricles in two; and the left auricle only in one. Of the twelve cases eight showed tuberculous pericarditis, in two the pericardium was unaffected and in two the condition was not stated.

Passamonti also reports a case of tuberculosis of the myocardium with no other tuberculous lesion except a nodule in the lower lobe of the left lung. He did not feel that the usual propagation of infection (glandular) had occurred in his case. In a discussion of the condition

9. Beifeld, A. F.: Tuberculosis of the Myocardium, with the Report of a Case, Tr. Chicago Path. Soc. **8**:104, 1909-1912.

10. Fraga, C.: Concerning a Case of Cardio-Tuberculous Cirrhosis, Brazil-med. **31**:398, 1917.

11. Adamson, W. W.: A Case of Tuberculosis of the Myocardium, J. Path. & Bacteriol. **23**:399 (Dec.) 1920.

12. Doermer, W.: A Case of Conglomerate Tuberculosis of the heart, Diss., Jena, 1918.

13. Binder, A.: Tumor-Like Tuberculosis of the Heart, Zentralbl. f. inn. Med. **41**:462, 1920.

he mentions that the finding is practically always a postmortem one, and from a study of the literature brings out the fact that there are no characteristic signs of tuberculosis of the heart. He states that attacks of dyspnea, cyanosis, arrhythmia and enlargement of the cardiac area have been observed but adds that hypertrophy and dilatation are not always noted. Raviart and Caudron record a case in a white male, aged 31, with vague symptoms of oppression and pain in the epigastrium, and no definite physical signs. Necropsy revealed a tracheobronchial glandular tuberculosis and tuberculosis of the heart (confined to the right auricle). Toldt's case, mentioned above, occurred in a woman of 58 who had been ill for eighteen months, but, with "no symptoms of localization." Examination showed deviation of the apex of the heart, arrhythmia and muffled apical meurmurs—no other physical signs.

Anders made note of the following symptoms: palpitation, feeble heart sounds, pericardial distress, diffuse pulsation, tumultuous and rapid heart action, fetal and gallop rhythym, rarely murmurs, sudden and recurring syncope, dyspnea, cyanosis, unconsciousness, general edema and sudden death. But he states, "in all this list there is nothing specific, no single symptom or combination of symptoms that is not seen in functional and organic disease of the heart other than tuberculosis. Often the patient dies without a symptom that would attract special attention to the heart." Eisenmeyer is quoted by Anders as stating that a diagnosis may occasionally be made by the presence in a victim of general tuberculosis of sudden, severe collapse, quickly passing; and the detection of weak endocardial murmurs varying in phase and intensity.

One point not mentioned in the cases cited, is the apparently, relatively frequent occurrence of this unusual form of tuberculosis in the colored race. Four cases, Ellis', Beifeld's and the two making up the present report, occurred in young, adult, colored males. For this reason it seems reasonable to suggest that when evidence of cervical and mediastinal glandular disease exists in a young colored man with indefinite symptoms referable to the circulatory system and possibly signs of cardiac enlargement—tuberculosis of the heart should certainly be considered. In this connection Biefeld's case merits particular mention. A colored male, aged 21, had dyspnea and cyanosis; cough; rapid, regular pulse of good quality; and an evening rise of temperature. Examination showed a heart enlarged to right and left. No murmurs were present but a systolic retraction was noted, in place of the apex beat. A clinical diagnosis was made of adherent pericardium, tuberculous in nature; the necropsy, as above described, confirmed this diagnosis.

SUMMARY

The brief clinical reports and necropsy findings of two colored, young, adult males are recorded. Symptoms and physical signs were vague; necropsy demonstrated an immense, fibrocaseous tuberculous involvement of the lymph nodes of the thorax, with extension to the pericardium and in the one case to the heart muscle, causing tremendous enlargement of the organ. Reference to the literature indicates that the heart involvement is almost always secondary to the disease of the mediastinal lymph nodes. The practical limitation of the process to the lymph nodes, the curious reaction of the tissues and the difficulties in the diagnosis of such conditions are some of the problems offered to pathologist and clinician by these case reports.

I am indebted to Dr. H. A. Hare and Dr. Thomas McCrae for permission to report these cases.

OBSERVATIONS FOLLOWING INTRAVENOUS INJECTIONS OF HYPERTONIC SALT SOLUTIONS IN CASES OF NEUROSYPHILIS*

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INTRODUCTORY

Weed and McKibben [1] and others [2] have shown that the administration of hypertonic salt solutions in the cat causes a marked and prolonged fall in cerebrospinal fluid pressure. By an ingenious method they were further able to show that with this fall in pressure a considerable amount of subarachnoid fluid was dislocated into the nervous system; that the fluid "passed along the perivasculars into the substance of the nervous system, reaching the interfibrous spaces in the white matter and the pericellular spaces in the gray." The method leading to these conclusions consisted in allowing a few cubic centimeters of iron-ammonium citrate and sodium ferrocyanid to run into the subarachnoid space as the cerebrospinal fluid pressure (after intravenous injection of hypertonic salt solution) reached zero or was rapidly falling; then fixation of the central nervous system in liquor formaldehyd acidified with 5 per cent. hydrochloric acid precipitated Prussian blue (readily demonstrable microscopically) at points to which the injected citrate and ferrocyanid had penetrated. Foley and Putnam [2] later showed that similar falls in cerebrospinal fluid pressure (presumably with the same dislocation of fluid) could be obtained in cats by administering approximately similar doses of salt per duodenum or per rectum.

In view of these observations, Foley raised the question as to whether or not intraspinal injections of arsphenamized serum in man might be more effectively distributed if followed by the administration of salt either by mouth, rectum or vein. In patients there is no way of determining how extensive the distribution of intraspinal injections actually is. Effective distribution can only be inferred from favorable clinical and serologic results. In the cat, when cerebrospinal fluid pressure (after intravenous injection of salt solution) is reduced to zero or to a negative figure, an intraspinally injected substance can be

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* From the Medical Service of the Peter Bent Brigham Hospital.

1. Weed and McKibben: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injections of Solutions of Various Concentrations, Am. J. Physiol. **48**:512 (May) 1919.

2. Foley and Putnam: Effect of Salt Ingestion on Cerebrospinal Fluid Pressure and Brain Volume, Am. J. Physiol. **53**:464 (Oct.) 1920.

shown to be dislocated into the substance of the nervous system. Consequently, in man it would seem reasonable to suppose that the fluid content of the subarachnoid space passes similarly into the brain substance after intravenous salt injections, if cerebrospinal fluid pressure falls in man as in cats. Such a displacement of injected serum would seem especially to be desired in cases of neurosyphilis with few or no posterior root symptoms, i.e. those cases[3] with cerebrospinal fluids showing pleocytosis, increased globulin and strongly positive Wassermann reaction, but with purely subjective evidences of disturbance and with reflexes for the most part intact.

The first problems were to determine the optimum salt dosage and means of administration, and to ascertain whether intravenous injection of hypertonic salt solutions cause a fall in cerebrospinal fluid pressure in man as in the cat. Foley and Morris, attempting alimentary administration of salt in several preliminary observations, were soon convinced of its impracticability; almost without exception doses of from 15 to 30 gm. (in capsules) were promptly rejected, whether given orally or rectally. Intravenous solutions of varying hypertonicity were later tried by me and 15 per cent. solutions were finally adopted as the optimum. It was soon found that patients could tolerate in this concentration with no very alarming symptoms 410 mg. salt per kg. of body weight. Slight variations in dosage above and below this figure produced such negligible change in effect that it was eventually decided to use as a routine salt dosage 200 c. c. of a 15 per cent. solution.

With the assistance of several cooperative patients it was possible to get actual graphic records in man of the changes in cerebrospinal fluid pressure during and for about thirty minutes after the intravenous injection of the routine salt solution. The procedure was as follows: Lumbar puncture was performed with a small bore needle (patient in the usual position on the right side) and a glass capillary manometer containing normal salt solution was attached, with the loss of as little cerebrospinal fluid as possible, usually only a drop or two. Five or ten minutes were allowed to elapse until a reliable normal could be read; no readings were taken unless cardiac and respiratory fluctuations in pressure evidenced the technical integrity of the apparatus. The intravenous salt solution was then given through a No. 19 needle by gravity, the patient having before lumbar puncture had his arm prepared, thus avoiding even the slightest change in position and consequent disturbance of the manometer during venipuncture.[4]

3. Only nine of the sixteen cases here reviewed are of this group; the other seven were cases of tabes, the only other cases available for the salt treatment at the time.

4. In three of these determinations Dr. F. E. B. Foley rendered, through his suggestions and cooperation, most valuable assistance.

In six cases studied thus there was a constant rise in pressure of from 30 to 50 mm. during the fifteen minutes occupied in giving the salt solution. A moment or two before the end of the injection the pressure would start down, and by thirty minutes after the end of the injection it would usually sink from 80 to 100 mm. below the original level. By this time the patients were invariably so uncomfortable that the lumbar puncture needle had to be withdrawn, which, of course, made further pressure observations impossible. However, the close correspondence in these initial pressure variations with those in the cat would make it reasonable to suppose that the depression increases till zero and possibly even negative levels are reached, as in the case of the cat.

Figure 1.

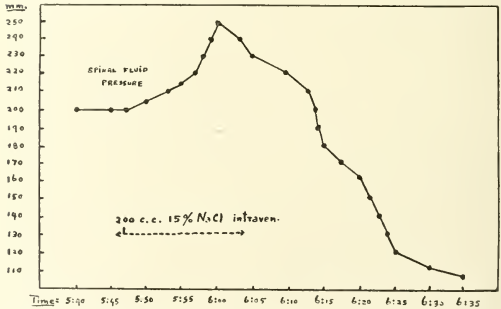

Fig. 1.—Vertical figures: pressure in mm. of cerebrospinal fluid. Horizontal figures: time. Dotted line: period during which 200 c.c. of 15 per cent. salt solution was given intravenously.

Normal pressures in the different cases often varied from 30 to 40 mm., but the relative changes after injection of salt solution have been remarkably constant. Figure 1 represents the course in one case quite typical of the group.

In view of these demonstrated pressure changes in man,[5] fluid displacement into the substance of the nervous system seemed an hypothesis reasonable enough to warrant the systematic use of salt

5. Three of these pressure determinations were carried out with Dr. F. E. B. Foley, and since charts of these will be published by him elsewhere, only one curve is reproduced here.

solutions in chosen cases of neurosyphilis, in an effort to render more effective arsphenamized serum distribution through the subarachnoid space.

PROPOSED CLINICAL PROCEDURE

It was decided that sixteen patients with neurosyphilis receiving intraspinal treatment [6] should receive 200 c. c. of 15 per cent. salt solution intravenously during the hour following intraspinal treatment, this to be repeated with each succeeding serum treatment, given at fortnightly intervals, till six salt injections had been given. Serologic and cytologic changes in the cerebrospinal fluid thus could be followed closely; with the return of the patients two months after the last treatment for follow-up examination and lumbar puncture, it would be possible to note any variation from the usual serological and clinical course of the cases.

ACTUAL CLINICAL COURSE OF THE PATIENTS GIVEN SALT SOLUTION

The actual procedure with the cases varied considerably from that planned, as will be apparent from a glance at Table 1, in which the results are tabulated. Only one patient in sixteen received all six proposed salt injections, three received five, five four, and the rest less. The reason for this deviation from schedule is apparent from Table 1. Five patients failed to return for completion of the course and were lost from observation. Six absolutely objected to completing the salt injections because of extreme distress produced by them on previous occasions. In five cases the Wassermann reaction and cell count became negative before the giving of all six injections of salt solution.

The column headed "subjective effect of salt," Table 1, shows that almost every patient experienced more or less marked discomfort from the hypertonic solutions, in six cases this discomfort being severe enough to necessitate abandoning subsequent injections. The symptoms associated with giving salt were surprisingly constant in all the cases; shortly after the start, marked facial flushing and a sensation of heat, involving first the face and then in succession neck, arms, trunk, legs

6. In this clinic the indications for intraspinal treatment are essentially those set forth by Fordyce [7] and others.[8]

7. Fordyce: The Treatment of Syphilis of the Nervous System, J. A. M. A. **63**:552 (Aug. 15) 1914; Intraspinal Therapy in Neurosyphilis, Am. J. Syph. **3**:337 (July) 1919.

8. Swift and Ellis: The Treatment of Syphilitic Affections of the Central Nervous System with Especial Reference to the Use of Intraspinous Injections, Arch. Int. Med. **12**:331 (Sept.) 1913; A Study of the Spirochaeticidal Action of the Serum of Patients Treated with Salvarsan, J. Exper. M. **18**:435 (Oct.) 1913.

TABLE 1.—Clinical Course of Patients Given Salt Solution

Diagnosis	Interval Since Primary	Reflexes*					Subjective Effect of Salt	Intraspinals Followed by Salt	Previous† Intraspinals: No Salt	Symptoms	Spinal Fluid Changes During Intraspinals‡				Reason for Incomplete Salts	Period of Observation, Mos.
											Wassermanns		Cell Counts			
		R	K	Ac	FN	B					O §	NaCl §	O §	NaCl §		
											C.c. C.c.	C.c. C.c.				
Neurosyphilis	10 yr.	A	P	P	P	A	Very distressing	2	2	Headache	1.0++→1.8++	1.8++→2.0++	20 → 15	15 → 5	Absent	4
Neurosyphilis	4 yr.	A	P	P	P	A	Very distressing	4	6	Headache	0.5++ 0.8++	0.8++ 1.0 —	40 18	18 7	Objected	7
Neurosyphilis	Unknown	A	P	P	P	A	Very distressing	4	6	Slight headache	0.2++ 0.6++	0.6++ 1.0++	25 12	12 10	Objected	7
Neurosyphilis	5 yr.	A	P	P	P	A	Very distressing	6	4	Nausea, vomiting	0.5++ 1.0++	1.0++ 2.0 —	104 50	50 10	.....	7
Neurosyphilis	10 yr.	A	P	P	P	P	Slightly distressing	1	3	Spastic gait	1.0++ 2.0++	2.0++ 2.0 —	14 10	10 8	Negative Wassermann	9
Neurosyphilis	2 yr.	A	P	P	P	A	Very distressing	2	4	Headache	1.2++ 2.0++	2.0++ 2.0 —	20 12	12 9	Negative Wassermann	5
Neurosyphilis	7 yr.	A	P	P	P	A	Slightly distressing	5	2	None	0.5++ 1.0++	1.0++ 0.8 —	20 9	9 9	Negative Wassermann	6
Neurosyphilis	20 yr.	A	P	P	P	A	Very distressing	5	22	Hot flashes	0.2++ 1.6+±	0.8++ 1.0++	60 10	9 9	Objected	15
Neurosyphilis	3 yr.	A	P	P	P	A	Slightly distressing	3	11	Nervousness	0.2++ 1.4 —	1.4 — 2.0 —	30 12	12 2	Negative Wassermann	9
Tabes.....	Unknown	P	A	A	P	A	Very distressing	2	2	Root pains	0.2++ 0.4++	0.3++ 0.4++	12 7	8 5	Absent	8
Tabes.....	8 yr.	A	A	A	P	A	Slightly distressing	5	3	Root pains	0.6++ 0.6++	0.7++ 1.2++	60 18	18 6	Objected	7
Tabes.....	Unknown	A	A	A	P	P	Very distressing	2	1	Ataxia	0.3++ 0.5++	0.5++ 0.6++	20 12	12 11	Objected	4
Tabes.....	35 yr.	P	A	A	A	A	Very distressing	3	5	Ataxia	0.5++ 1.2++	1.0++ 1.4+±	27 15	13 10	Absent	7
Tabes.....	12 yr.	A	A	A	A	A	No distress	4	4	Sensory	0.5+ + 0.8++	0.7++ 0.8++	15 7	8 5	Absent	6
Tabes.....	25 yr.	P	A	A	A	A	Very distressing	4	4	Ataxia	0.5++ 1.0++	1.0++ 1.4 —	30 15	12 9	Absent	7
Tabes.....	25 yr.	P	A	A	A	A	Very distressing	4	6	Ataxia	0.3++ 1.0++	1.0++ 1.8 —	10 3	2 2	Objected	8

* Reflexes: R, Romberg; K, knee-jerk; Ac, Achilles; FN, finger-nose; B, Babinski; P, present; A, absent.

† In this group it was planned to complete the intraspinal course in progress, giving salts, and then to give enough extra serum treatments to complete the set of six salts.

‡ These cell count and Wassermann figures include follow-up lumbar puncture two months after the last intraspinal treatment.

§ O, changes during intraspinal treatments without intravenous salt; NaCl, changes during intraspinal treatments with intravenous salts.

and feet; then intense dryness of the throat and at the end of the injection intense "boring" occipital or frontal headache, usually of only from ten to twenty minutes' duration, but relieved at the time by nothing except morphin.[9]

Comparison of cell count and Wassermann reaction improvement (Table 1) in patients receiving (a) intraspinal treatments alone and (b) intraspinal treatments plus salt solution intravenously would seem to indicate that the salt is of no therapeutic value.[10]

Furthermore, clinical evidences suggested that such use of hypertonic salt solutions might be positively harmful, for almost without exception there were aggravation of root pain and, in many instances, the occurrence of alimentary upsets persisting for four or five days during the intervals between treatments.

In view of these facts, it would seem that despite a sound theoretical basis, the use of hypertonic salt solution intravenously has no place in augmenting the intraspinal treatment of neurosyphilis. It may validly be objected that these observations are not conclusive, extending, as they do, rarely over nine months. However, it did not seem justifiable to push the work further in the face of no marked serological and cytological improvement and actual symptomatic retrogression.

EFFECT OF SALT INJECTIONS ON BLOOD PRESSURE, BLOOD AND URINE CHLORID

In Table 3 are tabulated the effects of intravenous injection of salt solutions on blood pressure, whole blood chlorid, and urine chlorid. The relation of these changes in a single case is shown in Figure 2. From Table 3 it is apparent that in this group immediately following the routine salt injections, there was from 51 to 61 per cent. increase in the whole blood chlorid, that an hour later the increase was from 20 to 35 per cent. Twelve hours after injection there was still from 14 to 22 per cent. elevation in blood chlorid; at that time approximately half of the injected salt had been excreted in the urine. In three cases (Nos. 5, 6 and 8, Table 3), because of previous disagreeable reaction to the routine dose of salt, smaller injections were given, with correspondingly less marked and prolonged elevation in blood chlorid. In one of these cases practically all of the injected salt had been excreted in the urine in twenty-two hours. In the other two cases excretion was not quite so rapid. In view of the marked and prolonged elevation in blood

9. The rate of giving the salt injections is shown in Figure 1.

10. Table 2 illustrates the course in one case which is quite typical of the series. It will be noted that the most striking change in the Wassermann reaction occurred on the day of the first salt injection which, of course, discredits the salt as being the effective agent in the subsequent unusually rapid improvement in the fluid.

chlorid in the cases receiving the routine salt injection, the triviality and transiency of the blood pressure changes is rather striking. It is worthy of special note that several of the determinations were made on the same patients at fortnightly intervals, and that in one such case the blood pressure levels were slightly lower during the second determination than during the first: Nos. 1 and 2 (Table 3) are consecutive determinations (eighteen day interval) on the same patient, and the average of the blood pressures during the first was 112 68, during the last 101/58.[11] These facts are of interest in view of the recent work on the relationship of hypertension and elevations in blood chlorid.

TABLE 2.—CLINICAL COURSE OF ONE CASE IN WHICH SALT SOLUTION WAS INJECTED

Date*	Treatment		Remarks	Reflexes	Spinal Fluid		
	Intravenous (Diarsenol in Gm.)	Intraspinal (50% diarsenolized Serum, C.c., and Diarsenol, Gm.)			Cells	Globulin	Wassermann
3/10/20	0.3	20 + 0.0002	No reaction	Negative	20	+	0.2 c.c. ++
3/17/20	0.4						
4/ 7/20	0.3	20 + 0.0003	Out of city since last treatment	Negative	18	+	0.4 c.c. ++
4/14/20	0.4						
4/21/20	0.3	20 + 0.0003	Symptom free	Negative	9	+	0.6 c.c. ++
5/ 5/20	0.4	20 + 0.0003	.....	Negative	9	+	0.6 c.c. ++
5/12/20	0.4						
5/19/20	0.3	20 + 0.0004	.....	Negative	7	±	0.8 c.c. ++
6/ 2/20	0.4						
6/17/20	0.4	20 + 0.0004	.....	Negative	7	+	0.8 c.c. ++
6/29/20	0.5	20 + 0.0004	.....	Negative	15	±	1.0 c.c. ++
7/13/20	0.4						
7/26/20	0.3	20 + 0.0002	.....	Negative	10	±	1.0 c.c. ++
8/10/20	0.3	20 + 0.0002	200 c.c. 15% salt solution intraven.	Negative	8	±	1.4 c.c. —
8/24/20	0.3	20 + 0.0003	Salt as above	Negative	7	±	2.0 c.c. —
9/10/20	0.3	20 + 0.0003	Salt as above	Negative	7	—	1.6 c.c. ±
9/25/20	0.3	20 + 0.0002	.....	Negative	5	—	2.0 c.c. —
Rest period							
12/17/20†	...	.....	.....	.....	3	—	2.0 c.c. —
Rest period							
3/ 1/21‡	...	.....	.....	.....	1	—	2.0 c.c. —
Rest period							

* The irregularity in treatment intervals is due to the fact that the patient was out of the city much of the time on business.

† Control lumbar puncture. Symptom free.

‡ Control lumbar puncture. Feels well.

With ten of the salt injections leukocyte counts were made immediately before and after injection, and the fresh and stained smears were examined at the same time. Red cells showed no morphologic evidence

11. The same general blood pressure tendency, though less striking, characterizes the consecutive determinations, Nos. 4, 5, and 6 (Table 3) and this despite the fact that the blood chlorid never got back to the original normal, once salt injections were started; the average of pressures in No. 6, though higher than in No. 5, is still lower than in the original determination, No. 4.

of injury; there were minor inconstant variations in the differential count, and in about half the cases a slight depression in the total white count. No effort was made to study variations in blood picture exhaustively.

SUMMARY AND CONCLUSIONS

1. Intravenous injections of 200 c.c. of 15 per cent. salt solution were given to six patients with neurosyphilis, with resulting disagreeable but not alarming symptoms. In these cases the cerebrospinal fluid pressure was found to rise sharply and then to fall, reaching a point about 100 mm. below the original level by thirty minutes after the end of the salt injection.

Figure 2.

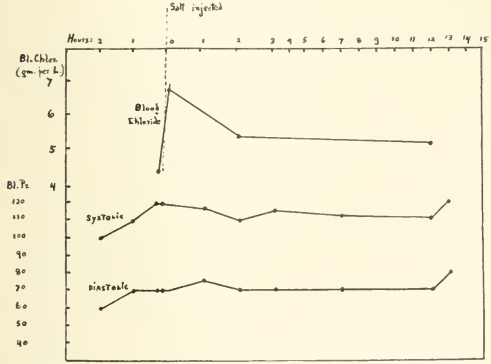

Fig. 2.—Upper left margin figures and top curve: whole blood chlorid in gm. per liter. Lower left margin figures and lower two curves: systolic and diastolic blood pressures. (During the three hours prior to injection, 200 c.c. urine were voided, containing 0.51 gm. salt; during the twenty hours after injection, 1,270 c.c. were voided containing 16.4 gm. salt.)

2. Salt injections were given according to a definite routine over a period of months, augmenting intraspinal treatment in a group of patients with neurosyphilis. There was no serologic or cytologic improvement over the usual course with intraspinal treatment alone, and symptoms were distinctly aggravated. Such injections hence would seem to have no therapeutic value in this group of neurosyphilis cases.

TABLE 3.—Effects of Intravenous Injection of Salt Solution on Blood Pressure, Blood and Urine Chlorids

No.	Amount 10% Salt Intravenous	Whole Blood Chlorid‡ (In Gm. per L. and Per Cent. Above Case normals§) With Reference to Salt Injection				Blood Pressure in (Mm. of Mercury) (i v = intravenous salt injection; i. s. = intraspinal injection)						Chlorids in Urine					
												Before Salt Injection			After Salt Injection		
		Before	After	2 Hrs. After	12 Hrs. After	2 Hrs. Before i. s.	Before i. s.	After i. s.	After i. v.	2 Hrs. After i. v.	12 Hrs. After i. v.	Volume Voided in C.c.	Period of Hours	NaCl, Gm.	Volume Voided in C.c.	Period of Hours	NaCl, Gm.
1	200 c.c.	4.4	6.8 54%	5.41 22%	5.2 18%	100 60	110 70	120 70	120 70	110 70	110 70	200	3	0.51	1,270	20	16.4
2*	200 c.c.	4.2	6.78 61%	5.36 27%	5.1 22%	95 55	100 55	88 50	110 65	110 65	110 60	120	2	0.77	1,540	22	17.8
3	200 c.c.	4.3	6.82 58%	5.38 25%	5.16 20%	110 60	115 65	115 70	115 70	115 65	115 60	90	2	0.86	990	14	9.6
4	200 c.c.	4.2	6.77 61%	5.69 35%	4.9 16%	110 65	112 70	110 65	140 80	125 80	112 70	110	3	0.46	1,700	20	16.8
5	170 c.c.	4.4	6.56 49%	5.34 21%	5.1 16%	110 65	110 60	110 60	130 65	115 60	110 65	230	3	0.53	1,600	15	10.0
6†	100 c.c.	4.8	6.13 27%	5.3 10%	4.8 0%	108 60	110 60	110 65	128 70	125 75	114 65	130	4	0.41	2,400	22	14.4
7	200 c.c.	4.5	6.81 51%	5.42 20%	5.14 14%	120 70	125 70	110 70	115 65	120 70	115 70	485	2	2.5	1,385	17	13.3
8	100 c.c.	4.6	6.08 32%	5.1 11%	4.6 0%	110 60	110 60	115 60	120 65	125 70	116 60	600	9	4.8	840	14	11.76

* This determination and No. 1 were on the same patient, this one two and a half weeks later than No. 1.
† Two of the blood chlorid determinations were made by Miss Mary Redmond and she has checked several of the others.
‡ This determination was two weeks later than No. 5, which was in turn two weeks later than No. 4, all on the same patient.
§ By "normal" is meant the figure in the column "Before."

3. In a short series of cases whole blood chlorids were determined before and at intervals after salt injections, the output of salt in the urine was ascertained, and blood pressures were followed; immediately after the intravenous injection of 200 c. c. of 15 per cent. salt solution the average whole blood chlorid elevation above normal (i.e., the first determination) was 57 per cent.; one hour later, 26 per cent.; twelve hours later, 18 per cent. In from seventeen to twenty-two hours, about half of the injected salt had been excreted in the urine. Variations in blood pressure were within physiologic limits.

A METABOLIC STUDY OF PROGRESSIVE PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY AND OTHER MUSCULAR ATROPHIES*

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We have recently had the opportunity to study the metabolism of nine cases of pseudohypertrophic muscular dystrophy in different stages of advancement. These cases will be reported from a clinical standpoint with about twenty more by Dr. R. V. Funsten. We also include some metabolic observations on other types of atrophic muscular involvement.

Endocrine disturbance in progressive pseudohypertrophic muscular dystrophy is indicated by (1) the hereditary character of the condition, (2) the metabolic abnormalities, (3) the occasional recovery at puberty when glandular readjustments occur, (4) reported improvement following endocrine therapy in some cases, and (5) the development of the disease in polyglandular dystrophies, notably in association with dystrophia adiposogenitalis. Necropsy findings with special reference to the ductless glands are urgently needed to elucidate further the pathogenesis of the condition.

The symptomatology and the pathologic changes have been well reviewed by Timme[1] and by Janney, Goodhart, and Isaacson.[2] Involvement of the pineal gland has been suggested by Timme from a study of the literature and from roentgen-ray examinations in three cases from the same family; pineal shadows were evident in two cases only of the series of nine studied by Janney, Goodhart, and Isaacson. These last named investigators, as does McCrudden,[3] attribute the condition to endocrine dysfunction affecting carbohydrate metabolism.

According to McCrudden, there is hypoglycemia, no increased heat formation, a rapid fall in blood sugar during the first twenty-four hours of starvation indicative of a diminished glycogen reserve, increas-

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1. Timme, W.: Arch. Int. Med. **19**:79 (Jan.) 1917.

2. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: Arch. Int. Med. **21**:188 (Feb.) 1918.

3. McCrudden, F. H.: Arch. Int. Med. **21**:256 (Feb.) 1918; J. A. M. A. **70**:1216 (April 27) 1918.

ing "fatty degeneration," an increased respiratory quotient, and lipemia. Since a prompt and marked rise in blood sugar follows the administration of epinephrin, the impaired glycogenesis is associated with damage to the suprarenals rather than to the liver.

One of our patients (Case 5) died of influenzal pneumonia and a necropsy was obtained. This was a polyglandular condition, Fröhlich's syndrome complicating the picture of progressive pseudohypertrophic muscular dystrophy. Through oversight, the pineal gland was not preserved for microscopic examination. The following description is abstracted from Dr. E. M. Medlar's records.

On gross examination, the suprarenals were apparently larger, though thinner than normal, with a very small medullary substance and a thin cortical layer. The thyroid was slightly hypertrophied and there was considerable colloid. The parathyroids (four, the size of small peas) were reddish in color; on section, they seemed to be made up of small round bodies. The pituitary contained a cyst filled with a clear fluid; the cyst was about 0.5 cm. in diameter; the remaining tissue was flattened and less in amount than normal.

Microscopic examination revealed that the bodies taken to be parathyroids consisted of acini filled with colloid material; "if these bodies are accessory thyroids, the parathyroids were so small that they could not be detected in gross." Sections of the pituitary showed a small cyst in the pituitary lobe, with an apparent marked increase in the secretory cells (and secretion) of the anterior lobe. Thyroid, thymus and pancreas exhibited little or no change, except that for the last two there was an ingrowth of fat tissue. The adrenals were congested, and there were areas of necrosis with infiltration of leukocytes in the cortex.

The muscle tissue showed the fatty infiltration and atrophy as described for pseudohypertrophic muscular dystrophy. It is of incidental interest that the respiratory muscles were less atrophied than the others, indicating a selective conservation of this group.

Because of the muscular changes, a study of the creatinin elimination in the muscular atrophies was made by Spriggs [4]; he observed a lowered creatinin excretion in pseudohypertrophic muscular dystrophy, in myotonia congenita, and in myasthenia gravis. Levene and Kristeller [5] determined the creatinin and creatin elimination in several types of muscular involvement, including five cases of muscular dystrophy, on high and low protein intakes; cases with considerable loss of muscular function gave a much diminished creatinin output and a creatinuria. In conditions of muscular atrophy or dystrophy practically 90 per cent. of ingested creatin (in beef) reappeared in the urine.

McCrudden and Sargent [6] found the daily creatinin excretion to be normal and constant (1.5 gm. or 22.6 mg. per kilogram of body weight) and a creatinuria (about 0.5 gm. daily) in a male, aged 33

4. Spriggs, E. I.: Biochem. Ztschr. **2**:206, 1907.

5. Levene, P. A., and Kristeller, L.: Am. J. Physiol. **24**:45, 1907.

6. McCrudden, F. H., and Sargent, C. S.: Arch. Int. Med. **17**:465 (April) 1916; **21**:252 (Feb.) 1918.

years. There was a low ammonia. Total nitrogen, uric acid, and calcium and magnesium elimination were normal, though the ratio calcium: magnesium was a little high. Blood findings were: creatinin, 1.43 mg.; creatin, 3.86 mg.; nonprotein nitrogen, 28.9 mg.; uric acid, 2.3 mg.; glucose, 0.075 per cent.; and cholesterol, from 0.05 to 0.144 per cent. They state that the metabolic picture is distinctly different in progressive muscular atrophy (two cases) in which there is creatinuria and normal blood sugar, and in myasthenia gravis (two cases) in which there is hypoglycemia without creatinuria.

The nine cases reported by Janney, Goodhart, and Isaacson were in patients in advanced stages of the disease, and from 11 to 48 years of age; one female case is included. They found a marked decrease in the urinary creatinin, creatinuria, hypoglycemia, normal blood urea, low blood creatinin, and normal (?) blood creatin. There was a retention of calcium and magnesium when the calcium content of the diet was adequate. Of importance is the delayed utilization of glucose for five cases when ingested (1.75 gm. glucose per kilogram of body weight).

Brock and Kay [7] have presented three adult cases of endocrinopathies associated with unusual manifestations in the muscular system. One was a case of dystrophia adiposogenitalis with a recent limited muscular dystrophy. This case showed a creatinuria, hypoglycemia, and a delayed glycogenesis without glycosuria following glucose ingestion. A. Gibson [8] has reported a case of familial "muscular infantilism" in an adult male. There was creatinuria, though histologic examination of the muscle showed but little departure from the normal. Blood sugar findings resembled the results we have obtained for our two adult cases of pseudohypertrophic muscular dystrophy.

Pemberton [9] has reported a somewhat lowered creatinin elimination and a negative calcium balance in myasthenia gravis, and a very low creatinin and slightly negative calcium balance in myotonia atrophica. Diller and Rosenbloom [10] obtained similar results for a case of myasthenia gravis; there was no creatinuria. Rosenbloom and Cohoe [11] found a normal nitrogen partition in myotonia congenita (Thompsen's disease); there was a negative calcium balance. Three studies of the metabolism in amyotonia congenita (Oppenheim's disease) in children are found in the modern literature; Gittings and Pemberton [12] reported a very low creatinin excretion in a boy 21 months old, with

7. Brock, S., and Kay, W. E.: Arch. Int. Med. **27**:1 (Jan.) 1921.
8. Gibson, A.: Arch. Int. Med. **27**:338 (March) 1921.
9. Pemberton, R.: Am. J. M. Sc. **139**:816, 1910; **141**:253, 1911.
10. Diller, T., and Rosenbloom, J.: Am. J. M. Sc. **143**:65, 1914.
11. Rosenbloom, J., and Cohoe, B. A.: Arch. Int. Med. **14**:263 (Aug.) 1914.
12. Gittings, J. C., and Pemberton, R.: Am. J. M. Sc. **144**:732, 1912.

no disturbance of the calcium elimination; Powis and Raper [13] obtained low creatinin and high creatin figures for a girl 4 years of age, ingested creatin being promptly eliminated, and calcium and potassium retention being normal; and Ziegler and Pearce [14] found low creatinin and high creatin values, normal uric acid, an increased undetermined nitrogen and neutral sulphur, blood glucose of 0.14 per cent., and blood creatin and creatin of 1.5 and 5.45 mg. respectively.

The nine cases of progressive pseudohypertrophic muscular dystrophy included in this report comprise: Two cases in young boys in which the atrophy was moderately advanced. Three cases in older boys (one with a coincident dystrophia adiposogenitalis) in which the muscular atrophy had progressed until movements were practically limited to the muscles of the thorax, distal upper extremities, neck, and face; and two male adult cases, the condition developing after puberty and progressing slowly, with muscular pseudohypertrophy, lordosis, and general weakness. Of particular interest from a comparative metabolic standpoint is the fact that two of the patients in the series were brothers, one with a moderately advanced case and the other presenting marked atrophic changes. One case of myasthenia gravis, one of muscular atrophy following acute anterior poliomyelitis, and one of myositis ossificans are also included. These three cases were adult males also.

Each case was transferred to our special metabolism unit for study. The diet was nonpurin and noncreatin, the constituents being kept essentially the same daily. The protein intake was set at a figure slightly above the physiologic requirement only, inasmuch as the literature on creatinuria indicates that an increased protein metabolism may be accompanied by a greater creatin elimination, a fact which we have verified in some of our cases.[15] Blood sugar determinations were made according to the Benedict modification of the Lewis-Benedict method: other analyses were made by the current procedures. Blood samples for Case 6 could only be obtained from the jugular vein. It was impossible to do a satisfactory venepuncture in the myositis ossificans case, and in Case 5, though micro-sugar determinations were made for the latter with 0.04 c. mm. of blood, centrifuging the precipitates, and using similar Sahli hemoglobinometer tubes as a dilution colorimeter.

Levene and Kristeller have pointed out that the creatinin elimination in muscular atrophy cases does not have the same constancy that obtains in the normal individual. From data obtained in our patients, we find this to be decidedly the case, the twenty-four hour collection

13. Powis, F., and Raper, H. S.: Quart. J. M. **10**:7, 1916.
14. Ziegler, M. R., and Pearce, N. O.: J. Biol. Chem. **42**:581, 1920.
15. Gibson, R. B., and Martin, Francis T.: J. Biol Chem. **41**: xxxvi, 1920.

of the urinary specimens being absolutely assured. However, we have found it possible to stabilize the creatinin excretion under constant conditions of diet over periods of several days.

A summary of the ages, weights, creatinin coefficients, and blood findings is given in Table 1. Brief clinical descriptions and the nitrogen partition in tabular form are presented also for the individual cases.

TABLE 1.—Creatinin and Creatin Coefficients, and Blood Analyses of Twelve Cases

	Age in Years	Weight, Kg.	Creatinin Coef. Belatt	Total Creatinin Coefficient	Ingested Creatin, % Recovered	Blood Sugar Control, %	Glycogenesis Test Blood Sugar, %	Blood Creatinin, Mg. %	Blood Creatin, Mg. %	Blood Fat, %	Blood Cholesterol, per Cent.	Blood Calcium, Mg. %	Hydrogen Ion Concentration
1. E. T.	5	18.0	5.2	9.0	48	0.070	0.098	0.75	10.3	0.61	....	....	...
2. D. R.	8	21.8	5.0	11.5	32	0.071	0.067	0.45	5.7	0.89	....	....	...
3. J. Schw. Adm. 1.	5	18.2	2.5	4.3	50	0.080	0.174	0.91	7.6	0.59	....	....	7.5
Adm. 2.	6	20.0	2.6	5.6	..	0.067	0.101	....	....	....	....	....	...
4. R. Stol. Adm. 1.	9	20.0	2.1	3.9	90	0.112	0.101	0.60	7.2	0.67	0.29	....	...
						0.119	0.115	1.06	7.5	0.57	0.28	....	...
5. O. Schaf.	15	90.0	1.0	3.4	70	0.089	0.178	....	....	....	....	....	...
6. Wm Schw. Adm. 1	15	21.3	1.0	3.7	80	0.089	0.160	0.76	5.7	0.61	....	....	7.6
Adm. 2	15	....	1.6	7.5	..	0.117	0.198	0.53	9.7	0.50	0.18	....	...
7. W. Stil.	12	39.6	1.7	5.0	100	0.125	0.147	0.50	7.0	....	....	....	...
						0.082	0.124	0.50	15.6	0.95	....	....	...
8. B. McD.	22	55.0	7.1	7.7	40	0.133	0.157	....	15.1	....	....	10.1	...
						0.116	0.143	2.45	12.9	....	....	....	...
								1.9	50.0	0.62	0.22	11.8	...
9. O. Sm.	38	50.0	4.2	5.7	...	0.101	0.123	1.0	12.1	0.51	0.27	12.6	...
10. Geo. S.	48	79.0	7.1	7.1	...	0.105	....	0.74	5.2	....	....	....	...
						0.125	0.185	1.4	7.7	....	....	....	...
11. L. W.	25	63.0	7.6	8.3	60	0.112	0.111	1.25	6.8	0.72	0.22	....	...
12. Geo. F.	26	54.0	5.3	5.3	...	.....	.....	....	....	....	....	....	...

Cases 1 to 9, inclusive, were pseudohypertrophic muscular dystrophy patients; Case 10 had myasthenia gravis; Case 11 muscular atrophy due to anterior poliomyelitis, and Case 12 myositis ossificans.

In the cases in the earlier stage of progressive pseudohypertrophic muscular dystrophy (Cases 1 and 2), there was creatinuria; this is a normal condition in childhood (Rose [16]). Shaffer [17] gives the creatinin coefficient for normal children as between 3.3 and 6.5, and for adults from 8.1 to 11.0. We regard creatinin coefficients of 5.2 and 5.0 for Cases 1 and 2 as a low normal. Ingested creatin (0.5 gm.) was destroyed only in part, 48 and 32 per cent., respectively, being recovered. Krause's [18] normal cases, given 0.3 gm. creatin by mouth, eliminated the following percentages; girl of 6 years, 56; boy of 8 years, 43; girl of 11 years, 31. The recovery of ingested creatin in our two cases is not to be regarded as abnormal. A rather high uric acid nitrogen for Case 2 was observed. Total nitrogen figures were quite low, and positive nitrogen balances are indicated. There was hypoglycemia in

16. Rose, W. C.: J. Biol. Chem. **10**:265, 1911.
17. Shaffer, P. A.: Am. J. Physiol. **23**:1, 1908.
18. Krause, R. A.: Quart. J. Physiol. **8**:87, 1913.

both cases. Diminished glycogenesis (Janney) and high blood creatin obtained for Case 1; normal blood creatin figures for children are not yet established satisfactorily, though Veeder and Johnston[19] found from 2.2 to 7.2 mg. with a mean for the nonextreme cases of 3.8.

Still lower creatinin coefficients (2.5 and 2.1) were obtained for Cases 3 and 4; in these boys, the muscular changes were more pronounced than for the previous group. There was creatinuria in both cases. Hypoglycemia and diminished glycogenesis were found for Case 3, but not for Case 4. Case 4 was clinically the more advanced, and this is reflected by the lower creatinin coefficient and the much greater recovery of ingested creatin.

Cases 5, 6, and 7 were older boys of 15, 15, and 12 years, respectively. There were most pronounced atrophic changes of the muscular system. Strikingly low creatinin excretion and creatinin coefficients (1.0 to 1.6) were obtained; however, the creatinin coefficient of Case 5 (with Fröhlich's syndrome) is based on a body weight of 90 kg. There was creatinuria, and ingested creatin was largely recovered, completely so for Case 7. Hypoglycemia was observed, though normal blood sugars have been obtained also for Cases 6 and 7. Glycogenesis was reduced; glycosuria followed the glucose ingestion (100 gm.) for Case 5. High blood creatins have been noted for Cases 6 and 7. The high blood fat for Case 7 is probably accounted for by an excessive diet. Case 6 was a brother of Case 3.

The adult pseudohypertrophic muscular dystrophy cases (Cases 8 and 9) present some differences that are noteworthy. The metabolic disturbance is not so intense. Case 9 presented a greater atrophic change with a much less creatinin coefficient and a greater creatinuria than Case 8. In fact, there was little or no creatinuria on some days for Case 8. Forty per cent. of ingested creatin (1 gm.) was excreted by Case 8. For Case 9, there was an increased creatin excretion following creatin ingestion at least over 40 per cent., but the metabolism was not stabilized, and the result was unsatisfactory. In the normal male adult, ingested creatin disappears. Normal blood sugar obtained for Case 8 (0.116 and 0.133) and a low normal figure (0.101) for Benedict's method was found in Case 9. Both patients showed a somewhat deficient glycogenesis without glycosuria following glucose ingestion (100 gm.). High blood creatinin and very high creatin were observed for Case 8, and high blood creatin for Case 9.

Such figures as we have obtained for blood fat (except as noted), blood cholesterol, hydrogen ion concentration of the blood, and plasma calcium are not to be regarded as significant.

19. Veeder, B. S., and Johnston, M. R.: Am. J. Dis. Child. **12**:136 (Aug.) 1916.

We found, as did McCrudden, no creatinuria in myasthenia gravis (Case 10). A rather low creatinin coefficient (7.1) was observed. There was a normal blood sugar rather than a hypoglycemia and a delayed storage of ingested glucose. Incidentally, combined therapy with calcium lactate, caffein citrate, desiccated whole pituitary substance, and epinephrin injections over a month resulted in no clinical improvement.

In the case of muscular atrophy resulting from acute anterior poliomyelitis in an adult (Case 11), there was creatinuria, a somewhat lowered creatinin coefficint of 7.6, and 58 per cent. of ingested creatin (1 gm.) was recovered. Normal blood sugar and glycogenesis were found.

A case of myositis ossificans (Case 12) is included in the present series. The metabolic picture is characterized by a high uric acid nitrogen, a low creatinin (coefficient 5.2), and no creatinuria. There was a daily nitrogen retention of 2.28 gm. and positive balances for calcium of 1.14 gm. and for magnesium of 0.46 gm. over a five day period.

Inasmuch as carbohydrate deficiency induces creatinuria (Mendel and Rose [20]), it has been argued that the faulty carbohydrate metabolism is responsible for the creatinuria in progressive pseudohypertrophic muscular dystrophy. We are inclined to believe that the atrophic dysfunction and actual diminution of the amount of muscle tissue are the conditions inducing the creatinuria, just as in the non-endocrine muscular atrophies where the carbohydrate metabolism is normal as in Case 11. The lowest creatinin coefficients occur in those cases in which the greatest muscular atrophy has occurred; likewise, the recovery of ingested creatin is greatest in the advanced cases. The creatinin and creatin figures are not particularly abnormal in the earlier atrophic changes of the disease, though the endocrine disturbance must be well established at that time. Again normal blood sugar may be obtained in the muscle dystrophy cases (Cases 4, 8 and 9; see also Cases 6 and 7) and even normal glycogenesis may be observed (Cases 2 and 4).

From the literature and our own observations, then, the outstanding metabolic features of progressive pseudohypertrophic muscular dystrophy are:

1. Those associated with the atrophic condition of the muscles, and which are intensified as the atrophy progresses:

1. Lowered creatinin excretion and creatinin coefficient.
2. Creatinuria.
3. Recovery in the urine of ingested creatin.
4. Creatinemia, though high blood creatins are not a constant finding.

20. Mendel, L. B., and Rose, W. C.: J. Biol. Chem. **10**:213, 1912.

2. Disturbances of carbohydrate metabolism of endocrine origin, usual but not constant findings.

1. Hypoglycemia.

2. Deficient glycogenesis following moderate glucose ingestion, and commonly without glycosuria.

The differential diagnosis of progressive pseudohypertrophic muscular dystrophy, myasthenia gravis, and progressive muscular atrophy may be checked according to McCrudden's suggestion by the metabolic and blood findings. The characteristic differences to be expected, with the addition of the glucose tolerance, are summarized as follows:

	Creatinuria	Blood Glucose	Glucose Tolerance
Progressive pseudohypertrophic muscular dystrophy	Present	Low	Diminished
Myasthenia gravis	Absent	Low or normal	Diminished
Progressive muscular atrophy	Present	Normal	Normal

There is little evidence on which to base a satisfactory therapeutic procedure for progressive pseudohypertrophic muscular dystrophy. McCrudden reports improvement in his case as the result of pituitary extract and epinephrin treatment, and a return of the blood sugar to normal. One patient (Case 1) in this series has apparently recovered, according to Dr. Steindler, so far as physical examination and strength tests may be depended on; we have not had the chance to make a further metabolic study. Whether or not the recovery was spontaneous with the prevention of overexertion and an adequate diet, or due to therapy with calcium lactate (0.3 gm., t.i.d.) is undetermined; calcium therapy was employed because of the suggested part it plays in carbohydrate metabolism (Underhill and Blatherwick [21]) and the reported favorable influence in other obscure myopathies. One patient (Case 3) has not improved on calcium lactate and dried whole pituitary gland. Pituitary extract (Parke, Davis, and Co., pituitrin, obstetric preparation) injections given daily for six weeks to one patient (Case 8) had little or no effect. All of the patients gained in weight and improved somewhat under conditions of hospitalization.

SUMMARY AND CONCLUSIONS

Seven cases of progressive pseudohypertrophic muscular dystrophy in boys and two adult male cases have been studied. One case each of myasthenia gravis, muscular atrophy following acute anterior poliomyelitis, and myositis ossificans are included in this report.

The progress of the atrophic condition of the muscular system in progressive pseudohypertrophic muscular dystrophy is indicated metabolically by a diminishing creatinin excretion and creatinin coefficient,

21. Underhill, F. P., and Blatherwick, N. R.: J. Biol. Chem. **19**:119, 1914.

by the creatinuria, and by the incomplete destruction of ingested creatin. The creatinin—creatin picture is quite similar to that in muscular atrophy where there is no disturbance of carbohydrate metabolism.

While hypoglycemia and deficient glycogenesis are characteristic for progressive pseudohypertrophic muscular dystrophy, normal blood sugar figures may be obtained, and normal glycogenesis may occur even when hypoglycemia is present.

McCrudden's metabolic differentiation (with the addition of glucose tolerance findings) of progressive pseudohypertrophic muscular dystrophy, myasthenia gravis, and progressive muscular atrophy is essentially confirmed and should be of value in the diagnosis of these conditions.

In a case of myositis ossificans, we have observed a diminished creatinin excretion without creatinuria, an increased output of uric acid, and positive nitrogen, calcium, and magnesium balances.

Apparent recovery over a period of a few months is reported in an early recognized typical case of progressive pseudohypertrophic muscular dystrophy. This case was a boy, 5 years of age.

The need of a study of the necropsy findings with special reference to the ductless glands in pseudohypertrophic muscular dystrophy is emphasized.

We are indebted to Dr. Arthur Steindler, who has referred several of the cases in this series to this laboratory for study.

The diets were calculated and prepared under the supervision of Miss Gertrude Whiteford and Miss Lela E. Booher.

ADDENDUM

Since this paper was written, we have studied another case of pseudohypertrophic muscular dystrophy in a boy, 10 years of age. The findings in this case bear out our contentions regarding the creatin and carbohydrate metabolism. The patient presented the characteristic picture of the disease; the atrophy had progressed to a stage intermediate between Cases 3 and 4. The clinical history and nitrogen metabolism are given under Case 13.

The creatinin coefficient was 2.2 and the total creatinin (creatinin plus creatin) coefficient was 5.6. About 60 per cent. of the 0.5 gm. creatin given by mouth was recovered for that day. Blood sugar was 0.144 per cent. and two hours after the ingestion of 44 gm. glucose it was 0.138 per cent., with the hourly urines negative for sugar. There was, therefore, a hyperglycemia and a normal sugar tolerance. Blood creatinin was 1.1 mg. and blood creatin was 5.2 mg. per hundred c.c. Blood cholesterol was 0.22 per cent. The basal metabolic rate was 51.8 calories per square meter of body surface per hour; the expected normal was 52 calories. The respiratory quotient was 0.85.

REPORT OF CASES

Case 1.—*Progressive pseudohypertrophic muscular dystrophy.*

E. T., white, male, 55 years of age, weight 18 kg. The condition was first noticed a month previous to admission to the hospital. He had always seemed normal, though easily fatigued. This patient has since discharge apparently recovered.

There was muscular atrophy as follows: adductors of the thumb; muscles of the thenar and hypothenar groups; muscles of the shoulder girdle; long muscles of the back; gluteal muscles; thigh muscles, and calf muscles. Histological examination of the muscle was characteristic for pseudohypertrophic dystrophy.

The case was transferred to the metabolism unit Oct. 22, 1919, and put on a nonpurin and noncreatin diet of 30 gm. protein, 37 gm. fat, and 125 gm. carbohydrate, the total calories being 1,000.

TABLE 2.—Urine Nitrogen Partition (Case 1)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
10/23	4.03	3.57	88.5	0.215	5.34	0.065	1.61	0.098	2.43	0.061	1.53	In bed
10/24	4.35	3.89	89.5	0.210	4.83	0.060	1.38	0.093	2.14	0.067	1.54	Active
10/25	3.96	3.45	86.5	0.195	4.92	0.058	1.47	0.089	2.25	0.066	1.66	Active
10/26	3.90	2.98	85.0	0.265	7.57	0.073	2.08	0.093	2.66	0.155	4.33	0.5 gm. creatin
10/27	3.50	2.64	75.4	0.262	7.49	0.058	1.66	0.089	2.54	0.055	1.57	

Case 2.—*Progressive pseudohypertrophic muscular dystrophy.*

D. R., white, male, 8 years of age, weight 21.8 kg. The patient first walked at 3 years of age, but could not turn. He tired easily. The condition was progressive. He was admitted to this hospital Nov. 17, 1919.

The patient had a distinctly asthenic gait; he walked with the legs abducted. There was contracture of the tendo Achillis of each leg, and the left foot showed a tendency to varus. Both calves were unusually developed. The muscles of the arms and back seemed normal.

While in the metabolism unit, he was on a diet of 35 gm protein, 45 gm. fat, and 115 gm. carbohydrate, with a caloric value of 1,000.

TABLE 3.—Urine Nitrogen Partition (Case 2)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
10/19	5.49	4.50	83.6	0.454	8.27	0.095	1.73	0.110	2.00	0.144	2.63	In bed
10/20	6.51	4.41	67.7	0.460	7.07	0.106	1.65	0.105	1.61	0.143	2.24	Active
10/21	4.76	3.72	78.1	0.335	7.04	0.103	2.17	0.114	2.51	0.108	4.00	0.5 gm. creatin
10/22	6.37	3.69	57.9	0.461	7.24	0.121	1.90	0.109	1.71	0.095	1.49	

Case 3.—*Progressive pseudohypertrophic muscular dystrophy.*

J. Schw., white, male, 6 years of age, weight 18.2 kg. The condition was noted at the time he began to walk, and was characterized by progressive muscular weakness. At the time of admission, the patient was unable to get up stairs, and had to brace himself when he got up from the floor.

There was a decided ataxic gait. The calf muscles were much enlarged. The arms were notably weakened. Lordosis was present.

Three boys by an earlier marriage of the mother had been similarly affected and died. An older brother of this patient by her present husband is one of our series (Case 6). One girl by the first marriage and two by the second are alive and well.

This case was under observation in the summer of 1919, and again in the winter of 1919-1920. Urinary nitrogen partition figures are given for the second admission. The diet was nonpurin and noncreatin. There were 30 gm. protein, 40 gm. fat and 150 gm. carbohydrate, with a total of 1,039 calories.

TABLE 4.—URINE NITROGEN PARTITION (CASE 3)

Day	Total N, Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N	
		Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
12/14	4.97	....	....	.....	....	0.091	1.83	0.048	0.97	0.089	1.79
12/15	4.55	....	....	.....	....	0.092	2.02	0.051	1.12	0.071	1.56
12/16	5.59	3.33	62.0	0.293	7.28	0.129	2.40	0.048	0.89	0.055	1.02
12/17	4.55	3.51	77.2	0.371	8.15	0.136	2.99	0.054	1.19	0.070	1.54
12/18	4.13	3.31	80.2	0.259	6.27	0.117	2.83	0.053	1.28	0.062	1.50
12/19	4.16	2.94	70.7	0.288	6.92	0.101	2.43	0.053	1.27	0.051	1.23

CASE 4.—*Progressive pseudohypertrophic muscular dystrophy.*

R. S., white, male, 9 years of age, weight 20 kg. The patient walked first at 2.5 years. The previous history of his illness was typical.

The patient walked with a peculiar gait, stumbled a great deal, but could get about slowly. He would get up from the floor only with difficulty, using the hands on the thighs; at times he could not get up unless assisted. The legs were weak and the ankles turned outward. There was lordosis, the scapulae were winged, and the calf muscles were pseudohypertrophied.

He was placed on a diet consisting of 32 gm. protein, 45 gm. fat, and 150 gm. carbohydrate, making a total of 1,165 calories, for a period from December 2 to Dec. 9, 1920. He was in the metabolism unit again during a second admission (Jan. 14, 1921) for an additional glucose tolerance test only.

TABLE 5.—URINE NITROGEN PARTITION (CASE 4)

Day	Total N Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
		Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
12/4	2.23	....	....	.....	....	0.072	3.23	0.042	1.88	0.036	1.61	
12/5	2.39	1.82	76.2	0.143	5.98	0.089	3.35	0.045	1.89	0.039	1.71	
12/6	2.00	1.49	74.8	0.105	5.26	0.098	4.91	0.035	1.75	0.029	1.46	
12/7	2.31	1.62	70.1	0.126	5.46	0.112	4.85	0.041	1.77	0.049	2.13	
12/8	2.70	1.99	73.7	0.102	3.78	0.125	4.64	0.051	1.89	0.145	5.38	0.5 gm. creatin
12/9	2.50	1.92	76.8	0.105	4.20	0.089	3.56	0.053	2.12	0.082	3.28	

The sulphur partition was determined on a composite sample of the urines for December 4 and 5. The results are given as grams of SO_3 per day

Total S, Gm.	Inorganic S		Ethereal S		Neutral S	
	Gm.	%	Gm.	%	Gm.	%
0.508	0.393	77.4	0.072	14.2	0.042	8.3

CASE 5.—*Progressive pseudohypertrophic muscular dystrophy; dystrophia adiposogenitalis (Frölich's syndrome).*

O. Schaf., white, male, 15 years old, height 140 cm., weight 90 kg. The condition was first noted eleven years previous to admission to the hospital (Nov. 28, 1919). He had not walked for three years. A sister is similarly affected. The patient died of influenzal pneumonia. The necropsy findings are discussed elsewhere in this paper.

The facies were typical for dystrophia adiposogenitalis. The muscles of the extremities, the thigh group, and the psoas appeared large and flabby. Flexion and extension of the arms, forearms, thighs and feet were little or

nil. The calf muscles were a fourth normal strength. On roentgen-ray examination, the sella turcica was irregular and indefinitely outlined; the antero-posterior diameter was 14 mm., the superior-inferior diameter 9 mm.

The patient was given a diet comprising 75 gm. protein, 70 gm. fat and 190 gm. carbohydrate, with a calorific value of 1,700.

TABLE 6.—URINE NITROGEN PARTITION (CASE 5)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
12/ 6	7.14	5.03	70.4	0.703	9.85	0.133	1.86	0.129	1.84	0.166	2.29	
12/ 7	7.70	5.17	67.1	0.503	6.53	0.171	2.22	0.075	0.97	0.250	3.25	
12/ 8	7.35	5.48	74.5	0.677	9.21	0.139	1.89	0.122	1.66	0.169	2.30	
12/ 9	8.33	5.87	71.3	0.706	8.58	0.172	2.09	0.082	0.99	0.218	2.65	
12/10	6.23	4.70	75.4	0.616	9.89	0.175	2.81	0.089	1.42	0.366	6.78	0.6 gm. creatin
12/12	9.06	6.54	72.1	0.687	7.58	0.208	2.30	0.092	1.02	0.269	2.96	
12/13	9.072	7.75	85.4	0.643	7.09	0.184	2.18	0.098	1.08	0.216	2.38	
12/19	9.02	7.24	80.3	0.528	5.97	0.190	2.10	0.079	0.88	0.278	3.08	
12/20	9.41	7.36	78.3	0.523	5.55	0.190	2.02	0.080	0.85	0.262	2.79	

CASE 6.—*Progressive pseudohypertrophic muscular dystrophy.*

Wm. Schw., white, male, 15 years of age, weight 21.3 kg. The condition was first noticed seven years previous to the first admission to the hospital (July 8, 1919). The history of the progress of the disease was typical. This case was an older brother to Case 3.

The patient could not walk. The muscular system was extremely atrophied, and there were contractures of the feet, knees, and flexion contracture of the hips. There was no motion in the shoulders, knees and hips, and but slight motion in the elbows and fingers. The back was considerably curved.

The urinary nitrogen figures below were obtained on the second admission. The diet for December 13-19 contained 30 gm. protein, 40 gm. fat and 150 gm. carbohydrate, with an energy value of 1,080 calories; for the later period, January 20-22, the patient was given 40 gm. protein, 40 gm. fat, and 150 gm. carbohydrate, equivalent to 1,120 calories. At this time he weighed 22.7 kg.

TABLE 7.—URINE NITROGEN PARTITION (CASE 6)

Day	Total N,	Urea N		Ammonia N		Uric Acid N		Creatin'n N		Creatin N	
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
12/13	4.20	2.64	62.9	0.363	8.64	0.109	2.60	0.029	0.69	0.122	2.91
12/14	3.99	3.13	78.4	0.440	11.0	0.136	3.41	0.057	0.68	0.111	2.78
12/17	4.89	2.59	52.9	0.384	7.84	0.125	2.47	0.028	0.57	0.160	3.27
12/18	3.78	2.56	67.7	0.280	7.41	0.122	3.23	0.030	0.79	0.149	3.95
12/19	4.20	3.34	79.5	0.293	6.98	0.123	2.93	0.073	0.79	0.153	3.64
1/20	5.04	3.53	70.0	0.321	6.37	.....	....	0.031	0.62	0.129	2.55
1/21	5.51	4.20	76.0	0.265	4.81	.....	....	0.033	0.60	0.126	2.29
1/22	4.97	3.76	75.6	0.367	7.36	.....	....	0.032	0.64	0.131	2.64

CASE 7.—*Progressive pseudohypertrophic muscular dystrophy.*

W. Stil., white, male, 12 years of age, weight 30.5 kg. The condition was first noted four years before admission (Sept. 5, 1919). The patient had not walked for two years. There was no familial history of the disease.

There was general muscular weakness, marked muscular atrophy (especially of the deltoids), and contractures of the hamstrings, toes and hips. The calf muscles showed the characteristic pseudohypertrophy.

The patient was observed for three months in the metabolism unit. At the time of his discharge he weighed 39 kg. The diet given for the metabolic period tabulated in Table 8 consisted of 32 gm. protein, 75 gm. fat and 200 gm. carbohydrate; the energy value was 1,600 calories.

TABLE 8.—URINE NITROGEN PARTITION (CASE 7)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
10/12	3.08	2.20	55.3	0.303	9.10	0.098	2.46	0.054	1.35	0.095	2.41	
10/13	3.01	2.16	71.4	0.238	7.91	0.067	2.23	0.047	1.56	0.100	3.32	
10/14	4.21	3.04	72.2	0.378	8.98	0.078	1.85	0.060	1.43	0.233	6.01	0.5 gm. creatin
10/15	3.59	2.30	64.1	0.288	8.03	0.057	1.59	0.059	1.31	0.127	3.54	
10/16	3.19	2.21	69.3	0.402	12.6	0.071	2.28	0.054	1.69	0.100	3.14	
10/17	3.12	2.16	69.2	0.411	13.2	0.073	2.34	0.053	1.69	0.099	3.17	
10/18	3.15	2.30	73.0	0.353	11.2	0.057	1.81	0.053	1.68	0.101	3.21	

CASE 8.—*Progressive pseudohypertrophic muscular dystrophy.*

B. McD., white, male, 22 years of age, weight 53 kg. The condition was first noted a year previous to entering the hospital. There was increasing weakness and the arms and shoulders were getting smaller. The patient's normal weight was 60 kg.

There was moderate lordosis and the trunk was tilted to the left. The neck muscles were normal as regards strength and motion. The shoulders were not winged. The biceps and triceps had a tendinous feel. The calf muscles had the firm consistency of pseudohypertrophy. The patient walked with a waddling gait, but was quite active.

The diet consisted of 70 gm. protein, 90 gm. fat and 250 gm. carbohydrate; the energy value was 2,000 calories. On days June 2 and June 3, 1920, the protein intake was raised to 95 gm.

TABLE 9.—URINE NITROGEN PARTITION (CASE 8)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
5/30	10.12	7.60	75.1	0.693	6.84	0.289	2.85	0.370	3.66	0.050	0.49	
5/31	9.03	7.26	80.3	0.619	6.86	0.217	2.41	0.396	4.39	0.027	0.29	
6/ 1	10.42	8.22	79.1	0.494	4.75	0.200	1.92	0.363	3.49	0.063	0.61	
6/ 2	13.16	11.21	85.2	0.686	5.21	0.234	1.78	0.390	2.96	0.058	0.44	Protein 95 gm.
6/ 3	14.20	11.94	84.1	0.661	4.66	0.278	1.61	0.399	2.81	0.078	0.55	Protein 95 gm.
6/ 8	7.81	6.34	81.1	0.608	7.78	0.212	2.71	0.375	4.80	0.051	0.77	
6/ 9	7.56	5.85	77.4	0.556	7.36	0.221	2.92	0.402	5.31	0.139	1.85	1 gm. creatin
6/10	7.73	6.40	82.8	0.601	7.78	0.238	3.08	0.428	5.50	0.000	0.00	

CASE 9.—*Progressive pseudohypertrophic muscular dystrophy* (juvenile form.)

O. Sm., white, male, 38 years of age, weight 50 kg. The condition was first noticed when the patient was 18 years old; enlargement of the calves and beginning atrophy of the muscles from the waist down were then noted.

There was general weakness, pronounced lordosis and enlarged calf muscles as compared with the remaining musculature. The trunk, shoulder and arm muscles were small.

The patient was transferred to the metabolism unit May 17, 1920. He was placed on a diet of 79 gm. protein, 100 gm. fat and 220 gm. carbohydrate, and equivalent to 2,172 calories. The metabolism was not sufficiently stabilized for a satisfactory creatin ingestion observation. (A part of the data obtained on this case will be used in another paper, and is not included here.)

TABLE 10.—URINE NITROGEN PARTITION (CASE 9)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
5/18	8.61	7.32	85.0	0.771	8.95	0.228	2.65	0.212	2.46	0.072	0.84	
5/19	6.63	5.54	83.5	0.546	8.23	0.176	2.03	0.180	2.71	0.176	2.65	1 gm. creatin
5/23	8.40	....	....	.....	....	.....	....	0.214	2.55	0.125	1.49	

Case 10.—*Myasthenia gravis.*

Geo. S., white, male, 51 years of age, weight 80 kg. The patient was admitted Sept. 4, 1919, complaining of increasing weakness of the arms and legs over a five year period.

There was bilateral external ophthalmoplegia and bilateral ptosis. Sensation of all types was normal. There was no ataxia of the upper or lower extremities. Knee jerk and plantar flexion were equal on both sides. Faradic stimulation of the anterior tibial group of muscles gave a poor response. Intermittent faradism induced fatigue of the flexors of the forearm, but the myasthenic reaction failed for the finger flexors.

The patient was in the metabolism unit for the period September 30 to October 4 only. The diet then given consisted of 51 gm. protein, 90 gm. fat, and 300 gm. carbohydrate, or 2,275 calories. A nonmeat and nonsoup diet was given September 5, and a general diet on September 24.

TABLE 11.—Urine Nitrogen Partition (Case 10)

	Total N.	Ammonia N		Uric Acid N		Creatinin N		Creatin N		
Day	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Remarks
9 5	12.23	.....	....	0.112	0.92	0.543	4.44	0.000	0.00	Nonpurine diet
9/24	8.79	.....	....	0.199	2.26	0.579	6.58	0.000	0.00	General diet
10/ 1	6.14	0.422	6.87	0.101	1.64	0.564	9.18	0.000	0.00	
10 3	5.80	0.398	6.86	0.078	1.34	0.564	9.72	0.000	0.00	

Case 11.—*Acute anterior poliomyelitis.*

L. W., white, male, 25 years of age, weight 63 kg. The patient entered the hospital Sept. 2, 1920, complaining of inability to walk without aid. The condition developed just previous to admission.

The arms were normal in strength with no tremor or ataxia. The legs were held in normal position in the bed, and the muscle tonus at rest was normal. The patient was unable to raise any part of the right leg; he flexed the left knee 50 per cent., but could not raise the foot. Faradic stimulation showed the least response over the right buttock and thigh. There was a 25 per cent. response on the right calf and a 5 per cent. response on the right anterior tibial group. Sensation was normal.

While in the metabolism unit, the patient was given 75 gm. protein and from 2,000 to 2,500 calories daily.

TABLE 12.—Urine Nitrogen Partition (Case 11)

	Total N.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		
Day	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Remarks
10/3	14.43	10.72	74.3	0.690	4.78	0.154	1.07	0.480	3.32	0.055	0.38	
10/4	12.63	9.13	72.3	0.667	5.28	0.134	1.06	0.478	3.78	0.074	0.58	
10/5	12.55	9.78	78.1	0.717	5.81	0.122	0.98	0.451	3.65	0.024	0.19	
10/6	12.05	9.46	78.5	0.616	5.11	0.139	1.15	0.436	3.62	0.259	2.15	1 gm. creatin
10/7	12.45	10.57	84.9	0.787	6.32	0.126	1.01	0.437	3.51	0.078	0.47	

Case 12.—*Myositis ossificans; chronic endocarditis, mitral stenosis and cardiac decompensation.*

Geo. F., white, male, 26 years of age, weight 54 kg. The patient was admitted to this hospital April 13, 1920. The duration of his illness was given as 18 months. It started with rheumatic symptoms.

The muscles of the trunk had a normal feel. The joints, except the hips and ankles were stiff and swollen. movements being restricted. The deltoid muscles seemed atrophied; the biceps and triceps were small. The muscles of the forearms had a bony feel. The thigh and calf muscles seemed hard and fibrous throughout.

The patient was transferred to the metabolism unit. He was placed on a nonpurin and noncreatin diet of 75 gm. protein, 72 gm. fat and 243 gm. carbohydrate, a total of 1,926 calories.

TABLE 13.—URINE NITROGEN PARTITION (CASE 12)

Day	Volume, C.c.	Specific Gravity	Total N, Gm.	Urea N Gm.	Urea N %	Ammonia N Gm.	Ammonia N %	Uric Acid N Gm.	Uric Acid N %	Creatinin N Gm.	Creatinin N %	Creatin N Gm.	Creatin N %
4/17	575	1.026	8.45	6.51	77.0	0.488	5.77	0.303	3.58	0.289	3.41	0.000	0.00
4/18	600	1.030	8.99	7.20	80.1	0.567	5.25	0.385	4.28	0.283	3.15	0.000	0.00
4/19	700	1.029	9.41	7.27	77.2	0.599	6.37	0.302	3.21	0.283	3.01	0.000	0.00
Balance period April 20-24 inc.													
Average per day....			9.62	....	....	.....	....	0.332	3.45	0.283	2.94		

	N Balance per Day, Gm.	Ca Balance for Period, Gm.	Mg Balance for Period, Gm.
Food	12.97	5.838	2.147
Urine	9.62	0.105	0.197
Stools	1.02	4.597	1.489
Total	10.69	4.702	1.686
Balance	+2.28	+1.136	+0.461

CASE 13.—*Progressive pseudohypertrophic muscular dystrophy.*

C. O., white, male, 10 years of age, weight 25 kg. The patient was referred to the medical service June 15, 1921.

The patient presented the characteristic picture of progressive pseudohypertrophic muscular dystrophy. There was lordosis and the patient walked with a waddling gait. When placed in a lying position on the floor and instructed to arise, he rolled on the side and pushed himself to a sitting position, but could not get up. He would stand with his feet widely apart in the characteristic lordotic position. The calf muscles were markedly hypertrophied.

TABLE 14.—URINE NITROGEN PARTITION (CASE 13)

Day	Total N, Gm.	Creatinin N Gm.	Creatinin N %	Creatin N Gm.	Creatin N %	Remarks
6/15	3.68	0.046	1.32	0.078	2.12	
6/16	4.30	0.055	1.28	0.098	2.28	
6/17	4.55	0.057	1.25	0.081	1.78	
6/18	4.13	0.065	1.57	0.169	4.09	0.5 gm. creatin by mouth

The diet given consisted of 46 gm. protein, 70 gm. fat and 175 gm. carbohydrate, the total calories being 1,564.

THE NITROGEN REQUIREMENT FOR MAINTENANCE IN DIABETES MELLITUS*

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The general acceptance of the principle of restriction of the total caloric intake in the dietetic management of diabetes mellitus in contrast to the older principle of overfeeding has increased the importance of an accurate knowledge of the minimum amount of protein that will maintain nitrogenous equilibrium in the diabetic patient. The ultimate effect of long continued gradual loss of body nitrogen is not known, but it seems probable that such a condition is very undesirable. The subject whose nitrogen excretion is constantly higher than his nitrogen ingestion is certainly suffering for want of one of the most important of the tissue repairing elements, and a diet so arranged as to induce this negative balance, even though not lethal, must produce a severe grade of inanition.

The following experiments were undertaken in an effort to determine the minimum protein ingestion that will safely maintain nitrogen balance in patients with diabetes mellitus.

1. The usual method of determining the state of the nitrogen equilibrium was followed, namely, the balancing of the nitrogen in the food against the nitrogen in the urine and stools. Because of the difficulties in the way of collecting specimens from women, male patients were used. Their ages vary from 18 to 80 years. The severity of the disease also varied, as can be seen from the protocols, but over half were of the more severe types. In general, we chose the more intelligent patients as the ones most likely to cooperate with us by strict adherence to diet and in the collection of specimens, and care was taken to impress each of them with the importance of this cooperation.

The diets were arranged by an expert dietitian, and their delivery to the patients was carefully supervised by an unusually competent nurse. Copies of the diet lists were delivered to us daily, and were frequently checked against the ward reports. Uneaten portions were measured and deducted. The nitrogen content was determined by dividing the protein by 6.25, and the protein was estimated by use of

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Atwater and Bryant's food tables.[1] The heat value of 1 gm. fat was considered 9 calories and of 1 gm. protein or carbohydrate as 4 calories.

The nitrogen determinations on the stools, and on the urines of about half the cases were made by the Kjeldahl method, and on the remaining urines by the Folin micro-Kjeldahl method, after the two methods had been checked against each other. In some cases the quantitative nitrogen determinations were made daily; in the others aliquot parts of the acidified daily specimens were used. The stools were collected for several days, and their nitrogen content divided equally among the days during which they were passed. In a few cases, where nitrogen determinations on the stool are not available, the nitrogen excreted by this route has been estimated as 0.75 gm. daily. Since the nitrogen of the stool is only in small part derived from the unresorbed products of protein digestion, and since it is not directly dependent for its quantity on the food nitrogen, this is thought more accurate than the estimation of Mosenthal and Harrop[2] that 10 per cent. of the ingested nitrogen is excreted in the stool. Rieder[3] found a fecal excretion of 0.54, 0.87 and 0.78 gm. nitrogen daily from a man fed on a protein-free diet. The average fecal nitrogen of those cases in our series who were in balance on small amounts of ingested nitrogen, and who were not undergoing active catharsis was about 0.77 gm. daily.

In most cases, the nitrogen studies were incidental to the treatment, and in only a few was an effort made to find the lowest level at which nitrogen balance could be established. It is probable that had such an effort been made it would have given us lower figures for some of the patients. The treatment used was the low protein, high fat, low carbohydrate diets previously described by Newburgh and Marsh.[4] These diets were arranged with the intention of satisfying the caloric needs.

REPORT OF CASES

Case 1 (19-293).—Patient was an American school teacher, aged 56, who entered the hospital, June 9, 1919, complaining of weakness. There was no history of diabetes in the family. The symptoms appeared five years before, with polyuria, polyphagia and polydipsia. There had been gradually increasing weakness, with obstinate constipation and mental depression. Nothing of

1. Atwater and Bryant: The Chemical Composition of American Food Materials, U. S. Dept. Agriculture, Bull. No. 28, 1906.

2. Mosenthal, H. O., and Harrop, G. A.: The Comparative Food Value of Protein, Fat and Alcohol in Diabetes Mellitus as Measured by the Nitrogen Equilibrium, Tr. Assn. Am. Phys. **33**:302, 1918; also Arch. Int. Med. **22**:750 (Nov.) 1918.

3. Rieder, H.: Bestimmung der Menge des im Kothe befindlichen, nicht von der Nahrung herrührenden Stickstoffes, Ztschr. f. Biol., N. F. **2**:378, 1884.

4. Newburgh, L. H., and Marsh, P. L.: The Use of a High Fat Diet in the Treatment of Diabetes Mellitus, Arch. Int. Med. **26**:647 (Dec.) 1920.

importance was found on physical examination. His blood sugar was 0.55 per cent., and his urine contained 50 gm. glucose per 1,000 c.c.

On a diet containing 16 gm. protein, 100 gm. fat and 10 gm. carbohydrate, with a total of about 1,000 calories, his urine became free of sugar on the fourth day, his ferric chlorid reaction became negative on the fifth day and his blood sugar had fallen to 0.14 per cent. on the sixth day. On an oatmeal diet, which was given him a few days later, and which contained 9 gm. protein, 155 gm. fat and 31 gm. carbohydrate, a total of 1,550 calories, his blood sugar rose to 0.23 per cent. and glycosuria returned. A day of starvation sufficed to clear his urine of sugar. The nitrogen determinations

TABLE 1.—PART OF RECORD OF CASE 1

	Food				Urine		Blood	Nitrogen				
Date 1919	Protein. Gm.	Fat. Gm.	Carbohydrate. Gm.	Calories	Glucose. Gm.	Diacetic	Sugar. per Cent.	Urine.* Gm.	Stool.† Gm.	In. Gm.	Out. Gm.	Balance. Gm.	Wt., Lbs.
7/1	16.0	97.4	9.1	975	0	+	....	5.74	0.50	2.56	6.24	—3.68	....
2	16.4	101.5	6.3	1,005	0	0	....	5.74	0.50	2.62	6.24	—3.62	....
3	16.6	96.8	11.3	980	0	0	....	5.74	0.50	2.66	6.24	—3.58	....
4	16.6	99.3	9.5	1,000	0	0	....	5.74	0.50	2.66	6.24	—3.58	....
5	15.2	93.1	10.7	940	0	0	....	5.74	0.50	2.45	6.24	—3.79	....
6	15.5	95.7	9.9	965	0	++	....	5.74	0.50	2.48	6.24	—3.76	....
7	17.3	100.5	10.3	1,015	0	0	....	5.74	0.50	2.77	6.24	—3.47	....
8	17.1	93.8	14.3	970	0	0	0.08	5.74	0.50	2.74	6.24	—3.50	....
9	17.1	93.8	14.3	970	0	0	....	5.74	0.50	2.74	6.24	—3.50	....
	Patient away from hospital for two weeks but did not adhere to diet												
22	....	....	....	....	+	0	0.25	....	....	....	....	.....	....
23	16.3	97.4	9.7	980	0	0	....	6.14	0.73	2.61	6.87	—4.26	142.5
24	16.3	97.4	9.7	980	0	0	....	6.14	0.73	2.61	6.87	—4.26	....
25	16.3	97.4	9.7	980	0	0	0.09	6.14	0.73	2.61	6.87	—4.26	....
26	16.3	97.4	9.7	980	0	0	....	6.14	0.73	2.61	6.87	—4.26	....
27	16.3	97.4	9.7	980	0	0	....	6.14	0.73	2.61	6.87	—4.26	....
28	16.3	97.4	9.7	980	0	0	0.11	6.14	0.73	2.61	6.87	—4.26	....
29	16.0	97.4	8.9	975	0	0	....	5.68	0.53	2.56	6.21	—3.65	....
30	10.7	59.9	5.3	605	0	0	....	5.68	0.53	1.71	6.21	—4.50	....
31	15.7	96.3	9.0	965	0	0	....	5.68	0.53	2.51	6.21	—3.70	....
8/1	18.4	135.0	4.8	1,310	0	0	0.08	5.68	0.53	2.94	6.21	—3.27	141.5
2	17.5	125.4	6.5	1,225	0	0	....	5.68	0.53	2.80	6.21	—3.41	....
3	17.5	125.4	6.5	1,225	0	0	....	5.68	0.53	2.80	6.21	—3.41	....
4	32.2	156.8	8.2	1,575	0	0	0.10	5.28	0.44	5.15	5.72	—0.57	....
5	33.8	157.0	8.0	1,580	0	0	....	5.28	0.44	5.41	5.78	—0.81	140
6	33.5	157.0	7.5	1,575	0	0	....	5.28	0.44	5.35	5.72	—0.37	....
7	33.5	157.0	7.5	1,575	0	0	....	5.28	0.44	5.35	5.72	—0.37	....
8	36.4	163.0	7.5	1,645	0	0	....	5.28	0.44	5.82	5.72	+0.10	....
9	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	....
10	34.3	168.4	6.9	1,680	0	0	0.10	5.23	0.40	5.49	5.63	—0.14	....
11	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	....
12	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	140
13	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	....
14	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	....
15	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	137
16	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	....
17	34.3	168.4	6.9	1,680	0	0	0.10	5.23	0.40	5.49	5.63	—0.14	138

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

were begun a week later. It will be seen from Table 1 that a diet containing 34 gm. protein and 1,680 calories, with only 7 gm. carbohydrate practically established nitrogen equilibrium. This represents 0.54 gm. protein and 26 calories per kilogram of body weight.

CASE 2 (19-306).—Patient was a very mild diabetic, an American, 66 years of age, attendant at a state hospital for the insane. His symptoms were few, beginning three years before with thirst and polyuria. He had been on no diet before entrance to the hospital, June 30, 1919, except that he avoided "sweets." Two days of a low caloric diet sufficed to render his urine sugar free, and his blood sugar was found to be normal on the tenth day. No difficulty was met in establishing nitrogen equilibrium with an intake of two-

thirds gram of protein and from 33 to 40 calories per kilogram of body weight. Part of his record is presented in Table 2.

CASE 3 (19-391).—Patient was an American factory inspector, who entered the surgical clinic for a herniotomy, and to obtain treatment for an infected leg. There was no diabetes in the family, and the patient had been well until six or eight years ago, weighing about 215 pounds. During the past few years he had noticed that he drank unusually large quantities of water and that he urinated frequently and copiously. His weight gradually fell to about 135 pounds, but he felt well and worked every day. Three weeks before entrance he injured his right leg. The wound became infected, was drained, but healed very slowly, and at the time of entrance was still draining pus. Except for the emaciation and dry skin, nothing of importance was noted in the examination. Throughout his stay in the medical ward he was afebrile.

The data from his study are presented in Table 3. The nitrogen studies were started after his blood sugar had been brought to normal by a diet containing 16 gm. protein, 100 gm. fat, 10 gm. carbohydrate and about 1,000 calories. It will be noted that on this diet his nitrogen output was large,

TABLE 2.—PART OF RECORD FROM CASE 2

	Diet				Urine				Blood Sugar,	Nitrogent			
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories,	Amount, c.c.	Glucose, Gm.	Diacetic	N.* Gm.	per Cent.	Stool, Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
7/23	16.3	97.4	9.7	980	1,610	0	0	4.19	0.14	0.60	2.61	4.79	−2.18	141
24	16.3	97.4	9.7	980	820	0	0	4.19	....	0.60	2.61	4.79	−2.18	...
25	36.2	219.2	11.4	2,165	990	0	0	4.19	....	0.60	5.79	4.79	+1.00	...
26	36.2	219.2	11.4	2,165	825	0	0	4.19	....	0.60	5.79	4.79	+1.00	...
27	36.2	219.2	11.4	2,165	710	0	0	4.19	....	0.60	5.79	4.79	+1.00	...
28	36.2	219.2	11.4	2,165	725	0	0	5.61	0.12	0.55	5.79	6.16	−0.37	...
29	35.8	219.1	10.6	2,155	1,255	0	0	5.61	....	0.55	5.79	6.16	−0.37	141
30	36.2	219.2	11.4	2,165	970	0	0	5.61	....	0.55	5.79	6.16	−0.37	...
31	36.2	219.2	11.4	2,165	925	0	0	5.61	....	0.55	5.79	6.16	−0.37	...
8/ 1	41.5	243.8	14.8	2,420	1,360	0	0	5.61	....	0.55	6.64	6.16	+0.48	...
2	41.5	243.8	14.8	2,420	1,130	0	0	5.61	....	0.55	6.64	6.16	+0.48	...
3	47.3	259.4	13.3	2,585	1,175	0	0	5.61	0.11	0.55	7.57	6.16	+1.41	...
4	45.8	222.6	13.2	2,240	990	0	0	4.80	....	1.28	7.33	6.08	+1.25	...
5	46.1	238.8	13.2	2,560	1,100	0	0	4.80	....	1.28	7.37	6.08	+1.29	143
6	33.7	231.7	13.2	2,360	1,000	0	0	4.80	....	1.28	5.39	6.68	−0.69	...
7	46.1	238.8	13.2	2,580	1,190	0	0	4.80	....	1.28	7.37	6.08	+1.29	...
8	46.1	238.8	13.2	2,290	1,475	0	0	4.80	0.10	1.28	7.37	6.08	+1.29	145

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

amounting to nearly 14 gm. daily. With the addition of moderate amounts of protein and large quantities of fat to his diet, the nitrogen elimination gradually decreased until it reached about 8 gm. a day. This very mild diabetic with a body weight of 60 kilograms did not establish nitrogenous equilibrium on 40 gm. protein, during the few days allowed. Two explanations may be offered: First, it may have been that not enough time was allowed; this factor will be discussed later; or, second, that there was an increased destruction of protein as a result of his chronic infection. Balance was readily established by a diet containing 0.90 gm. protein and 42 calories per kilogram of body weight.

CASE 4 (19-444).—Patient was an American farmer, 18 years old, who entered the hospital Sept. 5, 1919, complaining of weakness and excessive thirst. On one occasion, at the age of 14, he vomited a large quantity of blood. He noticed his polyuria and thirst a year and a half before; this was associated with increasing weakness. A physician found sugar in his urine, and under treatment the patient remained sugar-free for four months. After this he returned to an ordinary diet, and his weakness gradually increased. His best weight had been 135 pounds, two years before, and his weight at entrance was 95 pounds. For a year he had had crop after crop of boils.

Examination showed an emaciated young man with several boils on his hands and one on the left temporal region. The tendon reflexes were obtained only on reinforcement. The blood sugar was 0.525 per cent.

On a diet containing 16 gm. protein, 100 gm. fat and 10 gm. carbohydrate, with a total of 1,000 calories, his blood sugar fell to 0.20; at this time he left the hospital without permission, and ate a large quantity of carbohydrate. It was not until September 22 that his urine became free from sugar, and on September 25 his blood sugar was 0.15 per cent. A diet containing 28 gm. protein and 1,600 calories, representing 0.67 gm. protein and 38 calories per kilogram of body weight was found to establish nitrogen balance. Data from his case are presented in Table 4.

CASE 5 (19-537).—Patient, an American mailcarrier, 21 years of age, entered the hospital, Oct. 22, 1919, complaining of loss of strength. He had always been in excellent health until the onset of his diabetes a year before. His

TABLE 3.—PART OF RECORD FROM CASE 3

	Food				Urine			Blood Sugar	Nitrogen					
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
8/21	16.3	97.4	9.7	970	1,775	0	0	0.08	....	....	....	....	.....	134
22	16.3	97.4	9.7	970	2,272	0	0	0.09	....	....	....	....	.....	...
Average	16.3	97.4	9.7	970	.....	..	..	....	12.68	1.17	2.61	13.85	—11.24	
25	30.0	128.0	10.3	1,315	2,350	0	0	....	....	....	....	....	.....	...
26	29.6	144.0	9.5	1,450	2,460	0	0	....	....	....	....	....	.....	130
27	29.6	150.0	9.1	1,500	3,470	0	0	0.13	....	....	....	....	.....	...
28	30.1	158.0	10.7	1,615	4,825	0	0	....	....	....	....	....	.....	129
Average	29.8	138.0	9.9	1,400	.....	..	..	....	9.96	1.85	4.77	11.81	—7.04	
9/1	40.3	219.0	12.6	2,185	1,125	0	0	0.11	....	....	....	....	.....	...
2	40.6	234.0	13.4	2,320	1,660	0	0	....	....	....	....	....	.....	...
3	41.5	228.0	13.4	2,270	1,550	0	0	....	....	....	....	....	.....	128
Average	40.8	227.0	13.1	2,260	.....	..	..	....	7.19	1.23	6.53	8.42	—1.89	
4	54.1	240.0	13.4	2,430	1,830	0	0	0.10	....	....	....	....	.....	...
5	54.1	240.0	13.4	2,430	1,825	0	0	....	....	....	....	....	.....	128
6	54.1	240.0	13.4	2,430	1,900	0	0	0.10	....	....	....	....	.....	...
7	54.1	240.0	13.4	2,430	1,125	0	0	....	....	....	....	....	.....	...
8	54.1	240.0	13.4	2,430	1,135	0	0	0.12	....	....	....	....	.....	129
Average	54.1	240.0	13.4	2,430	.....	..	..	....	7.01	1.11	8.66	8.12	+0.54	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

only symptoms have been extreme weakness, a ravenous appetite, and a moderate polyuria. His weight fell from 165 to 119 pounds. Soon after the beginning of the diabetes he was placed by his physician on a diet consisting chiefly of milk, eggs, bran flour and fruit. The symptoms had become increasingly more severe. Examination showed a moderate emaciation, dry skin and absent knee reflexes.

On a diet containing 22 gm. protein, 110 gm. fat and 10 gm. carbohydrate, a total of 1,100 calories, he was sugar-free on the ninth day, though it was nearly a month before his blood sugar was found to be normal. It will be noted from the table that with a protein intake of 37.8 gm. and a total intake of 1,380 calories, he showed a negative balance of 2.11 and 2.83 gm. nitrogen, respectively, during the two periods in which the determinations were made, but that this fell to practical equilibrium when the total calories were raised to 1,650, though the protein and carbohydrate in the diet were unchanged. The diet contained 0.76 gm. protein and 36 calories per kilogram of body weight.

External circumstances made it necessary to discontinue the determinations before we were entirely finished. The large nitrogen content of the stool is explained by the fact that the patient took one-half ounce of magnesium sulphate daily.

TABLE 4.—PART OF RECORD FROM CASE 4

	Diet				Urine			Blood Sugar, per Cent.	Nitrogen			
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic		Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
9 30	24.9	141.4	9.9	1,410	2,500	0	0	....	....	....	....	....	.....	85 5
10/ 1	24.9	141.4	9.9	1,410	2,500	0	0	....	....	....	....	....	.....	85
2	24.9	141.4	9.9	1,410	2,250	0	0	0.16	....	....	....	....	.....	84
3	24.9	141.4	9.9	1,410	2,750	0	0	....	....	....	....	....	.....	84.5
4	24.9	141.4	9.9	1,410	1,510	0	0	....	....	....	....	....	.....	85
5	24.9	141.4	9.9	1,410	2,650	0	0	....	....	....	....	....	.....	86
6	24.9	141.4	9.9	1,410	2,085	0	0	....	....	....	....	....	.....	86
7	24.9	141.4	9.9	1,410	1,200	0	0	0.15	....	....	....	....	.....	86.2
Average	24.9	141.4	9.9	1,410	.....	..	..	....	6.71	0.94	3.98	7.65	—3.67	
8	24.9	141.4	9.9	1,410	.....	0	0	....	....	....	....	....	.....	88
9	24.9	141.4	9.9	1,410	.....	0	0	....	....	....	....	....	.....	87
10	24.9	141.4	9.9	1,410	.....	0	0	0.13	....	....	....	....	.....	88
11	36.8	192.9	9.9	1,925	2,500	0	0	....	....	....	....	....	.....	88
12	36.8	192.9	9.9	1,925	2,585	0	0	0.13	....	....	....	....	.....	88.5
13	36.8	192.9	9.9	1,925	2,800	0	0	....	....	....	....	....	.....	88
14	36.8	192.9	9.9	1,925	2,050	0	0	....	....	....	....	....	.....	88
15	36.8	192.9	9.9	1,925	1,460	0	0	0.18	....	....	....	....	.....	88
16	36.8	192.9	9.9	1,925	2,600	0	0	....	....	....	....	....	.....	88
17	36.8	192.9	9.9	1,925	1,750	0	0	....	....	....	....	....	.....	87
Average	36.8	192.9	9.9	1,925	.....	..	..	....	5.38	0.93	5.89	6.31	—0.42	
18 to 21	36.8	192.9	9.9	1,925	.....	..	..	....	....	....	....	....	.....	88
22	36.8	192.9	9.9	1,925	1,055	0	0	....	....	....	....	....	.....	89.5
23	36.8	192.9	9.9	1,925	1,115	0	0	....	....	....	....	....	.....	90
24	36.8	192.9	9.9	1,925	1,420	0	0	0.15	....	....	....	....	.....	92.5
Average	36.8	192.9	9.9	1,925	.....	..	..	....	4.86	0.91	5.89	5.77	+0.12	
25	36.8	166.2	9.9	1,685	.....	0	0	....	....	....	....	....	.....	92.5
26	36.8	166.2	9.9	1,685	1,430	0	0	....	....	....	....	....	.....	93.5
27	36.8	166.2	9.9	1,685	1,535	0	0	....	....	....	....	....	.....	94
28	36.8	166.2	9.9	1,685	1,500	0	0	....	....	....	....	....	.....	94.5
29	36.8	166.2	9.9	1,685	2,000	0	0	....	....	....	....	....	.....	94.5
30	36.8	166.2	9.9	1,685	1,710	0	0	....	....	....	....	....	.....	94.5
31	36.8	166.2	9.9	1,685	2,470	0	0	....	....	....	....	....	.....	94.2
Average	36.8	166.2	9.9	1,685	.....	..	..	....	2.43	0.42	5.89	2.85	+3.04	
11-1	36.8	166.2	9.9	1,685	2,030	0	0	....	....	....	....	....	.....	94.5
2	36.8	166.2	9.9	1,685	2,420	0	0	....	....	....	....	....	.....	93
3	36.8	166.2	9.9	1,685	1,760	0	0	....	....	....	....	....	.....	83
Average	36.8	166.2	9.9	1,685	.....	..	..	....	2.97	0.45	5.89	3.42	+2.47	
4	28.1	162.8	9.9	1,615	1,850	0	0	....	....	....	....	....	.....	92.5
5	28.1	162.8	9.9	1,615	2,120	0	0	....	....	....	....	....	.....	92.5
6	28.1	162.8	9.9	1,615	1,600	0	0	....	....	....	....	....	.....	92
7	28.1	162.8	9.9	1,615	1,920	0	0	0.15	....	....	....	....	.....	91.5
Average	28.1	162.8	9.9	1,615	.....	..	..	....	2.97	0.45	4.49	3.42	+1.07	
8-10	28.1	162.8	9.9	1,615	.....	0	0	....	....	....	....	....	.....	92
11	28.1	162.8	9.9	1,615	2,225	0	0	....	....	....	....	....	.....	91.5
12	28.1	162.8	9.9	1,615	2,365	0	0	....	....	....	....	....	.....	92.2
13	28.1	162.8	9.9	1,615	2,425	0	0	....	....	....	....	....	.....	92.5
14	28.1	162.8	9.9	1,615	1,950	0	0	....	....	....	....	....	.....	92
Average	28.1	162.8	9.9	1,615	.....	..	..	....	1.21	1.15	4.49	2.36	+2.13	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

CASE 6 (19-567).—Patient was a German coal dealer, 49 years of age, who entered the hospital, Nov. 11, 1919, complaining of weakness and polyuria. There was no history of diabetes in the family. He had always eaten heartily, but did not care for sweets and pastries. His symptoms first appeared eight

weeks ago, with increased thirst and polyuria, progressive weakness and loss of weight, the latter amounting to 30 pounds. A physician placed him on a diet consisting of eight slices of gluten bread, and half a dozen eggs daily, with all the meat he wanted. A second physician gave him nothing but milk and oatmeal. He noticed no improvement from either. There has been some numbness of the hands and feet, some constipation and no visual disturbances. Examination showed fair nourishment, with a dry skin. The tonsils were septic and the teeth in poor condition. There was moderate arteriosclerosis; the tendon reflexes were active.

TABLE 5.—PART OF RECORD FROM CASE 5

	Diet				Urine			Blood Sugar.	Nitrogen				
Date 1919	Protein. Gm.	Fat. Gm.	Carbohydrate. Gm.	Calories	Amount. C.c.	Glucose. Gm.	Diacetic	per Cent.	Urine.* Gm.	Stool.† Gm.	In. Gm.	Out. Gm.	Balance. Gm.	Wt., Lbs.
10/23	21.6	109.2	9.9	1,110	4,000	++++	+	0.30	....	....	....	....	.....	124
24	21.6	109.2	9.9	1,110	3,300	+++	+	....	....	....	....	....	.....	...
25	21.6	109.2	9.9	1,110	.....	+++	+	....	....	....	....	....	.....	...
26	21.6	109.2	9.9	1,110	1,800	++	+	....	....	....	....	....	.....	...
27	21.6	87.8	8.5	900	1,630	+	+	0.21	....	....	....	....	.....	119
28	15.5	42.1	9.5	480	1,530	++	+	....	....	....	....	....	.....	...
29	15.3	41.1	9.0	465	1,090	+	tr	....	....	....	....	....	.....	120
30	15.3	41.1	9.0	465	1,580	+	tr	....	....	....	....	....	.....	...
31	15.5	41.7	9.5	475	1,875	0	tr	....	....	....	....	....	.....	...
11/ 1	15.3	41.6	9.0	470	2,100	0	0	....	....	....	....	....	.....	122
2	15.5	41.7	9.5	475	2,430	0	0	....	....	....	....	....	.....	...
3	15.6	41.7	9.9	475	2,120	0	0	0.18	....	....	....	....	.....	120
Average	15.4	41.6	9.4	475	.....	..	..	....	8.50	0.84	2.47	9.34	−6.87	
4-5	37.4	133.7	8.0	1,380	2,450	0	0	....	....	....	....	....	.....	...
6	37.4	133.7	8.0	1,380	2,860	0	0	0.19	....	....	....	....	.....	116
7	37.4	133.7	8.0	1,380	2,825	0	0	....	....	....	....	....	.....	...
8	37.4	133.7	8.0	1,380	2,170	0	0	....	....	....	....	....	.....	114
9	37.4	133.7	8.0	1,380	2,500	0	0	....	....	....	....	....	.....	...
Average	37.4	133.7	8.0	1,380	.....	..	..	....	8.26	0.56	5.99	8.82	−2.83	
10-11	37.4	133.7	8.0	1,380	.....	0	0	....	....	....	....	....	.....	...
12	37.4	133.7	8.0	1,380	2,750	0	0	....	....	....	....	....	.....	113
13	37.4	133.7	8.0	1,380	3,500	0	0	....	....	....	....	....	.....	...
14	37.4	133.7	8.0	1,380	3,300	0	0	....	....	....	....	....	.....	...
Average	37.4	133.7	8.0	1,380	.....	..	..	....	6.75	1.35	5.99	8.10	−2.11	
15-18	37.4	133.7	8.0	1,380	.....	0	0	0.13	....	....	....	....	.....	113
19	37.6	147.6	8.0	1,510	.....	0	0	....	....	....	....	....	.....	...
20	37.6	165.6	8.3	1,675	.....	0	0	....	....	....	....	....	.....	116
21	37.6	165.3	8.3	1,675	.....	0	0	....	....	....	....	....	.....	...
22	37.6	165.6	8.3	1,675	3,670	0	0	....	....	....	....	....	.....	...
23	37.8	162.6	8.3	1,640	4,025	0	0	0.14	....	....	....	....	.....	118
24	37.6	163.6	8.2	1,650	4,000	0	0	....	....	....	....	....	.....	...
25	37.8	163.4	8.2	1,650	2,920	0	0	....	....	....	....	....	.....	...
26	37.8	163.6	8.2	1,650	3,955	0	0	....	....	....	....	....	.....	...
27	37.8	163.6	8.2	1,650	4,380	0	0	....	....	....	....	....	.....	120
Average	37.7	163.7	8.2	1,650	.....	..	..	....	5.11	1.51	6.05	6.62	−0 57	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

On the fifth day of a diet containing 16 gm. protein, 100 gm. fat and 10 gm. carbohydrate, a total of 1,000 calories, his urine was free from sugar, and on the tenth day the ferric chlorid reaction became negative. He was given a diet containing 65 gm. protein and 2.065 calories, and was able to add 2.6 gm. nitrogen to his body daily for several days. After a few days, his nitrogen output increased, and he was practically in balance. Part of his record is presented in Table 6.

Case 7 (20-18).—Patient, a locomotive fireman, 22 years of age, first entered the hospital, Jan. 16, 1920, complaining of excessive thirst and polyuria. There was no history of diabetes in the family. His symptoms were first noticed about six weeks before, and became gradually more severe, until he consulted a physician about January 1. The diagnosis of diabetes mellitus was made, and he was put on a diet of milk. His average weight was 130 pounds, and at admission it was 113 pounds. The physical examination showed nothing of importance.

On a diet containing 17 gm. protein, 100 gm. fat and 10 gm. carbohydrate, with a total of about 1,000 calories, his urine rapidly became sugar-free. His diet was increased gradually to 2,000 calories, with 40 gm. protein and 25 gm. carbohydrate, the remainder being fat. Through the summer, he reported to us at intervals, and his urine was always found to be sugar-free and his blood sugar within normal limits. He returned to the hospital in October, 1920, at

TABLE 6.—Part of Record from Case 6

	Diet				Urine			Blood Sugar.	Nitrogen				
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
11/22	15.9	97.2	9.9	980	1,800	0	0	0.12	....	....	....	....	.....	153
23	15.9	97.2	9.9	980	2,630	0	0	....	....	....	....	....	.....	...
24	15.9	97.2	9.9	980	2,250	0	0	....	....	....	....	....	.....	...
25	15.9	97.2	9.9	980	1,450	0	0	....	....	....	....	....	.....	...
26	15.9	97.2	9.9	980	1,550	0	0	....	....	....	....	....	.....	...
27	15.9	97.2	9.9	980	1,735	0	0	....	....	....	....	....	.....	...
Average	15.9	97.2	9.9	980	.....	..	..	....	6.02	0.58	2.54	6.55	−4.01	
11/28 to 12/2	65.0	197.0	9.9	2,065	.....	0	0	0.10	....	....	....	....	.....	...
3	65.0	197.0	9.9	2,065	2,450	0	0	0.07	....	....	....	....	.....	156
4	65.0	197.0	9.9	2,065	1,800	0	0	....	....	....	....	....	.....	...
5	65.0	197.0	9.9	2,065	1,850	0	0	....	....	....	....	....	.....	...
6	65.0	197.0	9.9	2,065	1,950	0	0	....	....	....	....	....	.....	156
7	65.0	197.0	9.9	2,065	2,440	0	0	0.10	....	....	....	....	.....	...
Average	65.0	197.0	9.9	2,065	.....	..	..	....	6.74	1.07	10.40	7.81	+2.59	
8–11	65.0	197.0	9.9	2,065	.....	0	0	....	....	....	....	....	.....	156
12	65.0	197.0	9.9	2,065	2,195	0	0	....	....	....	....	....	.....	156
13	65.0	197.0	9.9	2,065	2,535	0	0	....	....	....	....	....	.....	...
14	65.0	197.0	9.9	2,065	1,940	0	0	....	....	....	....	....	.....	155
15	65.0	197.0	9.9	2,065	1,760	0	0	....	....	....	....	....	.....	...
16	65.0	197.0	9.9	2,065	2,030	0	0	0.09	....	....	....	....	.....	...
17	65.0	197.0	9.9	2,065	2,305	0	0	....	....	....	....	....	.....	155
Average	65.0	197.0	9.9	2,065	.....	..	..	....	8.48	1.39	10.40	9.87	+0.53	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

our request, so that further adjustment of his diet might be made. It was during this period that the studies in nitrogen balance were made, the data for which will be found in Table 7.

This patient was the subject of an interesting experiment that will be discussed later. Nitrogen balance was established on a diet containing 0.58 gm. protein and 21 calories per kilogram body weight.

Case 8 (20-558).—Patient was a Syrian laborer, 36 years of age, who entered the hospital, July 25, 1920, complaining of excessive thirst and appetite, and polyuria. His symptoms were dated back eight months, during which period he had lost 35 pounds. He was a moderately severe diabetic who was able to tolerate 50 gm. carbohydrate and 30 gm. protein without glycosuria. His blood sugar was 0.37 per cent. at entrance, and his weight 162 pounds.

He was immediately placed on a diet consisting of 20 gm. protein, 90 gm. fat and 12 gm. carbohydrate, totaling about 950 calories. After three days,

his urinary sugar disappeared without the presence of a positive ferric chlorid test, and his blood sugar fell to 0.124 per cent. He remained on this diet until July 31. During the week following his carbohydrate intake was gradually increased each day, until August 7, he was eating 51.7 gm. without glycosuria. From August 8 to 12 he received 28 gm. protein, 115 gm. fat and 20 gm. carbohydrate with an energy value of about 1,225 calories. In the period from August 13 to 19 his average daily diet was 34 gm. protein, 165 gm. fat, 26 gm. carbohydrate and 1,725 calories. During this time his weight fell to 156 pounds. At this point the nitrogen determinations were started, the data for which are presented in Table 8. On the basis of a weight of 69 kg., nitrogen balance was established on 0.81 gm. protein and 33 calories per kilogram of body weight. There was a large positive balance at first which gradually fell, though there was a slight increase in the protein and caloric intake.

TABLE 7.—PART OF RECORD FROM CASE 7

	Diet				Urine			Blood Sugar.	Nitrogen					
Date 1920	Protein. Gm.	Fat. Gm.	Carbohydrate. Gm.	Calories	Amount. C.c.	Glucose. Gm.	Diacetic	per Cent.	Urine.* Gm.	Stool.† Gm.	In. Gm.	Out. Gm.	Balance. Gm.	Wt., Lbs.
11 12	11.1	45.4	9.2	490	.....	0	0	0.16	....	....	....	.....	.....	...
13	21.5	89.4	14.6	870	.....	0	0	....	....	....	....	.....	.....	128
14	20.6	87.6	14.6	850	.....	0	0	0.10	....	....	....	.....	.....	...
15	195.7	115.9	15.0	1,885	.....	0	0	....	....	....	....	.....	.....	...
16	196.5	96.0	15.0	1,710	1,350	0	0	....	9.58	1.42	31.44	11.00	+20.44	130
17	191.6	107.3	15.0	1,790	2,150	0	0	....	24.94	1.42	30.6	6.36	+4.30	...
18	197.9	104.5	14.0	1,790	2,450	0	0	....	14.68	1.42	31.66	16.10	+15.56	...
19	191.6	107.3	15.0	1,790	.....	0	0	0.12	....	....	30.66	.....	.....	...
20	146.6	80.6	14.0	1,370	1,800	0	0	....	18.38	1.67	23.46	20.05	+3.41	130
21	32.1	121.8	23.9	1,320	2,100	0	0	....	29.76	1.67	5.13	31.43	—26.30	...
22	33.6	169.4	27.5	1,770	1,500	0	0	....	19.18	1.67	5.37	20.85	—15.48	...
23	34.3	174.7	29.9	1,830	950	0	0	....	7.76	1.67	5.49	9.43	—4.06	127
24	33.8	153.6	28.5	1,630	875	0	0	0.08	7.30	0.75‡	5.25	8.05	—3.80	...
25	28.7	116.8	20.8	1,250	1,225	0	0	....	9.37	0.75	4.59	10.12	—5.53	...
26	33.5	158.8	26.3	1,670	950	0	0	....	7.85	0.75	5.40	8.60	—3.20	...
27	33.0	89.7	21.9	1,030	1,350	0	0	....	2.35	0.75	5.27	3.10	+2.17	127
28	33.1	159.1	29.2	1,680	1,300	0	0	0.11	2.42	0.75	5.29	3.17	+2.12	...
29	34.8	167.1	25.0	1,745	1,250	0	0	....	3.05	0.75	5.57	3.80	+1.77	...
30	32.3	149.8	24.2	1,540	950	0	0	....	8.53	0.75	5.17	9.28	—4.11	128
31	32.9	169.3	25.9	1,760	1,150	0	0	....	8.33	0.75	5.27	9.08	—3.81	...
1	34.9	196.0	25.9	1,975	950	0	0	....	4.30	0.75	5.59	5.05	+0.54	...
2§	22.8	153.7	28.2	1,625	1,900	0	0	0.08	15.05	0.75	5.25	15.80	—10.55	...
3	38.5	211.6	37.5	2,270	1,200	0	0	....	7.96	0.75	8.56	8.71	—0.15	130
4	58.6	202.0	31.3	2,180	1,275	0	0	....	7.92	0.75	9.37	8.67	+0.70	...
5	58.8	213.4	39.4	2,315	1,250	0	0	....	9.12	0.75	9.40	9.87	—0.47	...

* Daily determinations. † Daily average of each period obtained from all stools.
‡ Estimated. § Acute follicular tonsillitis.

CASE 9 (20-677).—Patient was a German pattern maker, 63 years of age, who entered the hospital, Oct. 19, 1920, complaining of failing vision, polyuria, polyphagia and polydipsia. There was no family history of diabetes mellitus. The diabetic symptoms were first noticed about three years before, and though he was placed on a diet containing little carbohydrate, he continued to lose strength and weight, until on admission to the hospital he was hardly able to get about the house. His best weight was 150 pounds twenty years before. In the past two years he had lost 25 pounds, reaching his entrance weight of 111 pounds. Examination showed a moderate degree of emaciation. There was a mature cataract in the left eye and a beginning cataract in the right. The peripheral arteries were markedly sclerotic. There was some edema of the ankles and the tendon reflexes were normal.

On a diet containing 18 gm. protein, 90 gm. fat and 12 gm. carbohydrate, his urine became free from sugar on the twenty-fourth day, and four days later his blood sugar was 0.11 per cent. His diet was increased until he was

getting 34 gm. protein, 170 gm. fat and 23 gm. carbohydrate, a total of about 1,760 calories. December 3, he was transferred to the department of ophthalmology for operation, and was returned to the medical ward December 23 with a moderate glycosuria and a blood sugar of 0.17 per cent. Three days of a diet similar to that which he received immediately after admission sufficed to render his urine sugar-free, and his blood sugar fell to 0.14 per cent. His diet was again increased, and it was found that 55 gm. protein, 210 gm. fat and 35 gm. carbohydrate, with a total of about 2,250 calories, kept the sugar content of his blood between 0.19 and 0.20 per cent. though there was no glycosuria. His diet was accordingly reduced to 32 gm. protein, 160 gm. fat and 24 gm. carbohydrate, containing about 1,650 calories. On this diet

TABLE 8.—PART OF RECORD FROM CASE 8

	Diet				Urine		Nitrogen					
Date 1920	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
9/20	33.6	181.3	25.8	1,870	0	0	....	....	....	....	....	156
21	34.7	151.1	26.4	1,605	0	0	....	....	....	....	....	...
22	33.5	174.7	26.5	1,850	0	0	....	....	....	....	....	...
23	31.0	209.5	26.7	2,115	0	0	....	....	....	....	....	...
Average	33.2	179.1	26.3	1,850	..	..	6.43	0.95	5.31	7.38	−2.07	
9/24	35.3	151.7	26.8	1,630	0	0	....	....	....	....	....	1'3
25	34.1	164.6	28.8	1,725	0	0	....	....	....	....	....	...
26	32.1	159.1	29.2	1,680	0	0	....	....	....	....	....	...
27	34.5	134.9	26.4	1,460	0	0	....	....	....	....	....	...
Average	34.2	153.1	27.8	1,625	..	..	6.70	1.14	5.47	7.84	−2.37	
9/28	54.8	206.9	29.8	2,240	0	0	....	....	....	....	....	152
29	54.0	207.6	37.0	2,350	0	0	....	....	....	....	....	...
30	57.6	209.0	39.3	2,370	0	0	....	....	....	....	....	...
Average	55.5	207.8	38.7	2,245	..	..	5.19	1.14	8.88	6.33	+2.55	
10/1	58.8	223.4	36.5	2,290	0	0	....	....	....	....	....	151
2	54.1	222.7	37.0	2,370	0	0	....	....	....	....	....	...
3	58.8	231.7	38.7	2,275	0	0	....	....	....	....	....	...
4	56.8	208.0	32.8	2,230	0	0	....	....	....	....	....	...
Average	57.4	221.4	36.2	2,370	..	..	7.08	1.08	9.18	8.16	+1.02	
10/5	54.3	223.7	33.6	2,365	0	0	....	....	....	....	....	151
6	56.4	252.7	37.7	2,350	0	0	....	....	....	....	....	...
7	65.5	211.3	35.3	2,305	0	0	....	....	....	....	....	...
8	59.8	249.2	39.3	2,640	0	0	....	....	....	....	....	...
Average	59.0	234.2	36.5	2,490	..	..	7.71	0.40	9.44	8.11	+1.33	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

his blood sugar remained 0.15 per cent., and, as is shown in Table 9, he was in nitrogen balance. With a body weight of 50 kg., he was receiving on this diet about 0.64 gm. protein and about 33 calories per kilogram of body weight.

CASE 10 (20-615).—Patient, a very mild, elderly diabetic, returned to the hospital two years after he had been discharged on a moderately restricted diet. In the interval he had had no symptoms, except those of an associated chronic bronchitis, and he returned for examination. At entrance, his weight was 200 pounds, his age, 80 years, and his blood sugar 0.15 per cent. At no time during his stay did he have glycosuria or a positive ferric chlorid test on his urine. He was placed immediately on a diet containing about 1,500 calories of which about 34 gm. were protein. This was rapidly increased to a very liberal diet, as shown in Table 10.

CASE 11 (21-276).—Patient was an American farmer, 22 years old, who entered the hospital complaining of polyuria, weakness and loss of weight. A brother died of diabetes mellitus at the age of 17. His symptoms started seven months before and the diagnosis was made immediately. His diet was only moderately restricted, however, and he constantly lost weight and strength. His best weight had been 164 pounds just before the onset; his weight at admission was 127. Except for septic tonsils, his examination was negative. His blood plasma was creamy, and the total lipoids in the whole blood were

TABLE 9.—PART OF RECORD FROM CASE 9

	Diet				Urine			Blood Sugar	Nitrogen				
Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	per Cent.	Urine,* Gm.	Stool,† Gm	In, Gm	Out, Gm.	Balance, Gm.	Wt., Lbs.
1 25	13.6	164.3	15.9	1,155	670	0	0	....	3.94	0.75	2.50	4.69	−2.19	...
26	28.7	124.5	19.2	1,210	680	0	0	0.15	4.08	0.75	4.59	4.83	−0.24	110
27	38.7	131.6	20.0	1,350	550	0	0	....	3.66	0.75	4.59	4.41	+0.18	...
28	32.8	147.3	24.5	1,555	670	0	0	....	3.98	0.75	5.23	4.73	+0.50	...
29	33.3	157.5	26.2	1,655	765	0	0	....	3.73	0.75	5.17	4.48	+0.69	109
30	34.7	185.4	26.7	1,915	.....	0	0	....	.....	.....	.....	.....	.....	...
31	34.7	159.1	28.2	1,685	735	0	0	....	3.32	0.75	5.55	4.27	+1.28	...
2 1	32.9	153.6	28.4	1,630	795	0	0	....	3.02	0.75	5.26	3.77	+1.49	...
2	32.6	172.8	29.6	1,840	745	0	0	0.15	3.17	0.75	5.25	3.92	+1.33	110
3	34.2	174.7	29.9	1,830	770	0	0	....	4.73	0.75	5.47	5.48	−0.01	...
4	34.7	190.1	25.9	1,950	.....	0	0	....	.....	.....	.....	.....	.....	...
5	34.6	170.5	19.8	1,750	1,255	0	0	....	4.70	0.75	5.54	5.45	+0.10	110
6	36.6	164.5	19.9	1,705	1,220	0	0	0.15	3.67	0.75	5.86	4.42	+1.44	...
7	33.2	167.3	18.4	1,710	1,020	0	0	....	3.40	0.75	5.17	4.15	+1.02	...
Average	31.8	157.4	23.8	1,640	.....	..	..	....	4.12	0.75	5.09	4.87	+0.22	

* Daily determinations. † Estimated

TABLE 10.—PART OF RECORD FROM CASE 10

	Diet				Urine		Nitrogen					
Date 1920	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
9 26	34.1	164.6	28.8	1,735	0	0	....	....	....	....	....	200
27	33.1	159.1	29.2	1,680	0	0	....	....	....	....	....	198
28	34.5	135.0	26.4	1,460	0	0	....	....	....	..8	....	197
29	33.8	111.1	29.3	1,255	0	0	....	....	....	....	....	199
30	34.1	143.0	26.3	1,530	0	0	....	....	....	....	....	200
Average	33.9	139.0	27.8	1,500	..	..	6.06	0.68	5.42	6.74	−1.32	
10/1	28.4	173.8	22.4	1,765	0	0	....	....	....	....	....	199
2	58.0	223.4	36.5	2,390	0	0	....	....	....	....	....	200
3	54.8	227.7	37.0	2,360	0	0	....	....	....	....	....	199
4	64.8	236.4	38.7	2,540	0	0	....	....	....	....	....	199
Average	51.4	214.1	33.9	2,260	..	..	8.83	1.17	8.22	5.00	+3.22	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

found to be between 8 and 9 per cent. on several examinations immediately after admission to the ward. Part of the data of this case are presented in Table 11. He was established in nitrogen balance on a diet containing 0.74 gm. protein and about 37 calories per kilogram of body weight.

CASE 12 (21-678).—Patient was an American clerk, 18 years old, who entered the hospital March 24, 1921, complaining of weakness. There was no family history of diabetes. His symptoms began with polyuria, polydipsia, polyphagia, and progressive weakness, and his weight fell from 135 to 95 pounds. Treatment had been erratic, though at times his diet was restricted to green vegetables. Twelve days before entrance starvation was started, lasting

seven days; during the next five days he received green vegetables and a few eggs. For three months he had numbness and tingling of his hands and toes and there have been a few boils. The physical examination showed nothing of importance. Nitrogen balance was established on a diet containing 30 gm. protein, 180 gm. fat and 15 gm. carbohydrate, allowing him 0.71 gm. of protein and 43 calories per kilogram of body weight. The data are presented in Table 12.

TABLE 11.—PART OF RECORD FROM CASE 11
(DAILY AVERAGES FOR EACH PERIOD)

		Diet				Urine			Blood				Nitrogen		
Dates	No. of Days	Protein Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic to 0	N, Gm.	Sugar, per Cent.	CO_2	Fat, per Cent.	Stool N, Gm.	Wt., Lbs.	In, Gm.	Out, Gm.	Bal., Gm.
2/ 8 to 2/16	9	20.0	90.0	14.0	950	24.7 to 0	+++ to 0	....	0.26	61.4	8.50	....	126	....	....	.....
2/17 to 2/21	5	20.8	82.8	13.7	885	0	0	9.72	0.12	56.6	....	....	121	3.23	....	.....
2/22 to 2/24	3	40.1	154.4	20.2	1,630	0	0	7.37	....	46.8	7.00	....	122	6.42	....	.....
2/25 to 3/1	5	40.2	152.6	20.5	1,615	0	0	7.84	0.13	62.6	7.90	....	122	6.43	....	.....
3/ 2 to 3/7	6	40.8	152.1	20.6	1,615	0	0	8.98	0.12	58.9	6.70	....	119	6.53	....	.....
3/ 8 to 3/12	5	40.0	180.3	20.4	1,865	0	0	6.75	....	....	6.25	....	124	6.40	....	.....
3/13 to 3/17	5	40.0	179.4	20.6	1,855	0	0	5.65	....	65.3	4.32	....	126	6.40	....	.....
3/18 to 3/20	3	40.5	200.3	25.0	2,065	0	0	5.28	....	59.8	3.12	1.39	125	6.48	6.67	−0.19
3/21 to 3/29	9	40.9	200.9	25.0	2,070	0	0	6.12	0.08	65.3	2.89	0.98	121	6.54	7.10	−0.56
3/30 to 4/ 4	6	40.6	200.2	25.0	2,065	0	0	5.53	0.10	60.7	2.71	0.95	121	6.50	6.48	+0.02
4/ 5 to 4/8	4	43.1	229.1	25.6	2,340	0	0	4.01	....	61.7	2.54	0.95	121	6.90	4.95	+1.94

TABLE 12.—PART OF RECORD FROM CASE 12

	Diet				Urine			Blood				Remarks		
Date 1921	Protein Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amt., c.c.	Glucose, Gm.	Diacetic N,* Gm.	Sugar, per Cent.	CO_2	Fat, per Cent.	Stool N,† Gm.	Wt., Lbs.	N In, Gm.	N Out, Gm.	N Bal., Gm.
3/24	....	.....	....	.....	.....	+++ +	....	0.330	61.4	2.63	....	93.0	....	....	.....
25	21.7	99.4	14.8	995	1,085	++ tr	....	....	....	....	....	....	....	....	.....
26	29.1	129.1	21.1	1,320	2,000	0	0	....	....	....	....	89.5	....	....	.....
27	19.1	95.4	14.2	990	2,225	0	0	....	....	....	....	....	....	....	.....
28	21.2	85.9	13.4	910	2,900	0	0	....	0.234	61.7	2.21	....	....	....	.....
29	30.2	92.4	14.6	960	2,925	0	0	....	....	....	....	....	....	....	.....
30	30.6	147.1	14.2	1,500	3,280	0	0	6.21	....	....	....	0.75	91.5	4.80	6.96	−2.16
31	31.7	151.9	15.5	1,535	4,480	0	0	6.21	....	....	....	0.75	....	5.07	6.96	−1.89
4/ 1	29.9	149.4	14.8	1,525	2,310	0	0	4.62	....	....	....	0.75	....	4.78	5.37	−0.59
2	30.2	149.2	14.9	1,525	3,435	0	0	4.62	....	....	....	0.75	91.0	4.83	5.37	−0.54
3	28.8	152.4	14.8	1,545	1,760	0	0	4.62	....	....	....	0.75	....	4.61	5.37	−0.76
4	30.3	152.0	14.9	1,550	2,220	0	0	4.62	0.164	63.6	1.44	0.75	....	4.85	5.37	−0.52
5	31.1	180.7	14.2	1,800	3,220	0	0	4.11	....	....	....	0.75	....	4.98	4.86	+0.12
6	30.0	179.2	14.2	1,785	2,260	0	0	4.11	....	....	....	0.75	92.0	4.80	4.86	−0.06
7	29.1	178.2	15.0	1,765	2,410	0	0	4.11	....	....	....	0.75	....	4.67	4.86	−0.19
8	29.7	180.2	15.3	1,800	3,080	0	0	4.11	0.164	61.7	1.40	0.75	....	4.75	4.86	−0.11

* Daily average of each period obtained from aliquot parts of urines.
† Estimated.

2. Recently Sherman [5] has added to his own careful studies of the protein requirement for maintenance of nitrogen balance in normal men a complete collection of data obtained from the literature, 109

5. Sherman, H. C.: Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, J. Biol. Chem. **41**:97, 1920.

experiments in all. An average of all minimum daily protein intakes on which nitrogen balance was established gave 0.635 gm. protein per kilogram of body weight. If the seventy-six determinations showing the least variation are averaged, a lower figure, 0.58 gm., is obtained. He points out that the more recent data are, as a result of more accurate methods and a better understanding of the problem, somewhat lower than those obtained by the earlier observers, and he himself was able to maintain several subjects in nitrogen balance on 0.5 or even 0.45 gm. protein per kilogram of body weight per day. The experiments of Hindhede,[6] Chittenden [7] and others are too well known to require comment. It is an established fact that nitrogen balance may be maintained on less than 0.66 gm. protein per kilogram of body weight per day, provided certain other conditions are satisfied.

The conditions necessary for the establishment of nitrogen balance at this low level are several. Chief among them is the presence of sufficient total calories in the ingested food; there must be enough fat or carbohydrate in the diet to supply all the body needs for heat and energy, so that the protein may be used only for restoring body tissue. The protein-sparing qualities of carbohydrate and fat were discovered by some of the earliest students of metabolism, and it is well known that carbohydrate is the more efficient of the two in sparing protein, though in a mixed diet fat may replace carbohydrate in isodynamic quantities. In spite of this difference in the effectiveness of the two foodstuffs, the ability of fat to spare protein cannot be doubted. For example, Thomas, quoted by Lusk,[8] "could not maintain nitrogen equilibrium when twice the amount of the fasting nitrogen elimination was given to man in the form of meat alone, but was able to accomplish this when meat to the extent of that destroyed in the fasting was administered with fat." It is important, then, to remember that if nitrogen balance is to be maintained on a low protein intake the total calories in the food must be sufficient to supply metabolic needs.

While a partial replacement by fat of carbohydrate in a low protein diet will not affect the protein metabolism, complete withdrawal of carbohydrate and substitution of fat will not permit the establishment of nitrogen balance at low levels. Fat alone will not decrease the amount of nitrogen found in the urine of a fasting animal.[9] It is generally believed that fat in a low protein diet loses part of its effectiveness when the carbohydrate calories fall below 10 per cent. of the total calories. Thus Zeller [10] found that a man receiving little nitrogen

6. Hindhede, M.: Skand. Arch. Physiol. **30**:97, 1913; **31**:259, 1914.

7. Chittenden, R. H.: Physiological Economy in Nutrition, 1904; Nutrition of Man, 1907.

8. Lusk, G.: Science of Nutrition, Philadelphia, 1919, p. 254.

9. Voit: Physiologie des Stoffwechsels und der Ernährung, 1881, p. 128; Bartman: Ztschr. f. Biol. **58**:375, 1912.

10. Zeller: Arch. f. Physiol., 1914, p. 213.

in his food and varying amounts of carbohydrate and fat showed little variations in his nitrogen excretion until the carbohydrate gave less than 10 per cent. of the total calories.

It was stated that fat alone will not decrease the amount of nitrogen eliminated during starvation. It is also of great interest in connection with diabetes to note that in an animal still possessing body fat, fat in the diet does not bring about any change in the amount of fat metabolized. Voit,[9] for example, gave 100 gm. fat to a dog, which in starvation burned 96 gm. fat, and found that it burned 97 gm. In other words, the same amount of fat was burned whether it was derived from the body or from the diet. The amount of fat stored in the body has, however, a direct influence on the amount of protein metabolized during starvation. Lean animals die of starvation sooner than fat animals, and as starvation progresses and the relative quantity of fat and protein in the organism decreases the output of urinary nitrogen

TABLE 13.—EFFECT OF PREVIOUS DIET ON NITROGEN EXCRETION (C. VOIT)

Amount of meat in previous diet...	2,500 gm.	1,500 gm.	Mixed diet poor in N
	Amount of Protein Used as Determined by Urine N		
First fast day	175	77	40
Second fast day	72	54	33
Third fast day	55	46	30
Fourth fast day	50	53	36
Fifth fast day	36	43	35
Sixth fast day	39	37	36

increases. Folin and Denis[11] found that the protein metabolism in fasting was low in people in whom ample fat was present. On the other hand, if the fat be supplied in the diet, there is no difference in the protein metabolism of a lean subject and that of a fat one. The total metabolism of an obese man is the same in proportion to his body surface as in a lean man. These facts are of practical value in the arrangement of diets for diabetics of different degrees of nourishment, and must not be ignored in the study of their nitrogen requirements.

A very marked effect of the previous diet is noted during the first few days of the study of nitrogen balance. This is shown very nicely in the experiment by C. Voit, tabulated by Magnus-Levy,[12] the data from which are shown in Table 13. The diets containing the amounts of meat indicated had been continued for several days before each experiment.

It will be noted that it is not until the sixth day that the nitrogen outputs reach a common level. This may be considered as due to the fact that excess of protein in the tissues or in the blood stimulates

11. Folin and Denis: J. Biol. Chem. **21**:183, 1915.

12. Magnus-Levy, A.: Von Noorden's Handbuch der Pathologie des Stoffwechsels, 1906, p. 312.

protein metabolism. The experiment is of great importance in emphasizing the fact that studies in nitrogen balance made during the first few days following a change in diet are of no value; the organism requires some time for its readjustment to the new dietetic regime.

On the other hand, Rubner, quoted by Lusk,[8] states that the "greater the impoverishment of the protein supply in an animal fed with fat, the more powerful is the protective effect of small quantities of ingested protein over the loss of body protein. Also the retention of protein depends on the protein content of the dog as well as on the quantity of protein ingested." This is illustrated in Table 14.

"It is evident from this that of the same diet of protein more will be retained when the nitrogen content of the dog is low than when it is high; and also that a small protein intake may cause the same retention of nitrogen as a large protein intake, if in the first instance there be a relative impoverishment of the protein content of the animal."

TABLE 14.—Protective Effect of Small Quantities of Protein when Body Protein is Impoverished
(Rubner)

Total N Content of Dog	N in Terms of 100 N in Dog	
	In Food	To Body
318.8	5.25	1.65
324.7	5.57	1.07
340.6	6.72	2.64
363.7	12.79	2.62

It has been stated that in order to maintain nitrogen balance on a diet with a small protein content, the total caloric requirement of the subject must be satisfied. This requirement is not represented by the rate of basal metabolism. The caloric needs of the fasting, resting subject are not the same as those of the same subject after the ingestion of food or in the performance of even the smallest amount of work. A certain amount of energy is used in the metabolism of the food, and this "specific dynamic action" is different for each of the three major foodstuffs. For protein the increased heat production is especially high, amounting to from 25 to 35 per cent. of the ingested calories. In the case of fat the figure is about 12 per cent.; for carbohydrate much less, about 6 per cent. This factor must enter into our calculations of the total daily requirement, and if the diet contains an excess of protein, the amount of food necessary to supply the caloric needs of the body, and hence to maintain nitrogen equilibrium, is considerably greater than when fat and carbohydrate furnish the major part of the calories.

The amount of work done by the subject obviously influences his caloric needs. A man whose resting requirements are satisfied by 1,500 calories daily may burn 9,000 calories in a bicycle race. It is evident that this fact must be considered in the formation of a low protein

diet that will maintain nitrogen balance. On the other hand, there is abundant evidence to show that work does not increase the rate of protein metabolism when the energy is supplied from other foodstuffs. The experiment by Shaffer [13] presented in Table 15 may be cited as an example; during the first period he was at rest in bed; during the second he was doing laboratory work, and during the third, laboratory work plus a ten-mile walk daily; the periods were six, five and four days respectively.

The other end-products of protein catabolism showed a similar constancy, and he concluded from this that muscular activity had no effect on protein metabolism. This fact is important because we may arrange the protein content of a diet without regard to the amount of work that the patient will do. If he is in nitrogen balance at rest, the calories required for energy for work may be added as fat or carbohydrate. Furthermore, it has been shown that there is no difference in value of fat and carbohydrate as a fuel for mechanical work.[14]

TABLE 15.—Effect of Work on Protein Metabolism (Shaffer)

Period	Food		Urine
	N	Calories	N
1	5.9	2,300	4.77
2	6.0	3,000	4.40
3	5.9	3,200	3.94

In the formation of diets the age of the subject must receive consideration. The total caloric requirement of children is much greater in proportion to their size than is that of adults, and this requirement declines as the subject becomes older. Furthermore, beside the "repair quota" of protein needed to replace that lost in the wear and tear of tissue, children require a "growth quota." While, as far as we know, there is no record of a careful determination of the minimum protein intake that will supply the normal growing child with the needed nitrogen, it must be considerably higher than that required by adults.

Sex is of no importance in this connection. Some of the studies discussed by Sherman [5] had for their subjects women. Since women have a somewhat lower metabolic rate than men, a diet that is sufficient to supply the needs of a man will certainly supply those of a woman of the same size. There is no change in the oxidation processes during menstruation,[15] and the amount of nitrogen lost is evidently

13. Shaffer, P. A.: Diminished Muscular Activity and Protein Metabolism, Am. J. Physiol. **22**:445, 1908.

14. Zuntz: Arch. f. d. ges Physiol. **83**:557, 1900.

15. Gephart, A. B., and Du Bois, E. F.: Basal Metabolism of Normal Adults, Arch. Int. Med. **17**:907 (June) 1916; Blunt, K., and Dye, M.: Basal Metabolism of Normal Women, J. Biol. Chem. **47**:69, 1921.

small. The pregnant woman requires an extra quota of nitrogen and extra calories during the gestation period in order to supply the embryo; as the weight of the child at birth is only 5 or 6 per cent. of that of the mother, the extra ration need not be very great.

The weight of the subject is of importance in giving us a basis on which we may calculate his nitrogen requirements and, roughly, his total diet. Gain and loss of weight during the periods of treatment when the diets are being changed mean little, as a rule, because such changes are very often due to changes in the water content of the body. In the normal subject, change from a carbohydrate diet to a fat or protein diet causes a loss of water [16] amounting to as much as a kilogram a day. Dehydrated subjects, on the other hand, may absorb and retain enormous quantities of water, with the resulting increase in body weight. This is seen not only in diabetes, but in other diseases, as pyloric obstruction. We therefore frequently see the apparent paradox of a patient who gains weight rapidly on a diet containing only 1,000

TABLE 16.—Effect of Ingested Water on Nitrogen Excretion (Abderhalden and Bloch)

	N Balance	N in Urine
Normal food	+1.36	18.5
Normal food plus 5 liters water	−2.19	21.75
Normal food	+1.47	18.09

calories daily. More than this, the more severe cases of diabetes show a marked tendency to the development of edema. Because of these facts, one is not entitled to draw conclusions as to the state of the patient's nutrition from changes in body weight. As pointed out before, the important consideration is the fat and protein content of the body.

A small increase in nitrogen elimination has usually been noted following the drinking of large quantities of water. Hawk,[17] for example, found that the ingestion of 4,500 c.c. water with an unchanged nitrogen content of the diet caused the urinary nitrogen to rise from 11.03 to 12.48 on the first day, and 11.82 on the second, with a fall of 10.91 on the succeeding day when no water was given. Alderhalden and Block [18] gave a subject on a fixed diet 5 liters of water with the results shown in Table 16.

It is probable that two factors explain this rise in nitrogen elimination; first, the water removes from the body any accumulation of the end-products of nitrogenous metabolism, and second, causes a true increase of the protein metabolism. This is of interest in the case of

16. Bischoff and Voit: Die Gesetze der Ernährung des Fleisch fressers, Leipsic, 1860; Benedict, Milner: U. S. Dept. Agric. Office, Exper. Stat. Bull. 175, 1907.

17. Hawk: Univ. Penn. Med. Bull., March, 1905.

18. Abderhalden and Bloch: Ztschr. f. Physiol. Chem. **53**:464, 1907.

a diabetic who drinks large quantities of water, either as a symptom of his untreated disease or during periods of very restricted diet when he attempts to relieve some of the pangs of hunger by filling his stomach.

There is also an irregular but important day to day variation in the nitrogen output that is independent of variations in fluid intake. These fluctuations are the result of lag in excretion, and in the long run they are compensatory. A nitrogen determination for a single day is an unsafe indication of the usual excretion; safety is in the average of several days.

Beside all these factors influencing the protein metabolism, there are a few manifestations of nondiabetic disease which may cause profound disturbances in the nitrogen balance. The great increase in the rate of total metabolism and especially of protein metabolism in hyperthyroidism is well known. In the diabetic, the most important cause of such disturbances is fever. The increase in nitrogen elimination during fever may be enormous. In a study of the metabolism in pneumonia, for example,[19] the daily loss in nitrogen on a diet adequate to protect a normal individual from loss may be from 20 to 25 gm., representing from 125 to 150 gm. protein. Of chief importance in the study of diabetes is tuberculosis, in which the destruction of protein, while smaller than in pneumonia, is continued over a much longer time.[20] Even during the afebrile periods there is some increase over normal in the protein destruction. Futhermore, in these infectious fevers, the total caloric requirement is greater than normal because of the increased heat production. The presence of such a fever must modify our diet in diabetes.

3. It is seen, then, that the normal subject may be maintained in nitrogen balance on less than 0.66 gm. protein per kilogram of body weight, provided the total caloric intake is sufficient to supply heat and energy. Certain fundamental laws governing protein metabolism have been discussed, and because of their importance are here restated.

In mixed diets carbohydrate and fat are equally efficient in sparing protein and of equal value as fuel for work. Carbohydrate may not be entirely replaced by fat, however. An animal having a supply of body fat will burn the same amount of fat, whether it is supplied in his diet or is used from his store. A good supply of body fat thus saves protein in the same way as ingested fat. More nitrogen is excreted during the days following a diet rich in protein than following one poor in protein. The increased heat elimination due to the metabolism of food

19. Wolf and Lambert: Protein Metabolism in Pneumonia, Arch. Int. Med. **5**:406 (March) 1910.

20. May: Ott's Chemische Pathologie der Tuberculose, Berlin, 1903, p. 335. McCann, W. S., and Barr, D. P.: The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.

has been pointed out, and the excessive "specific dynamic action" of protein has been emphasized. Work causes an increase in the total metabolism, but no increase in the protein metabolism provided the calories needed are supplied in other form. Children require more protein than adults, and the total requirement decreases as age advances. Sex is of no importance in studies of protein metabolism. There is a marked day to day fluctuation in nitrogen excretion, partially dependent on increased water intake. Changes in weight must be interpreted with caution, because they are often due to changes in the water content of the body. The infectious fevers cause a great increase in the amount of protein destruction.

The laws governing protein metabolism of normal subjects have been stated. The question then arises as to whether or not these facts apply equally to the diabetic. Is there any peculiar disturbance of his

TABLE 17.—Protein Sparing Qualities of Fat in Diabetes Mellitus (Weintraud)

Date	Protein, Gm.	Fat, Gm.	N in Food, Gm.	N in Stool, Gm.	N in Urine, Gm.	N Balance, Gm.
9	113	273	18.19	0.9	16.49	+0.80
10	113	273	18.19	0.9	16.34	+0.95
11	113	273	18.19	0.9	16.88	+0.41
12	113	273	18.19	0.9	16.01	+1.28
13	113	273	18.19	0.9	14.00	+3.29
14	111	28.5	17.74	1.04	17.2	−0.5
15	111	28.5	17.74	1.04	21.51	−4.81
16	111	28.5	17.74	1.04	23.37	−6.67
17	113	273	18.19	1.52	19.29	−2.62
18	113	273	18.19	1.04	19.29	−2.72
19	113	275	18.01	1.52	19.61	−3.12
20	113	275	18.01	1.52	17.07	−0.58
21	113	273	18.19	1.31	15.54	+1.34
22	113	273	18.19	1.31	14.39	+2.49
23	113	273	18.19	1.31	14 2	+2.68
24	113	275	18.19	1.31	13.88	+3.00

protein metabolism that makes his nitrogen requirement higher than that of his normal brother? Is his protein metabolism affected to the same degree and by the same factors as is that of a healthy subject?

That the urine in diabetes may contain more nitrogen than that of any other disease has been known for a long time and the French even gave this finding a name, azoturia. Von Noorden,[21] however, pointed out that this is due to the large nitrogen content of the diabetic's diet, either because of his own tendency to replace with protein the carbohydrate calories lost in the urine, or because of the very high protein content of the contemporary diabetic diet.

Weintraud [22] demonstrated conclusively as long ago as 1893 that fat fed to the diabetic subject was very powerful in saving his protein. An example of his experiments is shown in Table 17.

21. Von Noorden, C.: Die Zuckerkrankheit, Berlin, 1907, p. 97.
22. Weintraud, E.: Stoffwechsel in Diabetes Mellitus, Cassell, 1893.

It will be noted (1) that a decrease in fat calories without change in the nitrogen in the food resulted in the immediate production of a negative nitrogen balance; (2) the return to the diet rich in fat left the patient in negative balance for the first four days of the regime; but (3) during the second four days he was able to add nitrogen to his body. Had the experiment begun on the fourteenth and ended on the twenty-first, we would have been led to the conclusion that the fat did not spare nitrogen; a similar conclusion would result from the discontinuance of the experiment on the twenty-second, with the average nitrogen output of the first six days following the change. The fallacy of drawing conclusions from observations on the days immediately following changes in diet is apparent. The author also made quantitative determinations of the fat in the stools, in an effort to show whether or not there was any difficulty in the absorbtion of large quantities of fat from the intestinal tract of diabetics. Three normal subjects excreted an average of 3.2 per cent. of 150 gm. of fat. Table 18 presents his results in cases of three grades of diabetes.

TABLE 18.—Fat Absorbed from High Fat Diets in Diabetes Mellitus (Weintraud)

Severity	Food Fat, Gm.	Stool Fat, Gm.	Fat Absorbed	
			Gm.	Per Cent.
Severe	45.94	7.41	38.53	83.87
	146.4	4.53	141.86	96.90
	272.04	3.31	268.73	98.78
Moderately severe	39.42	2.16	37.24	94.47
	147.17	2.52	144.65	98.28
	206.02	3.10	202.92	98.61
Mild	55.41	3.15	52.26	94.31
	236.11	4.35	231.76	98.15

This general relationship held in all his determinations, namely that the percentage of fat in the stools fell with increase in the fat intake, and all of his diabetics showed an average absorbtion of about 98 per cent. of the ingested fat when the latter was over 125 gm. daily.

Dunlop [23] doubted the value of fat in sparing protein in diabetes, as demonstrated by Weintraud [22] and quoted in support of his doubt the experiment of Karsëner [24] who brought himself into nitrogenous equilibrium on a diet of protein and carbohydrate, and found that he was no longer able to maintain this equilibrium when he replaced a large part of the carbohydrate with the caloric equivalent of fat. Dunlop fed a diabetic patient 4,660 c.c. of skimmed milk for two periods of three days each, and then added to the milk diet a daily ration of 170 c.c. of olive oil. The results are shown in Table 19.

23. Dunlop, J. C.: Dietetic Values of Fat in Diabetes, Edinburgh M. J. **42**:399, 1896.

24. Karsëner: Von Noorden's Beiträge z. Lehre v. Stoffwechsel, Heft 1.

Because the oil did not decrease the nitrogen in the urine, the author argues that it did not act as a nitrogen sparer. This is, of course, only in accord with the established fact that a subject cannot be forced to store nitrogen, and that nitrogen ingested in excess of the requirement will be excreted rather than stored; the experiments show nothing in regard to the protein sparing qualities of fat. The experiment of Karsêner merely confirms the greater efficiency of carbohydrate than fat in sparing protein.

The excessive nitrogen excretion of totally depancreatized dogs is well recognized, and may reach five times the normal amount.[25] Sometimes these dogs develop a rapid and fatal cachexia without glycosuria, indicating, it would seem to us, that the excessive nitrogenous metabolism in such depancreatized animals was not part of the diabetic state. Furthermore, numerous pancreatic operations on human beings have been reported in which there was greatly increased nitrogen excretion

TABLE 19.—The Effect of Adding Fat to the Diet of a Diabetic Already in Nitrogen Balance
(Dunlop)

Period	Food		Nitrogen Output		
	N.	Added Oil	Urine	Stool	N-Balance
1	24.8	...	19.41	0.39	+5.00
2	24.8	170	18.02	0.44	+6.34
3	24.8	...	24.16	0.38	+0.26
4	24.8	170	25.06	....	−0.76
Av. 1, 3	24.8	...	21.8	0.38	+2.62
Av. 2, 4	24.8	170	21.54	0.44	+2.82

without glycosuria. On the other hand, occasional partially depancreatized animals have been described in which the D:N ratio was that of "total diabetes" and yet the cachexia (increased protein metabolism) was absent. Allen [26] has been able by excessive feeding of partially depancreatized dogs to develop a condition which he considers a very satisfactory imitation of human diabetes; in these dogs there is no increase in the protein catabolism. Although he is one of the staunchest supporters of the parallelism between such dogs and human diabetics, and of the dictum that "without disease of the pancreas there is no diabetes," he believes that the azoturia in the totally depancreatized dogs was due to other factors than those which caused the disturbance in carbohydrate metabolism. That is, in his opinion, the pancreas possesses other internal secretions in addition to that controlling carbohydrate metabolism, and in human diabetes these other functions are not disturbed. Even the most ardent adherents to the

25. Falta, W.; Grote, F., and Stachelin, R.: Versuche über Stoffwechsel und Energieverbrauch an pancrealosen Hunden, Hofmeister's Beitrage **10**:199, 1907.

26. Allen, F. M.: Glycosuria and Diabetes, Cambridge, 1913, pp. 427, 505.

hypothesis of the pancreatic origin of diabetes would not contend that there is as complete destruction of the pancreas in the human diabetic as there is in the depancreatized dog. Such animals by being deprived of the external secretion of the pancreas can no longer properly digest food and must accordingly be in a state of starvation. It is obvious that evidence of increased protein metabolism obtained from the study of depancreatized dogs must not be considered proof of a similar increase in human diabetes.

Lusk and others have shown [27] that in dogs with phlorhizin glycosuria the nitrogen excretion may be four or five times that of normal dogs. Allen [28] states that this is due (1) to the fever caused by the subcutaneous injection and is not always present if the drug is given by mouth, and (2) to the secondary breakdown of protein to replace the urinary loss of sugar in fasting or insufficiently fed animals. Sugar in doses above a certain quantity is burned and spares protein in the

TABLE 20.—STUDIES OF THE METABOLISM OF A SPONTANEOUSLY DIABETIC DOG (MAIGNON)

Régime	Carbohydrate as Desired	Meat, 500 Gm.	Starvation	High F..t
Days	4	2	1	10
Daily weight loss, gm.	300	250	500	0
Urea, gm.	12.24	34.60	16.38	5.99
Sugar, urine, gm.	125.47	51.71	19.17	3.78
Acetone, gm.	0.662	1.248	0.122	0.670

phlorhizinized as in the normal animal. Important as is the information concerning many of the processes of metabolism obtained by the use of phlorhizin, it may be applied only in a limited way to the problems of diabetes. Phlorhizin glycosuria and diabetes mellitus are two fundamentally different conditions.[28] The normal sugar content of the blood of the phlorhizinized subject, his ability to burn glucose in excess of a given quantity determined by the dose of the drug and the causation of his glycosuria by local renal disturbances offer sharp contrasts to the hyperglycemia of diabetes mellitus, the invariable appearance in the patient's urine of excess of ingested carbohydrate and his glycocuria because of a disturbance of the carbohydrate metabolism.

The studies by Maignon [29] of a dog who became diabetic spontaneously offer some interesting contrasts to the observations made on animals rendered "diabetic" by either phlorhizin or pancreatectomy. In Table 20 are found a summary of his experiments.

27. Reilly, F. H.; Nolan, F. W., and Lusk, G.: Phlorhizin Diabetes in Dogs, Am. J. Physiol. **1**:395, 1898. Lusk, G.: Ueber Phlorhizin-Diabetes, Ztschr. f. Biol. **42**:31, 1901. Mandel, A. R., and Lusk, G.: Respiration Experiments in Phlorhizin Diabetes, Am. J. Physiol. **10**:47, 1903.

28. Allen: Loc. cit., p. 617.

29. Maignon, F.: Du Rôle des Graisses dans la Glycogenie, J. Physiol. et Pathol. Gen. **10**:866, 1908.

The experiments of Benedict and Joslin [30] on the rate of nitrogen excretion of diabetics without food receive frequent mention in connection with the nitrogenous metabolism of diabetics. Allen [31] refers to this work as evidence of increase of nitrogen destruction, and Foster [32] similarly quotes these authors. If the evidence actually does show an increased protein destruction in the diabetic, it demands very careful consideration; it matters not whether this increase be held to be a specific action of some factor of the morbid state upon protein, or as one of the compensatory measures for the carbohydrate deficit, such an increase if real must be reckoned with in the preparation of a low protein maintenance diet.

The urines of thirteen fasting diabetics were collected in the morning and the hourly rate of excretion of nitrogen per kilogram of body weight determined. The average of all determinations was 8.4 mg. nitrogen per kilogram of body weight per hour, with variations among the individual cases of from 4.2 to 12.1 mg., and among different experiments in the same cases of as much as 5.3 mg. (from 4.2 to 9.5). In a series of fourteen normal subjects the average excretion per kilogram of body weight per hour was 6.8 mg., with variations between 4.8 and 8.9. Five of thirteen of the diabetic patients excreted less than the average of the normals, and three of fourteen of the normals excreted more than the average of the diabetics. The fact remains, however, that the average of the diabetics was higher than the average of the normals, and four of the diabetics eliminated more nitrogen than the highest of the normals.

If these cases be studied in relation to their degrees of emaciation, it will be noted that, in general, the more poorly nourished have the highest rate of nitrogen excretion. In Table 21 the subjects are arranged in the order of their rates of nitrogen excretion; added are columns showing the average weight for the age and height of each case as found in the actuarial tables, the number of pounds above or below this and the percentage of digression from this average.

Cases X and W were clinically only moderately severe, M was light and the rest were severe. It will be noted that if the difference between the weight of the patient and the average normal weight may be taken as a rough measure of the degree of emaciation the better nourished patients excreted less nitrogen than the more lean patients. The average nitrogen excretion of the seven patients showing the least loss of weight was 6.6 mg. per hour (the controls averaged 6.8 mg.) while the average of the other 6 was 10.3. The proper explanation of

30. Benedict, F. C., and Joslin, E. P.: Metabolism in Severe Diabetes, Washington, 1912, p. 112.

31. Allen, F. M.: loc. cit., p. 419.

32. Foster, N. B.: Diabetes Mellitus, Philadelphia, 1915, p. 173.

these figures then seems to be that, whereas none of these fasting patients could supply fuel for energy from the store of body carbohydrate, some had a sufficient store of fat to serve the purpose and to render it unnecessary for them to burn protein for fuel. These determinations offer further evidence of the ability of fat to save protein in the diabetic. The results are what one would predict from the laws of normal metabolism; they give no evidence of abnormal protein metabolism in the diabetic.

Very occasionally a case of unusually severe diabetes is seen in which even the power of burning the glucose derived from small amounts of protein is lost, as is indicated by the D : N ration of 3.65 : 1 on a carbohydrate free diet.[33] Mandel and Lusk,[34] for example studied carefully the metabolism of such a case . The data they obtained concerning his nitrogen metabolism are presented in Table 22.

TABLE 21.—Hourly Rate of Nitrogen Excretion Per Kilogram in Diabetes Mellitus
(Benedict and Joslin)

Case	Age	Sex	Average N per K per Hr., Mg.	Weight		Height		Average Normal Weight	Digression	
				K.	Lbs.	Cm.	In		Lbs.	%
N	14	M.	12.1	31.5	63	146	57	95	—32	—34
P	17	M.	11.9	39.5	87	173	68	140	—57	—41
R	47	M.	11.6	55.3	112	181	71	177	—65	—37
X	35	M.	9.8	63.3	139	170	67	160	—21	—13
I	24	M.	9.5	40.0	88	176	69	152	—76	—50
T	43	M.	8.9	51.2	113	180	71	179	—66	—37
H	38	F.	8.4	54.1	119	159	62	129	—10	—8
U	37	F.	7.9	39.5	87	160	63	130	—43	—33
O	16	F.	6.9	52.6	116	173	68	138	—22	—16
M	57	M.	6.4	81.7	180	172	68	162	+18	+11
Q	14	M.	6.2	51.4	113	168	66	95	+18	+19
S	57	M.	5.5	58.0	128	177	70	169	—41	—24
W	18	F.	4.2	58.9	130	161	73	118	+12	+10

The fact that this patient was not in nitrogenous equilibrium when his food contained 19 gm. nitrogen, and that he lost 14 gm. body nitrogen when he was fed boullion only with a nitrogen content of 7.7 gm. is frequently cited as evidence of increased protein metabolism in diabetes. Even after the fuel value of the food which was useless to the patient because of his inability to utilize carbohydrate is subtracted, his total caloric intake was sufficient to supply his metabolic needs. A moment's thought, however, will show that the increase in protein metabolism can be entirely explained by his total inability to burn carbohydrate, rather than any disturbance in the protein metabolism inherent in the disease. Not only is carbohydrate itself unavailable for energy, but as has been pointed out, the fat is also unavailable to

33. Geylin, H. R., and Du Bois, E. F.: A Case of Diabetes Mellitus of Maximum Severity, J. A. M. A. **66**:1532, 1916.

34. Mandel, A. R., and Lusk, G.: Stoffwechselbeobachtungen an einem Fall von Diabetes Mellitus, Deutsch. Arch. klin. Med. **81**:472, 1904.

spare protein because it requires some carbohydrate combustion to do this.

Mosenthal has recently studied in two series of cases the maintenance diet in diabetes mellitus as determined by the nitrogen equilibrium. In the first study [35] he fed diets in which fat and protein were about equal gram for gram containing ten to fifteen grams of carbohydrate. He started with diets low in calories and increased them until nitrogen balance was established, always feeding equal amounts of protein and fat. With such diets he found that it was possible to establish nitrogen balance on a caloric intake equal to that required by a normal person, and in some cases it could be established at an even lower level. To provide from 1,500 to 2,000 calories it is necessary on a protein-fat diet containing equal quantities of protein

TABLE 22.—Studies of Metabolism of a Very Severe Diabetic (Mandel and Lusk)

Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Urine		Stool N, Gm.	Nitrogen		
					Glucose, Gm.	N, Gm.		In, Gm.	Out, Gm.	Balance, Gm.
19		Mixed diet			137	23.3	1.3	....	24.6	.....
21		Mixed diet			119	24.0	1.3	....	25.3	.....
23		Mixed diet			150	22.2	1.3	....	23.5	.....
25	117.5	170.7	84.8	2,580	148	20.9	1.3	18.8	22.2	—3.4
26	117.5	170.7	84.8	2,580	144	19.0	1.3	18.8	20.3	—1.5
27	117.5	170.7	134.8	2,768	179	18.5	1.3	18.8	19.8	—1.0
28	117.5	170.7	184.8	2,956	210	17.7	1.3	18.8	19.0	—0.2
29	117.5	170.7	184.8	2,956	217	17.8	1.3	18.8	19.1	—0.3
1	113.1	164.0	6.6	2,207	83	17.5	1.3	18.1	18.8	—0.7
2	168.1	222.4	5.5	2,789	88	23.2	1.3	26.9	24.5	+2.4
3	168.1	195.1	5.5	2,552	93	24.1	1.3	26.9	25.4	+1.6
4	191.1	192.1	5.5	2,645	100	27.7	1.3	30.6	29.0	+1.6
15	48.1	0	0	.....	85	21.7	...	7.7	21.7	—14.0

and fat to raise the protein ration to from 100 to 150 gm., and therefore Mosenthal found that nitrogen balance was established with relatively large amounts of protein—amounts that would not be tolerated without glycosuria by severe diabetics. Because of the fear of acidosis no effort was made to establish balance on low-protein, high-fat diets. Since he increased the protein content of the diet at the same rate as he did the fat it was to be expected that he would not feed enough calories to supply the body needs until the diet contained large amounts of protein. He showed, then, that when one feeds a diet containing equal weights of protein and fat, one is compelled to supply large quantities of protein in order to establish caloric equilibrium. He did not show that the diabetic requires more protein than the normal subject.

35. Mosenthal, H. O.: The Maintenance Diet in Diabetes Mellitus as Determined by the Nitrogen Equilibrium, Tr. Assn. Am. Phys. **32**:159, 1917.

In the second series of experiments,[2] an effort was made to determine the food value of alcohol, fat and protein by their abilities to spare nitrogen. After a few days on a control diet which usually contained about 70 gm. each of fat and protein and a small amount of carbohydrate, and which induced a negative nitrogen balance because of its low caloric content, he tried the effect of adding to the diets either alcohol or fat or protein or combinations of these. These additions brought the total calories up to from 1,500 to 2,000. Each such new diet was tried four to six days.

Only in occasional instances did the addition of fat establish nitrogen balance; since these were not severe diabetics, tolerating as they did from 150 to 200 gm. protein without glycosuria, the factors contributing to the enormous nitrogen output in such cases as that of Mandel and Lusk do not have to be considered. Mosenthal reached the conclusion that "the addition of an equal number of calories of protein, fat or alcohol to a low caloric, carbohydrate-free diet in cases of diabetes mellitus results in the assimilation of considerable amounts of nitrogen when protein is used, a favorable nitrogen balance in only occasional instances with fat, and no change in the nitrogen equilibrium when alcohol is given," and he stated that "this would point to a high protein diet as the most advisable low-caloric, carbohydrate-free diet by which to conserve the body tissues and furnish a maintenance ration for the diabetic."

We cannot accept these conclusions, however, because the experimental periods employed by Mosenthal were too brief to permit the subjects to totally rid themselves of the metabolic products of the previous diet or to readjust themselves to the new diet.

It was shown by C. Voit (Table 13) that it took fasting dogs five days to reach a common level of nitrogen excretion and that the higher the nitrogen content of the previous diet the more striking was the fall of nitrogen output from day to day. Weintraud showed (Table 17) in diabetics that the addition of fat to a high-protein, low-fat diet which induced a negative nitrogen balance would induce a positive balance only after several days had elapsed. A subject to whom he was feeding 111 gm. protein and 28 gm. fat had a negative balance of 6.7 gm. nitrogen. It was not until six days after the addition of 245 gm. fat to this diet that the first positive balance of only 1.34 gm. was attained. Three days later, on the same diet, the balance was 3 gm. We have had this same experience and have convinced ourselves that one is not justified in judging of the effect of a diet until it has been fed at least a week.

In two of Mosenthal's ten cases, the increase in fat followed immediately after a period of high protein feeding. The results are shown in Table 23.

In each of these cases the negative balance during a high-fat period following immediately after a high-protein period was greater than the negative balance during the control period when the total calories were a third less; this negative balance represented merely the continued excretion of the previously ingested protein. Case 5 had, in fact, been in nitrogen balance on the added fat on a previous occasion, when it did not follow a high protein period. The extract presented in Table 24 from the record of Case 7 in our series shows a similar lag in the excretion of nitrogen, with the subsequent sweeping-out during the following few days, and the eventual establishment of practical nitrogen balance.

During the period of high-protein feeding there was an apparent retention of nitrogen in the body, but during the succeeding low-protein

TABLE 23.—Effect of Previous High Protein Diet on Nitrogen Balance (Mosenthal)

Case	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	N Balance, Gm.	N Balance on Control Diet, Gm.
5	150.6	89.4	13.4	1,502	+2.6	−2.7
	71.2	125.6	12.1	1,506	−3.1	
8	150.2	89.4	13.5	1,503	+5.7	−1.5
	71.4	125.2	12.0	1,510	−3.4	

TABLE 24.—Effect of Previous High Protein Diet on Nitrogen Balance

	Food, Daily Average				Daily Average			Total for Period		
Days	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	N In, Gm.	N Out, Gm.	N Balance, Gm.	N In, Gm.	N Out, Gm.	N Balance, Gm.
5	185.0	99.1	14.6	1,700	29.58	18.38	+11.20	147.88	91.89	+55.95
6	32.7	145.9	26.0	1,560	5.23	14.75	−9.52	31.38	88.48	−57.10
6	33.5	150.1	25.4	1,585	5.26	5.41	−0.05	32.16	32.48	−0.32

period this nitrogen was all excreted; the total nitrogen ingested was 179.26 gm. and the total nitrogen excreted was 180.37 gm., practically a balance.

Another error in these short period experiments arises from the fact that the organism apparently requires some time to adjust itself to new dietetic conditions. Sherman believes that the variations between the results of numerous investigators of the minimum protein intake that would support nitrogen balance was due, in part, to "the differing lengths of the investigations and the extent to which the individual had accustomed himself to a low protein diet." He says further that "while it is conceivable that a small loss of body nitrogen may represent a real inadequacy of the intake, perhaps as regards some particular amino acids, yet it is usually much more probable that a small negative balance means simply that the body has not yet completed the adjust-

ment of its output to its intake and that a continuation of the experiment would have shown a smaller output."

Several of Mosenthal's patients were returned to the control diet immediately following the diet to which fat had been added; the control period, the fat period and the second control period are shown in Table 25.

In all these cases the saving of protein by fat showed in the period following the one during which the fat was given, as shown by the smaller negative nitrogen balance on the control diet after the fat feeding than before it. It seems safe to conclude that if the fat feeding had been continued a longer time in each case, nitrogen balance would have been established.

TABLE 25.—Delayed Effect of Addition of Fat in Establishing Nitrogen Balance

Case No.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories, Gm.	N Balance Gm.
1	71.4	70.5	12.3	999	−2.8
	71.3	125.1	12.1	1,505	−0.5
	71.7	70.6	13.4	1,001	−0.9
3	71.5	70.5	12.4	1,000	−3.0
	71.4	125.2	12.2	1,507	−2.9
	71.5	70.4	12.8	1,000	−1.3
6	71.4	70.5	12.4	1,000	−3.0
	71.4	125.2	12.2	1,507	−2.9
	71.5	70.4	12.8	1,000	−1.3
7	71.8	70.4	12.5	1,000	−2.9
	71.2	126.6	12.4	1,520	+1.2
	71.6	70.6	12.5	1,001	−0.9
	71.4	125.4	12.2	1,509	+1.7
	71.9	70.2	13.1	997	−1.5

As the result of these studies and others of a similar nature, the belief has become general that patients with diabetes mellitus require more protein for the establishment of nitrogen balance than do normal subjects, and that there is, as an inherent part of the disease, an abnormally high rate of protein metabolism with an increased elimination of nitrogen.

Most of the previous investigators have been handicapped by the fear of the use of fat in the treatment of diabetes mellitus, and have hence in none but the mildest cases, been able to increase the nonprotein calories to a level that would satisfy the energy requirement without the production of glycosuria. The use of a high-fat, low-protein, low-carbohydrate diet in this clinic has enabled us to study in a more satisfactory manner than was hitherto possible, the minimal protein intake that will maintain nitrogen balance in the diabetic.

In Table 26 are presented the lowest diets on which nitrogen balance was established in our series. It must be remembered that this does not represent in every case the lowest possible level for balance, but the level at which, in the course of treatment, balance was established.

Some cases, as for example Case 6 in which the positive balance was at first over 2.5 gm. nitrogen or 16 gm. protein, could undoubtedly have been established in balance on a lower ration than that allowed.

In spite of the fact that these diets cannot be considered as the lowest on which nitrogen balance could have been established, they contained an average of 0.68 gm. protein per kilogram of body weight. This agrees with the figure found by Hindhede and others on normal subjects, and demonstrates that the diabetic patient may be maintained

TABLE 26.—Diets on which Nitrogen Balance was Established in Twelve Patients with Diabetes Mellitus

Case No.	Age, Years	Weight, Kg.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	N, Gm.	Protein per Kg., Gm.	Calories per Kg.	Per Cent. of Total Calories as Carbohydrate
1	56	63	34.3	168.4	6.9	1,680	5.49	0.54	27	1.6
2	68	66	39.2	231.4	13.8	2,295	6.27	0.59	35	2.3
3	37	60	54.1	240.0	13.4	2,430	8.66	0.90	41	2.2
4	18	42	28.5	162.8	9.9	1,615	4.49	0.68	38	2.4
5	21	50	37.8	163.6	8.2	1,650	6.05	0.75	33	1.9
6	49	70	65.0	197.0	9.9	2,065	10.04	0.93	30	1.9
7	22	59	32.5	150.1	25.4	1,585	5.26	0.53	27	6.4
8	36	69	55.5	207.8	38.7	2,245	8.80	0.79	33	6.9
9	63	50	31.8	157.4	23.8	1,640	5.09	0.63	33	5.8
10	80	80	51.4	239.1	33.9	2,295	8.22	0.57	25	6.0
11	22	55	40.6	209.2	25.0	2,065	6.50	0.74	37	4.8
12	18	42	30.0	179.6	14.7	1,705	4.80	0.71	43	3.3

in nitrogen balance on as low a protein ration as the normal subject. The average number of calories per kilogram of body weight given to this group of patients was 33.5 and of these calories, an average of only 3.8 per cent. were in the form of carbohydrate.

The average amounts of each of the foodstuffs used to make up these 33.5 calories are shown in Table 27. The fat in grams is ten times the carbohydrate in grams, or if the 58 per cent. of the carbohydrate that may be derived from protein be added, the weight of the

TABLE 27.—Average Amounts of Foodstuffs Per Kilogram of Body Weight Used in Establishing Nitrogen Balance

	Grams	Calories
Protein	0.68	2.72
Fat	3.28	29.51
Carbohydrate	0.32	1.37

fat is four and one half times that of the total carbohydrate. The carbohydrate calories are 3.8 per cent. of the total calories, or, if the protein carbohydrate be added, the total carbohydrate calories are only 8.6 per cent. of the total calories. Nitrogen balance can be established in the diabetic on diets low in protein whose energy is chiefly contained in fat.

To this law, however, there is an exception which for the sake of completeness must be mentioned again. A case such as that studied

by Mandel and Lusk, although very rare, is so severe as to have lost its ability to burn carbohydrate even in the small amounts necessary for the metabolism of fat. Such a diabetic who has so lost the ability to burn both carbohydrate and fat is inevitably thrown back on protein as a source of energy. The impossibility of satisfying his caloric requirement in other ways results in the excessive metabolism of protein. The rarity of such cases, however, makes them of little practical importance.

Several observations made during this study and already discussed should be mentioned again in this place. One case was cited which showed a delay in excretion of nitrogen during the administration of a high protein diet, with a sweeping-out during the following days of low protein feeding. As a result, there was an apparent large positive nitrogen balance during the high protein period, a large negative balance during the few days immediately following, and the ultimate establishment of balance after a few days (Table 23). Attention has also been called to the fact that nitrogen balance may be established on a given diet only after it has been administered for some time.

A diabetic patient suffering from advanced chronic pulmonary tuberculosis was studied. The data obtained were in accord with the observations of McCann and Barr and others regarding the increased protein destruction in tuberculosis.

Case 13 (20-461).—Patient was a German-American ward tender, 28 years old, who was brought into the ward in impending coma after having tried to treat his diabetes with drugs and without diet. The diabetes was of about three years standing, and there had been no symptoms of tuberculosis. After a few weeks of treatment, he was in excellent condition as far as his diabetes was concerned, but his tuberculosis was advancing rapidly and came to a fatal termination about a month after the first nitrogen determinations were made. The diagnosis of tuberculosis was made by physical examination and confirmed by roentgenogram, acid-fast bacilli in the sputum and necropsy. The day to day data of the last month of this patient's life are presented in Table 28 and a summary in Table 29. He died September 25, without glycosuria or a positive ferric chloride test on his urine, and there was no evidence of acidosis as measured by the VanSlyke method. During the last six weeks his temperature, which had previously been normal, reached from 100 to 103 F. daily.

The contrast between this patient who showed so large a negative nitrogen balance on 0.8 gm. protein and 40 calories per kilogram of body weight, and the nontuberculous cases summarized in Table 25 is striking. The increasing nitrogen output in both urine and stool as death approached is also interesting.

An observation is made concerning the relation of nitrogen output to the caloric intake which is very important and which could be predicted from the fundamental laws governing protein metabolism established by the earlier workers in this field. As calories are added to

the diet in the form of fat the break-down of protein as measured by the nitrogen excretion is diminished. This ability of fat to save protein is especially evident on Cases 5 and 11 in which with unchanged protein intake the nitrogen elimination was markedly decreased by the addition of fat to the diet. It is equally striking that as the diet including protein is increased, with the chief increase, however, in fat, the nitrogen excretion falls. In Table 30 are presented data from six

TABLE 28.—PART OF RECORD OF CASE 13; DIABETES MELLITUS COMPLICATED BY CHRONIC PULMONARY TUBERCULOSIS

Date	Diet				Urine		Blood Sugar, per Cent.	Nitrogen				Wt., Lbs.
	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic		Urine, Gm.	Stool, Gm.	In, Gm.	Out, Gm.	Balance, Gm.
8 25	28.8	138.4	20.3	1,440	0	0	0.21	....	....	....	....	.....	93
26	29.7	141.3	21.8	1,480	0	0	....	....	....	....	....	.....	..
27	28.8	138.4	20.3	1,440	0	0	....	....	....	....	....	.....	..
28	39.9	192.6	16.6	1,765	0	0	....	....	....	....	....	.....	..
29	29.9	140.8	19.0	1,465	0	0	....	....	....	....	....	.....	..
Aver. 8 30 to 9 13	29.6	134.3	19.6	1,405	..	..	....	5.71	0.72	4.74	6.43	—1 69	
	34.0	160.0	27.0	1,685	0	0	....	....	....	....	....	.....	90
9/14	34.9	179.7	27.3	1,865	0	0	....	....	....	....	....	.....	..
15	33.5	158.8	26.3	1,670	0	0	....	....	....	....	....	.....	94
16	32.0	142.2	28.6	1,540	0	0	....	....	....	....	....	.....	..
17	36.4	163.5	31.0	1,760	0	0	....	....	....	....	....	.....	..
Aver.	34.5	161.5	33.3	1,725	..	..	....	6.58	0.89	5.52	7.47	—1.95	
18	34.4	143.1	25.7	1,530	0	0	0.20	....	....	....	....	.....	94
19	34.7	182.6	24.4	1,880		0	....	....	.. ..	....	....	.....	..
20	30.7	156.1	25.5	1,630	0	0	....	10.42	0.99	4.91	11.41	—6.50	..
21	34.7	151.1	26.4	1,605	0	0	....	7.45*	1.00*	5.55	8.45	—2.90	..
22	33.5	174.4	26.2	1,805	0	0.24	7.45*	1.00*	5.40	8.45	—3.05	94	
23	35.0	209.5	26.7	2,130	0	0	....	6.26*	1.37*	5.60	7.63	—2.03	..
24	35.3	153.7	26.8	1,630	0	0	....	6.26*	1.37*	5.65	7.63	—1.98	..

* Average of two days' specimens.

TABLE 29.—SUMMARY OF CASE 13; DIABETES MELLITUS WITH PULMONARY TUBERCULOSIS

Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Nitrogen			
					Urine, Gm.	Stool, Gm.	In, Gm.	Out, Gm.	Balance, Gm.
8 25-8 29	29.6	134.3	19.6	1,405	5.71	0.72	4.74	6.43	—1.69
9/14-9/17	34.5	161.5	33.3	1,725	6.58	0.89	5.52	7.47	—1.95
9 20-9/24	33.8	169.0	26.3	1,760	7.57	1.15	5.41	8.72	—3.31
9/25	Death from pulmonary tuberculosis								

of the cases who show this decrease in protein metabolism; there are added to the tables the amounts of protein burned as estimated by multiplying the excreted nitrogen by 6.25 and the amount of glucose derived from this protein calculated as 58 per cent. of the protein. A diet too low in calories to meet the energy requirement may, because of its accompanying excessive nitrogen metabolism, produce (from the protein) large amounts of glucose which are avoided by the addition of more calories. In one of our cases the glucose so derived was

over 20 gm. To the diabetic this amount of glucose may be very important, and may be replaced by an equivalent amount of carbohydrates in the diet. By decreasing the ingested protein one may increase the carbohydrate in the diet without increasing the total carbohydrate metabolism. Furthermore, by decreasing the endogenous protein metabolism one may also increase the carbohydrate in the diet without increasing the total carbohydrate metabolism. Both of these desiderata may be achieved, with maintenance of nitrogenous equilibrium, through the addition of calories to the diet in the form of fat.

These facts show a fallacy of starvation in the treatment of diabetes. During the period of starvation, a subject well supplied with body fat burns this fat, and burns no less than he would if the fat were given him in the diet. This was demonstrated by Voit's experiment on a dog which has already been mentioned. In the case of the fasting lean diabetic, however, who cannot burn glucose, and whose supply of body fat is low, energy and heat are developed almost entirely by the combustion of protein. Destruction of body protein produces glucose exactly as much as does combustion of ingested protein. In the more severe grades of diabetes this is a factor of prime importance. Such patients become sugar free sooner if they are allowed a little carbohydrate and a relatively large amount of fat than they do if starved. One of our patients was starved ten days on several occasions before coming to us without his urine becoming sugar-free. On a diet containing about 15 gm. protein, 90 gm. fat and 15 gm. carbohydrate, he became sugar-free in ten days, and was in relatively excellent physical condition at the end of the period, in contrast to his exhaustion at the end of his periods of starvation. A diabetic boy, 6 years old, failed to become sugar-free after seven days of starvation following a period of two weeks of a low caloric diet. On a diet containing 12 gm. protein, 85 gm. fat and 15 gm. carbohydrate his urinary sugar gradually decreased in amount and finally disappeared. A young woman who had had a constant glycosuria during ten months on a diet containing 50 gm. protein, 20 gm. fat and 30 gm. carbohydrate and who had failed to become sugar-free on nine days of practical starvation became sugar-free in five days on a diet containing 15 gm. protein, 85 gm. fat and 14 gm. carbohydrate. The enormous metabolism of body protein during starvation with the production of large quantities of endogenous glucose explains, in part at least, the more favorable results of a diet relatively rich in fat.

The same undesirable production of glucose from body protein occurs to a lesser degree when an under nutrition diet is used in the treatment of diabetes mellitus. If the total calories fed the patient are not sufficient to supply caloric requirement, body protein is broken

down and glucose is produced. If an effort is made to supply enough protein in the diet to compensate for this excessive destruction of body protein, the ingested protein is a source of glucose. Just in so far as the carbohydrate burning function of the patient must be used for the combustion of glucose derived from protein, just so much more must his carbohydrate intake be limited. Fat offers the best agent in the diabetic for the sparing of protein, either endogenous or exogenous.

The increase in the metabolic rate, due to the specific dynamic action of protein, has been discussed.

That this increase in metabolism is not insignificant in such a condition as diabetes mellitus in which an effort is made to establish the metabolism at a low level is readily seen from a single example. Assuming that a fasting subject requires 2,000 calories a day, and

TABLE 30.—Decrease in N-Excretion with Increase in Caloric Intake

Case No.	Days	Calories	N In, Gm.	N Out, Gm.	Protein, Metabolism, Gm.	Glucose from Protein, Gm.
1	9	980	2.64	6.24	39.00	22.62
	6	980	2.61	6.87	42.94	24.91
	6	1,050	2.56	6.21	38.81	22.51
	5	1,590	5.42	5.72	35.75	20.73
	9	1,680	5.49	5.63	35.19	20.41
3	2	900	2.61e	13.85	86.59	50.22
	4	1,400	4.77	11.81	73.81	42.81
	3	2,260	6.53	8.42	52.62	30.52
	5	2,430	8.60	8.12	50.75	29.43
4	8	1,410	3.98	7.65	47.81	27.73
	6	1,925	5.89	6.31	39.04	22.99
	3	1,925	5.89	5.77	36.04	20.91
5	5	475	2.46	9.24	58.38	33.86
	4	1,380	5.99	8.82	55.13	31.98
	3	1,380	5.99	8.10	50.63	29.37
	6	1,650	6.05	6.62	40.97	23.76
11	4	1,500	5.42	6.74	42.13	24.44
	4	2,265	8.22	5.00	31.25	18.12
12	2	1,530	4.93	6.96	43.50	25.23
	4	1,535	4.77	5.37	33.56	19.46
	4	1,795	4.80	4.86	30.37	17.61

that the heat eliminated as a result of the specific dynamic action of the foodstuffs is for protein, 30 per cent., fat 12 per cent. and carbohydrate 6 per cent., one may easily calculate the actual increase over the 2,000 calories that will result from various types of diets. A diet of the von Noorden type will contain 2,000 calories if they are divided as follows: protein, 200 gm.; fat, 120 gm.; carbohydrate, 30 gm. When the calories resulting from the specific dynamic action be added, however, the diet becomes the following: Protein, 286 gm.; fat, 136 gm.; carbohydrate, 32 gm.; calories, 2,496. The original calories are, on the other hand, contained in a diet which still contains but 30 gm. carbohydrate, but in which the protein and fat amount to 35 and 193 gm., respectively. The diet resulting from the addition of extra calories is as follows: Protein, 50 gm.; fat, 219 gm.; carbohydrate, 32 gm.; calories, 2,299. In the case of the high protein diet, the increase was

500 calories, or 25 per cent. of the fasting requirement, and in the case of the high fat diet, the increase was 300 calories, or 15 per cent.

In passing, attention should be called to the well known fact that nitrogen in the food in excess of the body requirement is excreted and is not stored. This is true in the diabetic as in the normal. In Case 6, for example, the patient was given 65 gm. protein in his food daily; during the first few days of this diet he had a positive nitrogen balance of more than 2.5 gm. daily, but after a few days the nitrogen excretion rose until he was established in practical balance. The high protein diet which was given Case 7 has already been discussed and it was pointed out that there was no real addition of nitrogen to the body. Furthermore, this patient was in balance at one time on 33 gm. protein a day and later on 55 gm. protein a day. Since the excess of nitrogen above the requirement is excreted there is no apparent advantage in feeding the diabetic patient large amounts of protein. On the contrary, as has been pointed out, this excess of protein is undesirable in the diet of the diabetic.

CONCLUSIONS

1. Nitrogen balance can be established in the diabetic according to the laws applicable to the normal subject provided his total caloric requirement can be satisfied. This implies that he can burn enough glucose to metabolize fat. Diabetics who cannot burn this small amount of glucose are extremely rare.

2. Protein metabolism above the minimal is undesirable in the diabetic because of (1) the great glycogenic property and (2) the large specific dynamic action of protein. Excessive protein metabolism results from a diet containing either too much protein or too few total calories.

MYCOTIC EMBOLIC ANEURYSMS OF PERIPHERAL ARTERIES *

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The pioneer investigators of the etiologic factors and pathologic processes in arteries have, in a large measure, centered their attention on the more imminent problems of the subject, so that today a wealth of information has been contributed to our knowledge of syphilis and sclerosis of vascular channels. Again, the results of more acute bacterial invasion on the wall of both the aorta and the peripheral arterial tree, as well as the various manifestations of the same organisms on the different arterial systems of the tree, have been studied carefully by others. This is especially true in the case of acute rheumatic fever, with or without an attending acute or subacute bacterial endocarditis, and, to a lesser extent, in other acute affections, notably scarlet fever, septicemia, typhoid fever and pneumonia. Thus our understanding of the modus operandi of acute bacterial invasion of the peripheral arteries has broadened. It is only natural that more accurate data on the latter manifestations of these infections have gone far to clarify our conception of the detailed materies morbi of such a condition as aneurysm. While the greatest stress has been placed on aneurysm of the aorta, particularly on aneurysms of syphilitic origin, nevertheless, a certain light has been thrown on the aneurysms as encountered in the arteries of a smaller caliber whether specific or nonspecific.

L. Koch,[1] in 1851, described a case of ruptured aneurysm of the superior mesenteric artery associated with a verrucose aortic endocarditis. Two years later, Tufnell [2] called attention to the co-existence of aortic endocarditis and popliteal aneurysm. In 1864, Chauffard [3] reported a similar aneurysm of the superior mesenteric artery while three years after Waterman [4] discussed one of the brachial artery in a case of valvular disease of the heart. While these cases suggested that the aneurysms were mycotic-embolic in origin, Ponfick,[5] in dis-

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1. Koch, L.: Inaug. Dissertation, Erlangen, 1851.
2. Tufnell: Dublin Quart. J. M. Sc. **15**:371, 1853.
3. Chauffard: Union méd., 1865, p. 54.
4. Waterman: Western J. M., 1867, p. 584.
5. Ponfick: Virchows Arch. f. path. Anat. **58**: 1873.

cussing an aneurysm of the superior mesenteric artery in a patient with recurrent endocarditis, emphasized the mechanical effect rather than the infective character of the embolus. Legroux [6] recounted the instance of an infected embolus in the axillary artery, occurring in a girl with endocarditis. The embolus gave rise to an arteritis and resulted in aneurysm. Again, Jacobson [7] believed that his case of double aneurysm of the superior mesenteric artery precluded the possibility of an embolic origin. In this case there was a concomitant aortic endocarditis in which streptococci were isolated from the valvular vegetations. On the other hand, Humphry [8] described an instance of multiple embolic aneurysms of the pulmonary artery which had their genesis from vegetations around the orifice of the pulmonary artery. It was for Eppinger,[9] in 1887, however, to give the results of the first comprehensive study of a group of aneurysms of peripheral arteries which he called "mycotic-embolic." Since then analagous cases have been described by Lazarus,[10] Nasse,[11] von Gabriel,[12] Libman,[13] Schmey,[14] Routier,[15] Weinberger,[16] Roger and Gouget,[17] Lewis and Schrager,[18] Wieland,[19] Lindbom [20] and others. Save for the endeavors of the last three authors, few attempts have been made to collect the reported cases. At the present time it would appear that over a hundred well-authenticated instances of mycotic-embolic aneurysms of peripheral arteries are on record. Although no artery or system of arteries is exempt, this type of aneurysm apparently occurs most frequently in the superior mesenteric artery.

The term "mycotic-embolic" aneurysm, as coined by Eppinger,[19] implies that two factors are operative—the embolus and the mycosis or infection. It is imperative that this idea be borne in mind for it is recognized that an embolus which is not infective may produce an aneurysm, as in the case of a calcareous plaque cutting the intima (Libman [13]) and that all mycotic aneurysms are not necessarily embolic

6. Legroux: Semaine méd., 1884, p. 425.
7. Jacobson:: Bull. Soc. Anat., Par. **72**:569, 1897.
8. Humphry: J. Path. & Bacteriol. **17**:212, 1912.
9. Eppinger: Arch. f. klin. Chir. **35**:1, 1887.
10. Lazarus: Berl. klin. Wchnschr., 1891, p. 41.
11. Nasse: Deutsch. klin. Wchnschr. **24**:259, 1892.
12. Von Gabriel: Zentralbl. f. Chir. **31**:2, 1904.
13. Libman: Tr. New York Path. Soc. **88-91**, 1905.
14. Schmey: Cited by Roche and Burnaud: Semaine méd. **28**:145, 1908.
15. Routier: Semaine méd., 1905, p. 306.
16. Weinberger: Mitt. d. Gesselsch. f. inn. Med. u. Kinderh. **5**:4, 1906.
17. Roger and Gouget: Nouveau traité de medicine et de therapeutique de Bronardel et Gilbert, Paris **24**:25, 1907.
18. Lewis and Schrager: J. A. M. A. **53**:1808 (Nov. 27) 1909.
19. Wieland: Med. Cor.-Bl. d. Württemb. ärztl. Landesver. Stuttg. **82**:565, 1912.
20. Lindbom: Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, Separatabdruck, 1914.

in nature, the infection being capable of entering the arterial wall by direct extension from the adventitia, by way of the vasa vasorum, as in the acute mycotic aneurysms of aorta (Osler,[21] McCrae,[22] Klotz [23]) or from the lumen at the point of contact of a septic embolus or thrombus. Not only have there been misconceptions and misunderstandings in the interpretation of these cases but also considerable controversy has arisen and opposite views have been offered to explain the sequence of events after the lodgment of the bacteria laden embolus. Consequently, we feel that a consideration of at least the possibilities of the order of pathologic events and an adaptation of the experiences and observations of other workers to the two such cases we have encountered at necropsy will not be amiss.

Fig. 1.—Case 1. Ventral surface of mesentery showing branches of superior mesenteric artery and hemorrhage into mesentery.

REPORT OF CASES

Case 1.—A male, aged 38, was admitted to the hospital complaining of coughing, shortness of breath and intense pain in the epigastrium.

Previous Illness.—The history of his illness showed that he had had a number of attacks of "rheumatism" and that on more than one occasion there had

21. Osler: Allbutt's System of Medicine **6**:620, 1909.
22. McCrae: J. Path. & Bacteriol. **10**:373, 1905.
23. Klotz: J. Path. & Bacteriol. **18**:259, 1913.

been signs of a cardiac decompensation. The intense pain in the epigastrium, however, had been present only with the last attack.

Physical Examination.—The physical examination revealed an endocardial lesion of the aortic and the mitral valves associated with a moderate cardiac hypertrophy. The lesion was a regurgitant one at both orifices. The pulse was very rapid, between 120 and 140, weak and collapsing. The temperature was 102 F. There was some hypostatic congestion at the bases of the lungs. The abdomen was very painful to touch, and the abdominal muscles were quite rigid so that accurate palpation was difficult. The leukocyte count was 10,000.

Clinical Course.—The pain in the epigastrium, which commenced about twelve hours before his admission, persisted until his sudden death—a few hours after coming into the hospital. Although the pain gradually became less acute, at the onset it was very intense.

Necropsy.—At necropsy it was found that death had followed the rupture of an aneurysm of a branch of the superior mesenteric artery with a resultant hemoperitoneum. The heart showed hypertrophy and dilatation with a vegetative aortic, mitral and mural endocarditis, superimposed on a chronic sclerotic process of these valves. Passive congestion was present in the lungs and in the liver.

Description of Aneurysm.—The aneurysmal pouch was situated on the dorsal surface of the mesentery, near the attachment to the coils of the small intestine. It was irregularly oval in shape and measured 2.8 by 2.5 by 1.3 cm., being of such size as readily to accommodate a large marble. On the ventral surface, the aneurysm was supported by a massive blood clot while on the dorsum, where a ragged, linear slit indicated the site of rupture and the cause of the hemoperitoneum, it lay very close to the peritoneum. The aneurysm was continuous with a terminal branch of the superior mesenteric artery. The wall of the aneurysm was thin, though reinforced posteriorly by blood which had escaped into the mesentery, causing a marked thickening of it. The lining of the sac was roughly corrugated and consisted, for the most part, of a thick, friable layer of pinkish gray, granular organized blood clot. An intact rim of intima remained at the point where the artery entered the aneurysm. At a slightly higher level, another irregularly oval cavity, which could have easily admitted a hazelnut and represented a false aneurysm, occurred. It was encompassed by a thick layer of extravasated blood clot. The lining of the second cavity consisted only of several lamellae of well organized blood. Both cavities were connected by a small ragged opening. It was obvious that the true aneurysm had slowly ruptured at an earlier date with the formation of a false aneurysm and wholesale extravasation of blood into the mesentery. The process, as now seen, was relatively late so that the former embolus had disappeared in the thrombus. There was a stenosis of the artery at its entrance to the aneurysm. Above this, the arterial wall was thick and the intima was nodular.

Case 2.—The second aneurysm, that of the right posterior tibial artery, was recovered at necropsy from a man, aged 39, who for twenty-six weeks had pursued a typical clinical course of subacute bacterial endocarditis.

History.—He entered the hospital six weeks before his death, complaining of weakness with a little cardiac distress, particularly on moving in bed. At times he suffered from chilly sensations and felt feverish in the afternoon. This had been his condition since the onset of his illness, along with a progressive weakness. At this time the patient's temperature varied from 101 to 103 F., and the pulse from 120 to 130. There was a marked pallor.

Physical Examination.—The heart was somewhat enlarged and presented a double murmur which could be heard over the whole of the precordium, in the left axilla and at the back. The liver was palpable immediately below

the costal margin. Lying behind the head of the right fibula and just below it, there was an expansile round mass about the size of a small tangerine orange. One could palpate very easily a considerable portion of its surface. Its expansile pulsation was synchronous with the arterial pulse. This pulsating mass did not alter, to any great extent, the contour of the leg, although its pulsation was quite visible. The right leg below this appeared normal in every respect.

Laboratory Examination.—During the patient's stay in the hospital, which was a little over six weeks, *Streptococcus salivarius* was isolated from the blood stream on three occasions. The leukocyte count was about 12,000. Albumin, casts and red blood cells were present in the urine at various times.

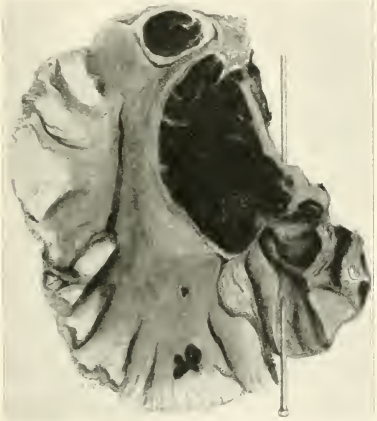

Fig. 2.—Case 1. Dorsal surface of mesentery showing ruptured mycotic-embolic aneurysm of superior mesenteric artery.

Clinical Course.—Two weeks before his death he complained of a sharp lancinating pain in the region of the pulsating mass below the right knee. Almost immediately afterward a diffuse indurated swelling, which gradually extended to the lower portion of the calf of the leg, appeared. The leg became very painful, quite hard and of a dusky brown color. It was now impossible to outline, by palpation, the pulsating mass behind the head of the fibula, although one could still feel the pulsation here, as well as in the dorsalis pedis artery, and the foot appeared warm. In a few days, however, the foot became edematous and it was then impossible to palpate this artery. Even to the end there was no evidence that the circulation in the foot had been cut off. One week after this accident had occurred, signs of fluctuation

were present in the calf of the leg. It was considered wiser to refrain from an incision. The patient became more septic, dying about two weeks after the rupture of the aneurysm in the leg.

Necropsy.—At necropsy, the enlarged heart showed an acute and subacute vegetative mitral endocarditis, which had been planted on the thick, sclerosed valve cusps. Recent infarcts occurred in the spleen and kidneys.

Description of Aneurysm.—At the inferior margin of the right popliteus muscle, and lying posterior to the interosseous membrane, was an aneurysm which had evidently arisen from the tibial artery, a few centimeters distal to the bifurcation of the popliteal artery. The aneurysm was large, irregular in outline and presented three definite sacculations. Into the largest of these the artery opened from above. This compartment was the size of an English walnut, possessing a thin wall and a smooth, white, corrugated lining. With this main portion, two smaller sacs were associated. One, the size of a hazelnut, was tortuous and lined by a gray, laminated blood clot so that its wall was thick and stratified. The other sacculation, which was the smallest, lay posteriorly and inferiorly to the medium-sized one and its lining was identical with that of the main chamber. In the dependent tip of the smallest sac, a tiny opening was all that remained of the distal portion of the artery which had disappeared in the intense secondary cellulitis of the surrounding soft parts. Posteriorly and above, the main aneurysm had ruptured, as a result of which a laminated blood clot, the size of an orange, intervened between the exterior of the true aneurysmal sac and the soleus muscle. All the sacs contained dark red fluid blood, in addition to the thrombus which had obscured, no doubt, the original embolus. The popliteal artery was thick-walled and its intima was nodose. Where the posterior tibial artery entered the aneurysm, its thick, fibrosed wall was constricted, causing a narrowing of the lumen. It was clear in this case also, that a rupture of the true aneurysm with slow leakage into the contiguous soft parts had led to the formation of a false aneurysm. In addition, an extensive secondary suppurative cellulitis had wrought havoc with the leg from the knee to the foot. The popliteal vein showed no demonstrable change.

Microscopically, the sections of the walls of these two aneurysms presented an almost identical picture. The walls were made up chiefly of a relatively recent fibrous tissue. In the fibrous tissue, one was able to distinguish some smooth muscle, representing the remains of the muscular coat of the artery. Attached to the inner lining was a hyaline thrombus, well-infiltrated with polymorphonuclear leukocytes, lymphocytes, plasma cells and numerous endothelial cells containing blood pigment. This cellular infiltration extended through the wall to its periphery where there was considerable hemorrhage and marked invasion of all types of inflammatory cells. On staining for elastic tissue, remnants of the elastica interna were occasionally seen. In the deeper portions of the wall a few broken elastic fibrils were found. In the second case, gram positive cocci in short chains were noted in the cellular infiltration at the periphery of the wall. The aneurysmal wall, therefore, consisted largely of chronic inflammatory tissue. The finding of muscle and elastic tissue indicated that the media of the artery had shared in its formation.

Comment.—A comparison of the salient features of these two cases shows that in both an aneurysm of a peripheral artery occurred, one in the superior mesenteric and the other in the posterior tibial artery. Both were associated with a definite acute and subacute vegetative endocarditis of the mitral or aortic valves. In one case infarcts were found in the spleen and kidneys. *Streptococcus salivarius* was isolated from the blood stream of one case during life. Unfortunately, the

sudden death of the other case prohibited antemortem cultures, while the autopsy cultures, taken 24 hours after death, showed only secondary invaders. No suggestion of syphilis was found in either case at necropsy. Both aneurysms had ruptured, at first slowly, with the formation of a false aneurysm. Clinically the rupture of the aneurysms was characterized by severe, sudden, lancinating pain, which persisted.

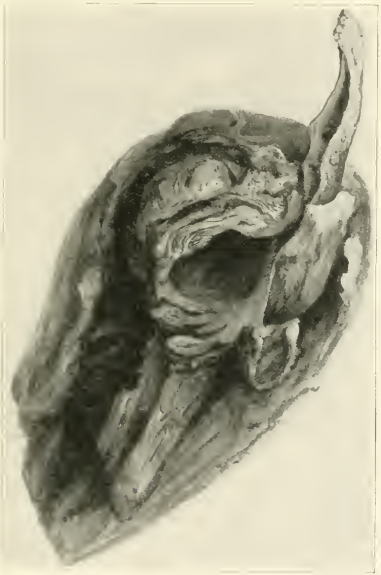

Fig. 3.—Case 2. Mycotic-embolic aneurysm of posterior tibial artery.

While no embolus was found at the aneurysmal sites in either case, it must be remembered that the aneurysms were far advanced and that well organized thrombi were present in them. This, in itself, could cause a complete disappearance of the original small embolus and does not preclude the liklihood of the one-time presence of the

embolus. From the evidence at hand, it seems clear that both aneurysms had their beginning in the bacteria-laden embolus which was swept off the affected heart valve, lodging at the bifurcation of the artery involved.

As had been stated, the aneurysms, as they came to us, represented the end results of an acute inflammatory process wherein, at this time, it was impossible to recognize the sequence of events from the primary endarteritis produced by the infected embolism. It has been definitely shown by Virchow [24] and Klotz [25] that a primary inflammation of the intima can occur and that the cellular exudate found in the intima appears to arise by a direct immigration of the wandering cells from the lumen of the artery. Eppinger,[9] in his exhaustive studies of mycotic-embolic aneurysms associated with acute vegetative endocarditis, held that the infected embolus produced an inflammation of the vessel wall at the point of contact. He believed that the infection spread from this point in the intima to the adventitia and that the aneurysm was due to the inflammatory process extending inwards from adventitia to the media, causing a rupture of the internal elastic lamina with subsequent arterial dilatation. Eppingers' work has been quite generally accepted, although other conceptions of the mode of formation of these aneurysms have been advanced. Benda [26] and, later, Wieland [10] considered the condition to be secondary to an extension of the inflammation in the intima through the elastica interna to the media and then to the adventitia, regarding the primary intimal lesion as an ulcerative endarteritis. In support of this view, McMeans [27] has shown that when the process is particularly acute and incited under conditions of septic thrombosis or infected embolus, there is destruction of the intima with extension of the inflammation through the vessel wall. On the other hand, where the process is not so acute, Klotz [28] has demonstrated that both the intima and the adventitia can be involved simultaneously and independently, the media escaping—stating that the infection reaches the intima from the lumen and the adventitia from the vasa or perivascular lymphatics. Furthermore, McMeans,[29] in studying the vascular changes in the meningeal arteries in septic meningitis, mentioned the primary polymorphonuclear infiltration of the intima with proliferation of the fixed cells of this coat and the extension of the process to the internal elastic membrane, with the later involvement of the media from both adventitia and intima. Moreover, inflam-

24. Virchow: Virchows Arch. f. path. Anat. **77**:380, 1879.
25. Klotz: Ref. McMeans, J. M. Research **32**:388, 1915.
26. Benda: Ergebn. d. allg. Path. u. Anat. **8**:236, 1902.
27. McMeans: J. M. Research **32**:388, 1915.
28. Klotz: Brit. M. J. **1**:1767, 1906.
29. McMeans: Am. J. M. Sc. **151**:249, 1916.

mation of both the intima and adventitia has been produced experimentally by Klotz [28] and others, employing *B. typhosus* and streptococcus in rabbits, by Saltykow [30] with *Staphylococcus aureus* and by Sumikawa [31] with turpentine and silver nitrate, where the inflammation occurred in all coats or in the intima alone. Benda [26] further believed that some of the aneurysms were metastatic in origin, the infection being carried to the wall through the vasa vasorum. Thus it would appear that the infection in a given case, as suggested by Chiari [32] in discussing tuberculosis of arteries, can and does occur either from within outwards or without inwards, whether carried by vasa or the perivascular lymphatics, as in periarterts nodosa (Klotz [33]) or by direct extension from without, as in the instance of secondary involvement from a neighboring tuberculous process—a view concurred in by Haythorn [34] in reporting such a condition. It is our belief that the ideas of both Eppinger and Benda are applicable to certain cases and, in addition, it is conceivable that the infection in the case of mycotic-embolic aneurysms may attack the artery from within outwards with direct extension from the intima through the elastica interna to the media and adventitia or, with the accompanying devitilization of the tissues at the point of lodgment of the embolus, any bacteria which may be present in the blood stream can enter the wall by way of the vasa and the mainstay of the arterial coat be approached, therefore, from both sides.

There are certain clinical phases of this subject which we would like, in conclusion, to emphasize. Mycotic-embolic aneurysms, though a very definite clinical entity, should be regarded only as an arterial manifestaton of the disease—"subacute bacterial endocarditis." This fact is important to remember, especially in reference to treatment. Some peripheral aneurysms, not of this type, can be treated radically by surgical measures but in these cases the local condition is not complicated by an endocardial infection. Radical surgical treatment of the mycotic-embolic aneurysm, as a rule, is a useless procedure because the cardiac condition remains unaltered. From the histories of cases of surgically treated peripheral aneurysms there is good reason to believe that a certain number were associated with an active endocardial lesion. The end result in these cases is practically always bad as the patient usually dies eventually from his endocarditis, if not from the immediate effects of the operaton. Finally we would call attention to the symptom of sharp stabbing pain at the time of rupture of the

30. Saltykow: Beitr. z. path. Anat. u. z. allg. Path. **43**:147, 1908.
31. Sumikawa: Beitr. z. path. Anat. u. z. allg. Path. **23**:242, 1903.
32. Chiari: Verhandl. Deutsch. Aerzte in Prag., Dec. 5, 1902.
33. Klotz: J. M. Research **37**:1, 1917.
34. Haythorn: J. A. M. A. **60**:1413 (May 10) 1913.

aneurysm. The pain is more severe and prolonged than that due to embolism which is a common occurrence in this form of endocarditis. Pain of this intense and persistent character in a case of subacute bacterial endocarditis may therefore be suggestive of a rupture of an aneurysmal sac. With the knowledge that infective embolism is of frequency in this disease, one wonders that mycotic-embolic aneurysms of peripheral arteries are not encountered more commonly. No doubt a certain number are overlooked so that it behooves the clinician and pathologist to be alert to the probabilities of this condition.

BOOK REVIEWS

NUTRITION AND CLINICAL DIETETICS. By Herbert S. Carter, M.A., M.D., Assistant Professor of Medicine, Columbia University. Second edition, thoroughly revised. Pp. 681. Philadelphia and New York: Lea & Febiger, 1921.

This volume affords an authoritative treatise on the highly important subject of nutrition and diet in health and disease. The book is divided into four parts. Part 1 deals practically entirely with food and nutrition in health. Part 2 deals with food, per se. Part 3 describes feeding in infants and children. Part 4 is devoted entirely to the subject of diet in disease.

The authors have brought the subject matter up to date and have added much new material in the chapters on chemistry, metabolism, and physiology of digestion, vitamins, etc. Much obsolete matter has been eliminated. In the last chapter of the book there are numerous tables which are accurate and very valuable for quick reference. The book is very readable and should be part of the armamentarium of most any medical practitioner.

LA GENESE DE L'ENERGIE PSYCHIQUE. J. Danysz. Librarie J. B. Bailliere & Fils, Paris.

M. Danysz, a scientist of renown in France, has, after devoting a large part of his life to material investigations in the Pasteur Institute, turned to less concrete and more speculative fields. Evolution has always attracted him, as seen in two volumes dedicated to the principles of evolution in infectious diseases and to the origin, evolution and treatment of noncontagious diseases. This has led him to fields purely metaphysical, and the present volume is a scientific and scholarly attempt to define the status of the human mind in relation to its surroundings—geological, biological, and sociological—past, present and future. Human intelligence, developing very slowly during the vast prehistoric ages, progresses with a constant acceleration, particularly in the recent, relatively short space of our authentic knowledge, and leaves us at our present point aghast at the possibilities, even certainties, of the future, with a mental power that will surpass physical forces. Present man is merely a momentary stage, will be rapidly surpassed, and man of the future will become, through this accelerated intellectual evolution, vastly superior—in fact, may dominate in the conquest of nature.

These seemingly startling predictions are no mere conclusions reached after hasty and enthusiastic considerations—but are deductions drawn from evidence presented by a large, sound and unusually complete summary of our existing state of knowledge. Inorganic chemistry, selective solubilities, chemical stability, followed by colloidal states of activity, are thoroughly considered before the biological realm is entered. Here the ordinary biological principles are discussed, followed by a minute consideration of the possibilities of evolutionary progression and the forces for and against such progress, including anaphylaxis, the rôle of vitamines, and the final result, the individual animal, later the various species of animals.

The final chapter is concerned with conclusions more of an ethical pedagogical, and psychological character—the differentiation and classification of individuals according to their reactions and the motives stimulating them, with an attempt to define the type most worthy of bearing the torch onward.

The volume is far above the level of the ancient metaphysicians, in spite of the rather startling conclusions. Fundamentally it is sound. There is no one point at which one can disagree or take exception—but though he has made a brave effort to bridge that seemingly limitless abyss between human anatomy

and physiology on the one side, and the cerebral processes on the other, M. Danysz has only led us a step nearer our own brink, from which we may, on arriving, possibly see across.

THE BLOOD SUPPLY OF THE HEART (In Its Anatomical and Clinical Aspects). By Louis Gross, M.D., C.M., Douglas Fellow in Pathology, McGill University and Research Associate Royal Victoria Hospital, Montreal. With Introduction by Horst Oertel, Strathcona Professor of Pathology, McGill University. Montreal. Pp. 165. 34 illustrations, New York, Paul B. Hoeber, 1921. Price, $5.00.

This monograph is a comprehensive work including a critical survey of the literature. The points of the author are well illustrated. The work is divided into eight chapters. In the first chapter the author discusses the various methods that have been employed in the study of the blood supply to the heart, and in conclusion describes his own technic, which is an improvement over any heretofore reported. In the second chapter the blood supply to the ventricles and auricles is described. The author points out that there is a wide variation in the distribution of the coronary arteries which he reserves for consideration in the third chapter. He overcomes this difficulty by describing the theoretical heart representing the average construction from the study of one hundred normal specimens. The fourth chapter details the result of a careful study of the blood supply to the neuromuscular tissue. The author concludes from the study of one hundred normal hearts that a specific blood supply exists for both the sino-auricular and auriculoventricular nodes, the main bundle, the first portion of the left limb and a large portion of the right limb of the neuromuscular system.

The fifth chapter deals with the blood supply to the heart valves. Six per cent. of the hearts studied showed valvular injection; of these the aortic cusp of the mitral valve was involved most frequently. The author believes that in those instances in which the valves were not injected, vessels did not exist. These conclusions were substantiated by microscopic examination of serial sections of the valves. He calls attention to the presence of musculature in the valves with blood vessels, and points out that the incidence of endocarditis is strikingly closely related to the existence of these two structures. He suggests that this may explain the frequency of right sided endocarditis in the fetus, left sided endocarditis in the child and the relative infrequency of this condition in adult life.

In the sixth chapter the anastomoses between the coronary arteries are discussed. The conclusions reached are largely confirmatory of those of former investigators. In the seventh chapter the venous supply of the heart is described. The eighth and final chapter deals with the changes in blood supply to the heart incident to different age periods. The author shows that in infancy and early childhood the vascularity is greatest on the right side. As the age advances the blood supply to the left side gradually becomes greater. Finally, in the sixth and seventh decades there is a great preponderance on the left side with a relative anemia of the right side. He attributes a part of the abundant vascularity of the left side to the development of the arteriae telea adiposae, or fat vessels. He considers this a compensatory mechanism in this critical period of life. He suggests that the insufficient blood supply to the right side may account for some of the sudden deaths in the aged and the high mortality from pneumonia at this period.

The most notable addition to the present conception of the blood supply of the heart is supplied by Chapters 4, 5 and 8. This work will be especially interesting and helpful to the anatomist and the physiologist in the investigation of fundamental problems concerning the heart. It will, perhaps, be equally interesting and valuable to the pathologist and clinician in a more comprehensive understanding of the pathologic processes and the clinical manifestation of cardiac disease.

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TRACHEAL AND BRONCHIAL STENOSIS AS CAUSES FOR EMPHYSEMA *

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During the past ten years much research has been done on emphysema and asthma and on the chemistry of blood and respired air, but few studies on the mechanism of bronchiolar spasm and emphysema have been published. Some of the most recent work on this subject has been based on the assumption that the time-honored teaching of the causal relation between expiratory dyspnea and emphysema and asthma is unassailable. To me it seems that the prevailing teaching on these subjects needs revision. To learn the mechanism of emphysema and asthma by way of the chemistry of the blood gases and of the respired air seems quite hopeless. When a clear understanding of the mechanism of emphysema and asthma has been attained, we shall be in a much stronger position to interpret our chemical studies of the blood gases and respired air.

BIERMER'S THEORY

The modern interpretation of bronchiolar asthma originated with Biermer, of Zurich,[1] who in 1870 published an exposition of the subject. Biermer referred to Paul Bert as having proved that vagus excitation causes bronchiolar contraction, although it had been suspected, claimed, in fact, by Williams in 1840 at a meeting in Glasgow.[2] Biermer said that the low position of the diaphragm could not be reconciled by his contemporaries to bronchiolar spasm as an explanation for pulmonary emphysema. Bamberger believed phrenic spasm to be the source of acute pulmonary emphysema, and Lehman took the same view.

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* Read before the Meeting of the Association of American Physicians at Atlantic City in May, 1921.

1. Biermer: Innere Medicin, Volkmann's Sammlung klin. Vorträge, No. 3, Leipzig, 1870-1875.

2. Tenth meeting of the Association for the Advancement of Science.

It is with much satisfaction that Biermer quotes the experiments of Paul Bert.[3] Biermer conceived an essential difference to exist between stenosis in the remote branches of the bronchi and stenosis in the trachea. He regarded dyspnea of bronchiolar stenosis as essentially expiratory, because he believed that the active character of the expiration of asthma produced a vicious cycle; an active pressure on the lung compressed the boundaries of the respiratory units, the air cells were subjected to compression, and the air passages connecting them with the larger bronchi were also compressed; that is, the more active the expiratory effort, the greater grew the resistance to exit of air from the respiratory units. On this account the expiratory phase was supposedly much prolonged. Biermer says that the difference between tracheal and bronchiolar stenosis lies in the fact that the former is an inspiratory and the latter an expiratory dyspnea. As an evidence of this point of view, he calls attention to the inspiratory retraction in the supraclavicular, suprasternal and epigastric regions in tracheal stenosis, and contrasts it with the labored expiration of asthma; and he calls attention to the want of evidence of active vigor in the expiratory phase in cases of tracheal stenosis.

NATURE OF ACUTE EMPHYSEMA

By way of introduction to the subject, let it be understood that we are dealing with two phenomena; viz., bronchiolar hypertonus and emphysema of the lungs which consists solely of an increase in the pulmonary residual air. In such cases there is only altered physiologic function and no anatomic disease of the lung.

Bronchiolar spasm is immediately attended with emphysema, diminution of vital capacity, inspiratory and expiratory dyspnea and lessened extensibility and compressibility of the lungs. Thus far, we have no evidence that disturbances in the pulmonary circulation contribute to rigidity of the lungs in acute pulmonary emphysema. The loss in extensibility is due entirely to emphysema and narrowing of the bronchial tree. Although we have no positive evidence for hyperemia of the pulmonary circulation in bronchiolar spasm, there is good negative evidence against its responsibility for rigidity of the lung. That hyperemia can reduce the vital capacity of the lung quite as much as does bronchiolar spasm has often been observed. Both conditions may reduce the vital capacity of the lung to 800 c.c. in persons who normally may have a vital capacity of 4,000 c.c. It is, however, incomprehensible how such an hyperemia could occur without causing great resistance to the work of the right heart and thus causing ectasis of the right ventricle and right auricle. I have never seen any evidence

3. Bert, Paul: The Comparative Physiology of Respiration, 1870.

of enlargement of the right side of the heart in acute bronchiolar spasm. Evidence for it has never been adduced, although in the literature on the subject this assumption commonly appears. The mechanism of bronchiolar spasm, with all its attending attributes, may appear and disappear with such suddenness that it seems inconceivable that the collective phenomena can have any other origin than a neuromuscular performance.

This aspect of acute emphysema is best seen in patients who have periodic bronchiolar spasm from vagus excitation due to mediastinitis. Such a patient came under my observation during an attack.

Case 1.—The patient was a little girl, 8 years old, who for the last two years had been quite well, according to the grandmother's account, except for asthma, which occurred every few weeks and lasted only half an hour. The last attack of asthma this child had suddenly terminated while I was observing the volume and excursion of her lungs. The lungs filled the pleural sinuses, and the child was employing her utmost effort to breathe during both inspiration and expiration. Each respiratory cycle exhibited her vital capacity, when suddenly in the midst of a single respiration, the lower border of the lung was seen to ascend 4 cm., and with this rapid disappearance of emphysema there was a complete return of respiratory comfort.

It can truthfully be said that this child began a respiratory cycle with emphysema, lessened vital capacity, inspiratory and expiratory dyspnea, lessened extensibility and compressibility of her lungs, and ended the cycle with respiratory euphoria. It is inconceivable that such a rapid disappearance of all these symptoms could be produced by any other than a neuromuscular phenomenon. The recovery was too rapid to include vasomotor phenomena, with consequent changes of blood distribution, as among the causes of the symptom complex. There is, therefore, very good reason for excluding all proposed possibilities except bronchiolar spasm as the cause of acute emphysema. But we find the theory of the mechanism by which bronchiolar spasm is supposed to produce emphysema and its attendant symptoms does not withstand clinical and experimental criticism.

TRACHEAL STENOSIS

Biermer's theory teaches that bronchiolar spasm is attended with an expiratory effort, which produces a vicious cycle by compressing the bronchiolar exits from the respiratory units. If this be true, a resistance anywhere in the tracheobronchial tree which is sufficient to demand expiratory compression of the lung should lessen the volume flow toward the latter part of expiration, as the intrapleural pressure rises, and result in emphysema and prolongation of the expiratory phase. If a strong muscular effort is needed to accomplish expiration against tracheal resistance, the same mechanism of expiratory stenosis should be operative that Biermer's theory teaches for bronchiolar

hypertonus. If active compression of the distended lung by the employment of expiratory muscles produces a vicious cycle of expiratory stenosis when there is bronchiolar hypertonus, then there is no reason apparent why the same process should not operate when the resistance to expiration is located in the trachea.

According to the prevailing theory, in the presence of great resistance to expiration located in the trachea there should be pulmonary emphysema and a prolongation of expiration proportionately greater than the prolongation of inspiration, but the clinician rarely has an opportunity to investigate this theory. By the time the patient with tracheal stenosis comes under observation, there is nearly always a complicating tracheobronchitis with infection of the bronchial tree. What the clinician usually sees is tracheobronchitis complicating tracheal stenosis. Under these conditions the patient may have much moisture in the air spaces and there may be a complicating bronchiolar hypertonus, so that it is quite impossible to separate the effects of the two lesions so far as the clinical manifestations are concerned. I have seen patients with laryngeal diphtheria who had pulmonary emphysema, but these same patients had tracheobronchitis as well as the laryngeal stenosis, so that one would not be justified in saying the patient's emphysema was the result of laryngeal stenosis. It could just as well originate from the bronchitis. However, during the influenza epidemic of 1919 I had an opportunity to see a case of uncomplicated tracheal stenosis.

Case 2.—A well-grown girl, about 17 years of age, had been ill for three days with epidemic influenza. There had been a very considerable amount of tracheitis from the start. There was some dulness at the base of the right lung, but there was no elevation in the pitch of the respiratory sounds and the patient was not cyanotic. Until the evening of the third day no alarming symptoms had developed, but about 10 o'clock on the night of the third day of her illness, she became quite dyspneic. At 12 o'clock she had severe stenosis of her trachea, about half way between the glottis and the bifurcation, which was due to edema of the tracheal mucosa. With the laryngoscope the livid swollen mucosa and the very narrow slit in the lumen of the trachea could very plainly be seen. This patient was doing her utmost to breathe. She employed a violent effort of all the inspiratory muscles during inspiration, and likewise employed violent contraction of all her abdominal muscles and intercostals during expiration. There was no undue prolongation of the expiratory phase and there was no evidence of increase in the volume of the lung. The patient died about two hours later from respiratory exhaustion due to stenosis of the trachea, but there was not the slightest evidence of emphysema.

It might be objected that in this particular patient the equality of resistance to inspiration and expiration was the reason why she did not have emphysema, but later we had the opportunity of seeing a patient who had an expiratory resistance in the trachea which greatly

exceeded the resistance to inspiration, and there was no pulmonary emphysema.

Case 3.—A man having an aneurysm of the ascending arch of the aorta, which compressed the trachea at the bifurcation, was brought into the hospital in one of his attacks. It was quite apparent that the patient accomplished his inspiratory act with comparatively little effort. There was some resistance to inspiration, but the inspiratory dyspnea was not excessive, and it was quite plainly apparent that there was less dyspnea during the latter part of inspiration than at the beginning of the phase. In other words, as the man lifted his thoracic cage, the compression of the trachea lessened, but during expiration it was equally apparent that the resistance to the exit of air increased as the expiratory phase progressed. The expiratory phase was greatly prolonged and was attended with violent contractions of the abdominal and intercostal muscles. The man was employing his utmost effort to expel air from his lung during the latter part of the expiratory phase. This was due to the fact that, as the expiratory phase progressed and the thoracic cage was driven downward on his aneurysm, the stenosis of the trachea increased, so that the stronger his expiratory effort, the more ineffectual it became.

This was an instance of expiratory dyspnea, of a high degree, located in the trachea, but the volume of the patient's lung was not increased during the attacks. We had an opportunity to see him in several of these experiences, which were very distressing and seemed to threaten the patient's life, but the volume of the lung during the paroxysms (which lasted several hours) did not increase. This patient's expiratory dyspnea was just about as severe as a patient could endure and yet survive.

I could not conceive of a more successfully designed experiment to prove the fallacy of Biermer's theory of expiratory stenosis than this patient exhibited in his several paroxysms. It was this experience that suggested animal experiments to see what effect obstruction to inspiration and expiration, respectively, may have on the volume of an animal's lung when the seat of the obstruction is in the trachea.

EXPERIMENTAL TRACHEAL STENOSIS

A wooden box, 31x10x9 inches, was constructed with a shelving top, which enabled us to seal the open top of the box with a glass plate laid in petrolatum. With an animal confined in this box, which served as a plethysmograph, we could connect the cannula inserted in the animal's trachea with the exterior through a tube, which was passed through a rubber cork placed in a hole in the side of the box. Through a Meltzer cannula inserted in the pleural cavity, we were able to register the intrapleural pressure by means of a tambour, which was connected with the tube leading from the Meltzer cannula through a cork in the side of the box. By the same means we connected a cannula in the dog's jugular vein with the exterior. The animal could breathe the room air, or any other atmosphere, and by connecting the cavity of the box with the spirometer of a Benedict apparatus, we could record the respiratory excursions and detect any modifications in the volume flow of air during inspiration and expiration quite as accurately

as when the tracheal cannula was connected with the spirometer. In fact, the plethysmographic excursions of the spirometer were perfect reproductions of the excursions of the spirometer when the animal breathed directly into the reservoir. Each millimeter of elevation of the reservoir represented a volume of 22 c.c. When the spirometer was used for recording the plethysmographic excursions, the tubes leading to the canister were cut off, so that there was simply a to and fro movement of air between the Benedict reservoir and the air of the box which contained the dog. We could thus accurately measure not only the character of the inspiratory and expiratory excursion and its exact volume, but we could accurately measure any variation in the minimum volume of the animal's lung.

The tracheal cannula connected through the side of the box with room air, and on the end of this tube one could fix various sorts of appliance; for instance, a screw clamp was used on a piece of rubber tubing which was attached to the tube connected with the tracheal cannula, and in this way we could give the animal any degree of stenosis to inspiration and expiration alike. By a Y tube fixed to the tracheal cannula and clapper valves, we could give the animal any degree of stenosis to expiration only and leave inspiration unobstructed; or we could do the reverse and give the animal any degree of resistance to inspiration and leave expiration unobstructed.

The animals employed varied greatly in size, the largest weighing seventeen kilos. Many times there was no change in the volume of the animal, and we never got an increase in volume above 66 c.c. when tracheal stenosis to inspiration or expiration was employed.

The dog was given chlorbutanol (dissolved in oil) in the peritoneal cavity, and morphin was given hypodermically. We attempted to use the minimum dose of chlorbutanol and morphin, but it was necessary to keep the animal at rest while fixed within the plethysmograph.

One of the greatest difficulties was to procure active expiration in an anesthetized animal. Obstructing respiration and permitting the carbon dioxid to accumulate within the body, or having the animal rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid, would not secure active expiration. Resistance to inspiration very readily activated the muscles to increased effort, but when tracings of intrapleural pressure were made, we found that resistance to both inspiration and expiration was not sufficient to induce active expiratory effort. *It was only after a high degree of hyperpnea was induced by having the dog rebreathe an atmosphere of oxygen and carbon dioxid that we could induce an active respiratory effort by shunting in a resistance to expiration.* This is mentioned because, in the literature on the subject of respiratory excursions, many writers

have assumed that, because respiration had been suspended or the animal was compelled to breathe an atmosphere with a high concentration of carbon dioxid, therefore the hyperpnea was accompanied by an active expiratory effort. *It was found after many trials that, to procure an active expiratory effort so that during expiration the pressure in the pleural cavity would be raised above barometric pressure, it was necessary first to induce a very active hyperpnea and then during the period of hyperpnea to shunt in the expiratory resistance.* Under these circumstances the threshold for active respiration was passed and a positive pressure in the pleural cavity was obtained above that of barometric pressure.

Experiment 1.—Figure 1, line A, should be read from right to left. From 1 to 2, we see four normal respiratory excursions recorded by the plethysmograph. Line A is the base line and marks the minimum volume of the dog at the end of expiration. At 2 the animal was made to rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid. Each 5 mm.

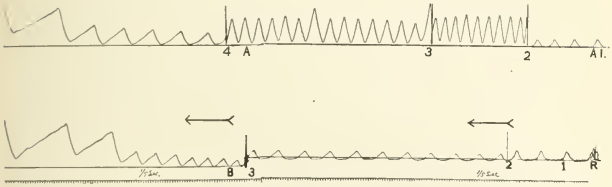

Fig. 1.—Experiment 1.

in the time marker represents 1 second, so that 1 mm. equals 1/5 second. As can be seen by the tracing, inspiration and expiration were of about the same duration; and while the animal was breathing room air, 1 second was occupied to complete the respiratory cycle, and the animal breathed about 70 c. c. with each respiration.

When the dog began rebreathing the high concentration of carbon dioxid, the time occupied in the respiratory cycle was 1 second; the rate was very much increased, and the volume of each excursion was 286 c. c. From 2 to 4 the animal was rebreathing the carbon dioxid without resistance to either inspiration or expiration, and then at 4 a valve was inserted in the end of the tube connecting with the tracheal cannula, which gave the animal a perfectly free inspiratory movement but very greatly restricted the expiration. The volume flow through the expiratory valve under a pressure of 80 mm. of water was 1,200 c. c. per minute. Inspiration occupied 3/5 second, but the duration of the respiratory cycle was 13·5 seconds; so that the proportional duration of inspiration to expiration was 3 to 10. The volume of excursion as the animal began breathing at 4 was 132 c. c. As will be seen by the tracing, in the first five respiratory cycles there was a gradual rise in the volume of each respiration, and then it is seen that the stimulus to respiration due to the carbon dioxid accumulation produced a large excursion of 400 c. c. The duration of inspiration in this cycle was 5/5 second, but the duration of expiration was

25/5 seconds, and the volume of the dog at the end of expiration had increased 154 c.c. As this tracing was continued, the respiratory excursion became more rapid, and the minimum volume of the dog at the end of expiration had increased about 250 c.c. above the original volume. So that we can say that this experiment shows that, when an expiratory obstruction is shunted into the trachea in an animal with great hyperpnea, the residual air in the lung is very greatly increased. When, however, one carried out the experiment in reverse order, and as shown in line B, the dog breathed room air from 1 to 2 and then at 2 the expiratory valve was placed in the end of the tracheal cannula, so long as the dog was breathing room air and there was no occasion for hyperpnea the volume of the dog was unchanged. At 3, however, the animal continued to breathe with an expiratory resistance, when he was connected with a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid. By the end of the seventh respiratory cycle, there was a large inspiration of 352 c.c., and the same increase in the residual air of the dog became apparent as in line A at 4. As seen in one of the larger excursions, the duration of the respiratory cycle was 30/5 seconds, inspiration occupying only 4/5 second, and expiration 26/5 seconds.

Although in this experiment the intrapleural pressure was not measured (because I wished to leave the thorax intact), I think we are justified in assuming from repeated trials in former experiments that with this resistance to expiration added to the great hyperpnea from breathing carbon dioxid, the animal was actually employing effort during the expiratory phase. This experiment showed that the only way in which tracheal resistance will increase the residual air in the lung is in conjunction with increase in the volume of respiratory excursion. In this animal the volume of excursion was increased from 70 c.c. up to 300 c.c. by rebreathing carbon dioxid, and the rate of respiration was increased from 36 to 52 per minute.

The phenomena described in this experiment do not occur in bronchiolar spasm. A patient who has a violent spasm can supply his oxygen needs perfectly well by a 25 per cent. increase in the oxygen consumption and the minute volume of air. I have repeatedly taken Benedict tracings on patients during periods of bronchiolar hypertonus, and during severe spasm we have found both the minute volume of respired air and the consumption of oxygen just about 25 per cent. greater than in the interims of respiratory comfort. The increase in each is imposed on the patient by the additional work required to ventilate his lungs. This introduces another essential consideration of asthmatic breathing—that is, that the residual air in the lung is greatly increased, although the increase in the minute volume of ventilating air is slight. In bronchiolar hypertonus without hyperpnea, emphysema is produced, but in tracheal expiratory dyspnea, emphysema is obtained only in the presence of hyperpnea, which must be superadded to the expiratory resistance.

The clinical and experimental evidences reveal an essential difference between the results of bronchiolar hypertonus and stenosis of the

trachea. When the tracheal resistance to inspiration and expiration are equal, there is no increase of residual air in the lung. In the absence of hyperpnea, resistance to expiration in excess of that to inspiration will not increase the volume of the lung.

BRONCHIAL HYPERTONUS, REGIONAL AND OF ANY DEGREE

The Biermer doctrine of the mechanism of emphysema in bronchiolar hypertonus demands an active expiratory compression of the lungs. But moderate bronchiolar hypertonus produces emphysema when there is no active effort attending expiration. Expiration may remain a passive procedure and still be attended with emphysema. When the conception of emphysema from bronchiolar hypertonus first appealed to me as a problem for investigation, I was in the habit of thinking of bronchiolar hypertonus as a neuromuscular performance that belonged to the all-or-nothing law, and also that it was equally distributed throughout the bronchial tree. Neither of these conceptions is true. Neuromuscular reaction in the bronchial tree may, like vasomotor reaction in the arterial bed, be of any degree and may also be universal or regional. A patient may have a moderate bronchiolar hypertonus attended with demonstrable emphysema of the lung but without sufficient bronchiolar resistance to call out an active expiratory effort on the part of the patient. A few clinical cases will suffice to prove these statements.

REPORT OF CASES

Case 4.—A man, 60 years of age, who had suffered from bronchitis and occasional asthmatic paroxysms for a period of five years, had a very moderate pulmonary emphysema, which at the borders of the lungs was sufficient to fill the pleural sinuses, but the total lung volume was not increased so that the diaphragm was sufficiently flattened to change the normal direction in the movement of the costal margins during inspiration. According to this man's account, his breathing was never completely shunted out of the field of consciousness. He was always aware of a certain degree of respiratory discomfort, but from physical examination and roentgenograms of the lung one could not determine how much of his discomfort should be ascribed to atrophic emphysema and how much to bronchiolar hypertonus. When he was given a subcutaneous dose of 20 minims 1:1000 epinephrin, the vital capacity of his lung increased from 2,000 to 2,500 c. c., and he then said that for the first time in a year he experienced complete respiratory euphoria. Before the epinephrin was given, this patient did not have an active expiratory phase, although he had a certain degree of bronchiolar hypertonus with consequent emphysema, as shown by the respiratory comfort and increase in vital capacity directly after adrenalin was given. His respiratory discomfort had evidently consisted in an increased effort during inspiration. Of this effort he was conscious, but his pulmonary ventilation was still adequate to preserve the passive character of his expiration. His expiration was prolonged, but the moderate dyspnea permitted the expiratory prolongation.

Case 5.—Another patient was a young, vigorous man, 25 years of age, who complained of respiratory discomfort, which had lasted for twenty-four hours. It was quite apparent that the man had labored breathing, but examin-

ation revealed that his labor was all on the inspiratory side; there was no effort during the expiratory phase, the abdominal muscles being perfectly relaxed. The costal margins moved outward throughout their entire extent during inspiration. There was sufficient emphysema, however, at the borders of the lungs so that they filled the pleural sinuses as far as the eighth interspace in the nipple line and the eleventh rib in the axillary line.

The patient showed very marked relief from the administration of adrenalin. Before the administration his vital capacity was 3,350 c. c. when seated, and 2,951 c. c. when recumbent. Ten minutes after he had been given 20 minims 1:1000 epinephrin hypodermically, his vital capacity when seated was 3,478 c. c., and 3,415 c. c. when recumbent. His respiratory rate both before and after epinephrin varied between 22 and 24. Before he had his epinephrin when the respiration was traced on a rotating drum, which was running at the rate of 5 mm. per second, in a respiratory cycle during which he breathed 528 c. c. the duration of the entire cycle was 22 5 seconds. The inspiratory phase was 10/5 seconds, and the expiratory phase 12/5 seconds. After he had epinephrin, in a respiratory cycle in which he breathed 726 c. c., the duration of the cycle was 19/5 seconds, the inspiratory phase occupying 8/5 seconds and the expiratory 11/5 seconds. So it is quite apparent that both before and after epinephrin there was no active expiratory phase.

Although the test showed only a comparatively slight increase in his vital capacity after epinephrin, the lung passively expelled 726 c. c. in 11/5 seconds, whereas prior to the administration of epinephrin the lungs passively expelled 528 c. c. in 12/5 seconds. The rigidity of the lung was considerably less after epinephrin than before. The inspiratory effort had been quite apparent to inspection, and the inspiratory and expiratory phases were accompanied by a number of coarse, moist and sibilant râles, all of which disappeared after epinephrin took effect. The only direct evidence we procured to show diminution in volume of the lung after epinephrin was that, while the lower border of the lung had been at the eleventh rib in the axillary line before epinephrin, it was afterward at the ninth interspace. In the midclavicular line, it was at the eighth interspace both before and after epinephrin was given. However, it was quite apparent to the observer that the epinephrin relieved the man of a very considerable degree of respiratory discomfort.

These patients with demonstrable bronchiolar hypertonus had a very considerable degree of respiratory discomfort (that is, inspiratory), but the vital capacities of the lungs were very little modified by the hypertonus. According to the size and conformation of the second man's thorax, he should have had a vital capacity of at least 5,000 c.c. Without the use of epinephrin it would have been impossible to show that bronchiolar hypertonus played a part in his respiratory discomfort.

The following cases showed regional hypertonus:

Case 6.—This patient had had a moderate general bronchiolar hypertonus, but on one occasion it was only regional. The resident physician found one night that his right thorax was comparatively immobilized, with no respiratory excursion perceptible in the arches of the right ribs. The whole right thorax was distinctly larger than the left. There was a distinct asymmetry, which had not been visible on other occasions. During the inspiratory phase, the entire right costal border was drawn strongly toward the median line, but the left moved vigorously in a lateral direction, and the respiratory excursion of the entire left thorax plainly exhibited an exaggerated excursion. The arches of the left ribs moved in their normal bucket handle manner much more actively than during interims of comfort. It was plainly apparent that

the right thorax was enlarged, that the right diaphragm was flattened, and that there was very slight respiratory excursion on that side. It was also apparent that there was a compensatory increase in the respiratory excursion of the left side, the minute volume of air in the left lung being equal to that of both lungs in the interims between attacks. In other words, the man had an acute unilateral bronchiolar spasm. This was also confirmed by auscultation. Over the entire right side there was an abundance of squeaking and moist râles during inspiration and expiration, but the left lung was free. The respiratory sounds were only faintly audible over the right side, whereas they were distinctly heard over the left, where the excursion was magnified. This patient was probably breathing a little larger minute volume of air than he employed during his interims of comfort, but the greater part of the pulmonary ventilation was accomplished with the left lung.

Twenty minims of 1:1000 epinephrin were given this patient hypodermically, and within a very few minutes he recovered his normal thoracic excursion. The two sides were again symmetrical, with symmetrical outward movement of both costal margins during inspiration. Most of the râles of the right side disappeared. The patient was perfectly comfortable, and so far as physical examination enabled us to determine, he was again ventilating both lungs equally.

Case 7.—This patient had severe bronchitis and atrophic emphysema, and he had been studied during very many asthmatic paroxysms. On one occasion, however, he complained of discomfort when the auscultatory evidence of asthma was limited to the lower lobe of the right lung. The right costal border was drawn toward the median line during inspiration, whereas the left costal margin moved in an outward direction. After the hypodermic injection of epinephrin, the patient's respiratory comfort was restored within a very few minutes. The auscultatory signs of asthma disappeared from the lower lobe of the right lung, and the right costal border resumed its outward inspiratory excursion, which was quite symmetrical with that of the left side. So far as physical examination enabled us to determine, this patient had a regional bronchiolar spasm attended with emphysema restricted to the lower lobe of the right lung.

Case 8.—On another occasion we had a patient suffering from chronic bronchitis and emphysema who had an attack of asthma in which all the evidence of asthma was limited to the two upper lobes. There was no evidence of flattening of the diaphragm, but the auscultatory signs of asthma, though very pronounced in the upper lobes, were entirely wanting over the two lower lobes.

It does not seem possible that a patient could produce the expiratory vicious cycle which supposedly occurs in asthma and confine the exhibition of compression of the bronchioles in one instance (Case 6) to the entire right lung, in another instance (Case 8) to the two upper lobes, and still in a third instance to the lower right lobe only (Case 7). Such cases alone offer sufficient evidence to disprove the need of an active expiratory phase to produce emphysema during an asthmatic attack.

DURATION OF EXPIRATION

To return to our cases of general bronchiolar hypertonus (Cases 4 and 5), attended with moderate emphysema and prolongation of the expiratory phase. The expiratory phase in all the patients with moderate hypertonus was longer than the inspiratory phase simply because the resistance to expiration was not sufficient to demand an active

compression of the lungs. To cause a transition from passive to active expiration, the obstruction to the passage of air must be so great that the time required for passive expiration exceeds the tolerance of the patient's respiratory needs. So long as bronchiolar hypertonus will allow a passive expiratory phase, the patient will instinctively refrain from active compression of the lungs by simultaneous action of the abdominal and intercostal muscles. The active expiration demanded by stenosis of the bronchial tree is very exhausting. Resistance to inspiration requires only an increase in the force of activation of the muscles normally employed; but resistance to expiration not only requisitions muscles which are not normally employed (which in itself is very exhausting), but produces an unfavorable effect on the hydraulics of the blood circulation in the thorax. In animal experiments the extremity of the measures which are required—namely, hyperpnea plus obstruction—before the animal can be induced to raise the expiratory pressure above the barometric pressure, plainly illustrates the height of this threshold for active expiration. These facts clearly explain why a patient with moderate bronchiolar hypertonus will have the duration of the expiratory phase shortened after the administration of adrenalin. Adrenalin given to such a patient will also have the effect of diminishing the residual air in the lung and will increase the pulmonary vital capacity.

How is the expiratory phase affected in a patient who has a bronchiolar hypertonus so severe that an active expiration is demanded? Figure 2 is a tracing taken with the Benedict apparatus during an attack of bronchiolar hypertonus. On line B is a tracing after the hypertonus was relieved by 20 minims of 1:1,000 epinephrin given hypodermically. When the tracing in line A was made, the patient was in great distress. The volume of each lung was so increased that the flattened diaphragm drew the costal borders toward the median line during inspiration, and the expiratory phase was accomplished by violent contraction of the abdominal muscles. These conditions are exactly such (according to Biermer's doctrine) as to create a vicious cycle of dyspnea, and should have caused a prolongation of the expiratory phase with a lessened volume flow of air toward the latter part of expiration. But the tracing reveals the opposite of that expected under the Biermer theory.

Experiment 2.—This tracing was taken on a drum with the speed of 1 mm. per second. The respiratory rate before adrenalin was given was 16 per minute. The line of the inspiratory phase on the upstroke is straight, and the line of the expiratory phase is equally straight. There is no lagging or horizontal drag as must occur in such a tracing should the volume flow lessen toward the end of expiration. The transition from inspiration to expiration and that from expiration to inspiration show very sharp peaks. The tracing indicates just what we were able to observe in the patient at the time. He

was employing his utmost muscular strength during all of inspiration and expiration, and the volume flow of air was uniform throughout the entire respiratory cycle.

On line B we see the effect of the respiratory cycle after the bronchiolar spasm had been relieved by the hypodermic injection of 20 minims of 1:1000 epinephrin. The respiratory rate was then 14 per minute. The inspiration on the upstroke is not quite so nearly vertical as before the epinephrin was given, and we can see toward the end of the expiratory phase a distinct slope

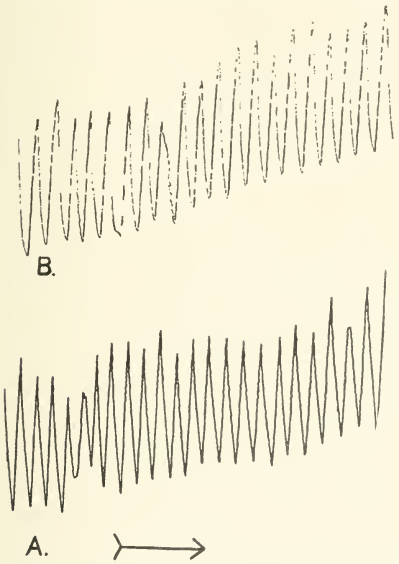

Fig. 2.—Tracing taken with Benedict apparatus during attack of bronchiolar hypertonus.

to the right, which means the volume flow toward the end of the expiratory phase was distinctly lessened. During the time the tracing in line B was taken, the patient had distinct inspiratory widening of his subcostal angle. Expiration was not attended with contraction of the abdominal muscles. In fact, he was breathing with perfect comfort. The difference was that before he had his epinephrin he was able to attain his required pulmonary ventilation at the

expense of great muscular effort during both inspiration and expiration. The expiratory labor was very exhausting, although the actual increase in oxygen consumption was only 25 per cent. in excess of what he employed during tranquil breathing at rest. The source of exhaustion is not in this instance measurable by the increased consumption of oxygen but by the employment of an unusual kind of expiratory effort.

With the Biermer doctrine of expiratory dyspnea in mind, one would be disposed to say that line B was traced before epinephrin was given, and that line A was traced after the bronchiolar hypertonus had been relieved. This tracing shows a longer expiratory phase after bronchiolar hypertonus was relieved simply because the patient had a passive expiratory phase and his respiratory needs did not demand compression of the lungs during expiration. Tracing A not only shows that the patient employed a positive pressure in his pleural cavity during the expiratory phase, but it shows that the minute volume flow of air during the latter part of the expiratory phase was more constant than when he was breathing with a passive expiration.

These experiments not only prove the fallacy of the doctrine of expiratory dyspnea in asthma, but they also show the error of employing the prolongation of the expiratory phase as an index of the severity of bronchiolar spasm.

EXPIRATORY COMPRESSION STENOSIS OF THE BRONCHI

The question of expiratory dyspnea arising from compression stenosis in the bronchial tubes remains for experimental consideration. If bronchiolar spasm is severe enough to require active compression of the lungs in expiration, there are two forces employed to expel air from the lungs: one the positive intrapleural pressure due to activation of the abdominal and intercostal muscles, and the other the retractile property of the visceral pleura and the elastic tissue within the lungs. If active compression of the lungs produces stenosis of the small branches of the bronchi in the presence of bronchiolar spasm, why should it not do the same in the absence of bronchiolar hypertonus? It seems reasonable to suppose that in the absence of hypertonus the bronchi would be more compressible than when they are hypertonic. If hyperpnea is induced in an animal by suffocation or by breathing a high concentration of carbon dioxid, and then tracheal stenosis is added to the respiratory burden so that compression of the lung is required to accomplish expiration, then under such experimental conditions we can measure the volume flow of air from the trachea and also the pressure on the proximal side of the tracheal stenosis, and synchronously with these air pressure and air volume flow measurements we can also trace the expiratory pressure in the pleural cavity. In such an experiment the expiratory forces are pitted against the tracheal resistance, with a certain volume flow as a result. Should an expiratory resistance to the outflow of air intervene between the air cells and the tracheal obstruction, then the volume flow of air should lessen toward the latter part of expiration, and the sum of the expulsive forces should exceed the air

pressure maintained in the trachea on the proximal side of the stenosis. The expulsive forces are of course the pressure within the pleural cavity and the retractile power of the lung.

Experiment 3.—A dog weighing 16 kilos was anesthetized with chlorbutanol and morphin. Tracheotomy was then done, and two cannulas introduced, one into the trachea and one into the right pleural cavity, after which the dog was placed in the plethysmograph. The cavity of the box was connected with the reservoir of a Benedict apparatus and the passages to the canister clamped so that there was a free movement to and fro between the confined air in the box which contained the dog and the air in the registering reservoir. The volume flow of air during each respiratory cycle could thus be accurately traced on a revolving drum, which had a speed of 5 mm. per second (Fig. 3, line *Pleth*). The time is marked in fifths of seconds. By a tube which passed through a cork in the side of the box, the Meltzer cannula in the pleural cavity was connected with a calibrated tambour, which traced the pressure in the pleural cavity for each respiratory cycle (see line *Pleura*). A T tube was inserted in the tube to the pleural tambour, by means of which we could

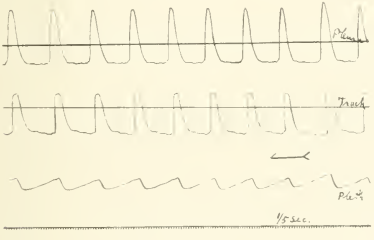

Fig. 3.—Experiment 3.

introduce into or remove from the pleural cavity any desired quantity of air. The tracheal cannula was connected with a tube which passed through a cork in the side of the box, and to the end of this tube was fitted a Y tube, the afferent limb of which was fitted with a clapper valve, while the efferent limb had its lumen modified at will by means of a screw clamp.

On the proximal side of this Y tube which terminated the tracheal cannula, was introduced a T tube, which connected with a calibrated tambour by means of which could be traced the air pressure on the proximal side of the expiratory obstruction. The writing styles for the plethysmograph and tracheal and pleural tambours were then perfectly aligned, so that a vertical line drawn anywhere would enable us to make accurate comparison of the three tracings in any phase of the respiratory cycle. In both the pleural and tracheal pressure tracings, the horizontal line traces the line of barometric pressure. The time tracing is in fifths of seconds. In all three tracings the upstroke records inspiration and the down stroke expiration, and they are read from right to left. They were made after 1,050 c. c. of air had been injected into the right pleural cavity. This injection was to prevent any error in getting the exact intrapleural pressure and also to procure any evidence of expiratory bronchiolar compression which the partial collapse of the lungs might offer.

Preceding this part of the tracing the screw clamp on the efferent limb of the tracheal Y tube was screwed down to procure the maximum resistance against which the animal would breathe. Respiration was arrested by complete obstruction of the tracheal cannula for one minute, and the drum was started as the complete obstruction of the tracheal cannula was released. The afferent clapper valve offered slight resistance to inspiration, as shown by the rise of the pressure curve of the tracheal tambour above the line of barometric pressure (minus pressure). The combination of hyperpnea with resistance in the efferent limb of the Y tube to the tracheal cannula induced an active expiratory phase, as shown by the rise above barometric pressure in the pleural cavity (below the pleural barometric line).

The plethysmographic tracing shows each respiratory cycle to have a duration of 17/5 seconds, the inspiratory phase occupying 3/5 seconds, and the expiratory 14.5 seconds. The volume of each respiration was 110 c. c. The volume flow tracing of expiration is straight; there is no drag to the left as there would be if the flow diminished toward the latter part of the expiratory phase.

When the positive pressure below the barometric lines of pressure for the trachea and pleura are measured, the pleural pressure of 9 mm. registered by the tambour style is found to equal 70 mm. of water, and the 12 mm. registered by the tracheal tambour style at the same time equals 100 mm. of water. But to the air pressure within the pleural cavity must be added the elastic contracile force of the lung. In this dog the intrapleural pressure measurements were taken when the animal was breathing freely without obstruction, and the pleural cavity was free of all but 50 c. c. of air. The intrapleural tracings then showed a pressure below the barometric pressure of 70 mm. of water at the height of inspiration, and 30 mm. of water at the end of expiration. If these 30 mm. are added to the maximum intrapleural pressure attained during the expiratory phase, we find the sum of the two factors (70 + 30) exactly equals the positive pressure measured on the proximal side of the screw clamp on the efferent limb of the tracheal cannula, and furthermore the minute flow is constant during the entire expiration. *We are justified in saying that under these experimental conditions there can be no resistance to the exit of air intervening between the air cells and the point of obstruction on the efferent limb of the tracheal cannula.*

Repeatedly hyperpnea was produced by having the animal rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid, and then resistance was applied in the tracheal path. By these means we were able to develop a high pressure in the pleural cavity during expiration, and the same results were always procured. After each experiment the tambours were calibrated for pressures above and below barometric pressure. In the dog the mediastinal reflections of the pleura are so mobile and offer so little resistance that a positive pressure obtained on one side of the thorax by producing an active expiration will be the same on both sides.

In measuring the volume of an animal under these experimental conditions, great care must be observed to guard against leakage of air into the pleural cavity. If air enters, the volumetric measurements of the plethysmograph will record an increase in volume of the thorax which apparently varies with the resiliency of the animal's thoracic cage. In one experiment, 100 c.c. air injected into the right pleural cavity increased the volume of the dog 120 c.c., and when 500 c.c were

injected, the dog increased 360 c.c. in volume. If this source of error is not considered, the increase in volume may be interpreted as an increase of the residual air in the lungs.

Thus far the studies of tracheal obstruction show several results that are of interest in relation to the study of resistance to the respiratory passage of air:

1. If the obstruction is the same during inspiration and expiration, there will be no increase of residual air, although hyperpnea is demanded for breathing an atmosphere of 80 per cent. oxygen and 20 per cent. carbon dioxid. When there is no hyperpnea, equal resistance to inspiration and expiration fails to produce emphysema.

2. When there is no hyperpnea, equal resistance to inspiration and expiration fails to produce emphysema.

3. In an animal under chlorbutanol anesthesia, the threshold for active expiration is very high and is passed only when hyperpnea is added to tracheal resistance.

4. Expiratory resistance with unobstructed inspiration will not cause emphysema unless the resistance occurs in company with hyperpnea.

5. When active expiration is induced by the combination of hyperpnea with tracheal expiratory resistance, there is no intervening resistance to the exit of air from the lungs that can be located in the bronchial tree, as Biermer's theory assumes there should be to produce emphysema.

These experimental results are quite consistent with the previously described observations on a patient who suffered from severe stenosis of the trachea (Case 3), which caused equal resistance to inspiration and expiration; and they are also consistent with the observations made on the patient who had severe expiratory with moderate inspiratory resistance without the development of emphysema (Case 4)—although the expiratory phase in both patients was accomplished with the utmost prolonged muscular effort of which the patients were capable.

Acute emphysema was procured by animal experiment only when the hyperpnea was combined with expiratory dyspnea in the absence of inspiratory dyspnea. On the other hand, we have shown that emphysema with bronchiolar hypertonus occurs in man when there is no further cause of hyperpnea than a slight effort during inspiration, and when expiratory dyspnea is so moderate that an active expiration is not required and expiration remains a passive procedure.

EXPERIMENTAL BRONCHIAL HYPERTONUS FROM HISTAMIN

We should, then, expect to find emphysema in dogs accompanying the bronchiolar hypertonus that follows intravenous injection of his-

tamin. With this in mind, twelve experiments were performed which were designed to show modifications in the volume of the lung of a dog during the period of bronchiolar hypertonus. The histamin was administered through a cannula, which was previously fixed in the internal jugular vein; and a tube from the cannula led through a cork in the side of the box, so that we could give histamin without disturbing the plethysmographic tracings of respiration. I was never able to find an increase of lung volume above 60 c.c. during the period in which the effect of histamin was apparent, and that was in a dog weighing 16 kilos. This increase in size is practically negligible so far as a consideration of increase in the residual air of the lung is concerned, for such a moderate increase might occur under a variety of disturbances in the cardiorespiratory function.

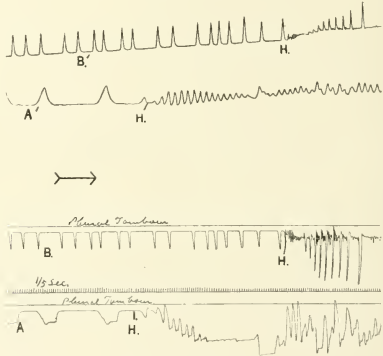

Fig. 4.—Experiment 4.

Experiment 4.—In Figure 4 there is a tracing from an experiment which was designed to show the intrapleural pressure during the period of the histamin effect, with the idea that, if histamin produced a decided bronchiolar hypertonus, then there should be a lessened respiratory excursion in the presence of a lowering minus pressure within the pleural cavity. In this experiment the plethysmograph was not used. The animal breathed through a tracheal cannula directly into the Benedict reservoir. The tracing reads from left to right, and the time-marker is in fifths of seconds. Lines A and A′ were taken simultaneously. The horizontal line marks the line of barometric pressure in the pleural tambour. Line A′ was a simultaneous tracing in the Benedict apparatus.

After the injection of 5 c.c. of 1:10,000 histamin into the jugular vein, the respiratory rate became very rapid and the volume of excursion was very small. To the right it will be seen that, during the period in which the pleural tracing

showed a very great descent in pressure, the volume of tidal air in the lung diminished. In fact, when the excursion of pleural pressure was very considerably extended, from the barometric line to a considerable distance below, the excursion of the lung was quite small. So we are certainly justified in saying that in the presence of a low barometric pressure in the pleural cavity, and also in great excursions of the pressure within the pleural cavity, there was a marked rigidity of the lung.

Line B and B′ are tracings taken from the same animal after a second injection of the same dose of histamin. The beginning of the histamin effect is apparent at H in the tracings both of pleural pressure and of lung excursion. The two experiments show essentially the same thing.

Thus far our investigation has shown that equal tracheal stenosis to inspiration and expiration in both men and dogs failed to produce emphysema. It has also been shown in both men and dogs that, when tracheal stenosis to expiration is greatly in excess of that to inspiration, there is no emphysema. It has further been shown in dogs that, when tracheal expiratory resistance is much greater than resistance to inspiration, emphysema can be induced only with the addition of hyperpnea, as follows of course when the animal is made to rebreathe into a bag containing a high concentration of carbon dioxid.

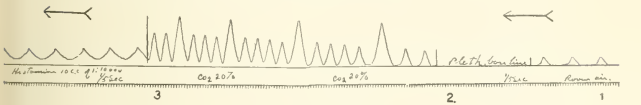

Fig. 5.—Experiment 5.

Furthermore, the experiment in which the tracing of Figure 4 was made proved that, when a general bronchiolar hypertonus was produced by the use of histamin, there was a great lowering of the barometric pressure in the pleural cavity during the entire respiratory cycle, but in spite of it there was a very small respiratory excursion and the total volume of the lung was not increased.

Experiment 5.—An experiment was made for the purpose of tracing the character and volume of the respiratory excursion and measuring the volume of the animal under the effect of a large dose of histamin with an intact thorax. The only operative procedure was the introduction of cannulae into the trachea and the jugular vein, into the latter of which the histamin was injected. The tracing (Fig. 5) should be read from right to left, and is simply the plethysmographic respiratory tracing of a 9 kilo dog. The first part, from 1 to 2, shows the animal breathing atmospheric air, and then at 2, the animal was made to rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid. Under the influence of hyperpnea thus induced, with perfectly free tracheal cannula, the total volume of the dog was increased about 50 c.c. Then during this period of hyperpnea 10 c.c. of 1:10,000 histamin was injected into the jugular vein, and immediately, at 3, there followed a great modification in the respiratory excursion. Before the effect of the histamin was apparent and while the animal was rebreathing a high concentration of carbon dioxid, the volume of respirations varied between 500 and 264 c.c. Then before the histamin

took effect, the duration of the respiratory cycle was 6/5 seconds. After the histamin took effect, the volume of the respiration was 110 c.c., and the time of a respiratory cycle was 13/5 seconds, the expiratory and inspiratory phases having exactly the same duration. It is quite apparent from the prolongation of both inspiration and expiration, with a great diminution in the volume of the tidal air, that the animal was breathing against a great resistance in both inspiration and expiration, and although in this experiment there is no tracing of the intrapleural pressure, I believe we are justified in assuming from our former experiments that the animal was employing a vigorous respiratory effort. *The tracing shows that the volume of the dog was not increased, although the bronchiolar spasm was induced at a time when great hyperpnea was demanded by rebreathing 20 per cent. carbon dioxid; and just as we have seen in our patients with severe bronchiolar spasm when active expiration was demanded, inspiration and expiration are of equal length.*

This experiment, in the light of all the preceding observations, offers very conclusive evidence that a uniform hypertonus throughout the bronchial tree will not prolong the expiratory more than the

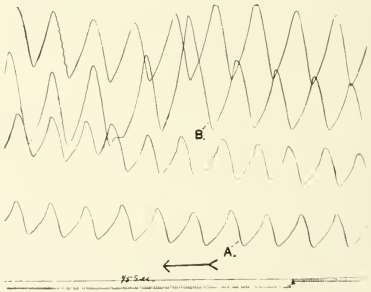

Fig. 6.—Case 9. Bronchiolar spasm not preceded by bronchitis.

inspiratory phase and will not produce emphysema. Furthermore, in the experiment from which the tracing in Figure 3 was made, there is very satisfactory evidence that active compression of the lung does not create a vicious expiratory cycle by compressing the outlet of the respiratory units, as the Biermer theory demands.

The following case offers clinical confirmation of the foregoing statements:

Case 9.—The tracing shown in Figure 6 was made from a young, vigorous man, who had an attack of bronchiolar spasm which was not preceded by bronchitis, and so far as we are able to determine, the bronchiolar hypertonus was a symptom of anaphylaxis from hay fever and not a hypertonus of the bronchial musculature which could be traceable to any nervous excitation within the bronchial tree or within the mediastinum. There was a considerable

amount of nasopharyngeal irritation. The results of the tracing, which was made during his period of bronchiolar spasm and continued after epinephrin was given hypodermically until he had perfect respiratory relief, present very good evidence that in clinical experience we may have bronchiolar hypertonus which will greatly reduce the vital capacity of the lung and not increase its residual air. In fact, we have in this patient with a uniform bronchiolar hypertonus quite the same results so far as the vital capacity and lung volume are concerned as has been shown in dogs when bronchiolar hypertonus was induced by intravenous injections of histamin.

This patient went to bed with perfect respiratory comfort, and was awakened in the middle of the night by a feeling of great respiratory discomfort. Inasmuch as the patient was one of the interns on the medical service in Lakeside Hospital, he was very conversant with the methods of studying respiratory phenomena, and was able to give ideal cooperation. The tracing should be read from right to left. The time marker is in fifths of a second. The two lower lines were traced before the effect of adrenalin was apparent, and the two upper lines were traced after the bronchiolar hypertonus had been relieved by hypodermic injection of 1:1,000 epinephrin.

Before epinephrin was given, the vital capacity of his lung had been 2,699 c.c. seated, and 1,932 c.c. recumbent. After the effect of epinephrin was produced, the vital capacity was 4,264 c.c. seated, and 3,893 c.c. recumbent. The respiratory rate before epinephrin was 18 per minute, and afterward 14. Before epinephrin there was a great abundance of fine and coarse sibilant râles over each portion of both lungs, but after epinephrin all traces of adventitious sounds disappeared. His sense of discomfort was purely on the inspiratory side.

Expiration was a passive procedure, involving no contraction of the abdominal muscles. The patient said that on former occasions he had had attacks much more severe and exhausting, and during them he had been compelled to employ the abdominal muscles during expiration.

In the lower line at A, the duration of the respiratory cycle is 18/5 seconds. The duration of inspiration is 6/5 seconds, and as will be noted in the tracing of the inspiratory phase, the up stroke shows a drag toward the left after the top of the excursion is approached. In other words, there is evidence of a slowing of the volume flow toward the end of the inspiratory excursion. The expiratory phase lasted 12/5 seconds, just double the duration of the inspiratory phase, and the amount of air expelled during the 12/5 seconds was 374 c.c. At B, after the bronchiolar hypertonus had subsided, we find a respiratory cycle which lasted 24/5 seconds, the duration of inspiration being 11 5 seconds and the expiratory phase 13/5 seconds, and the amount of air expelled was 2,210 c.c. So, before epinephrin was given 324 c.c. were passively expelled in 12 5 seconds, and after epinephrin was given 2,210 c.c. were passively expelled in 13/5 seconds. In spite of the fact that the vital capacity during the attack of bronchial spasm was lowered over 1,500 c.c., there was evidence of only a very slight increase in the volume of the lung. Before epinephrin the lower border of the lung was in the ninth interspace in the axillary line, and after epinephrin it was in the eighth interspace; and during the attack, although his diaphragm was coordinately activated with his intercostal muscles, all of both costal margins moved in an outward direction during inspiration. So we are justified in saying that the reduction in vital capacity was not traceable to an increase in residual air in the lung, but was due purely to bronchial stenosis.

Dr. L., from whom the tracing was taken, has repeatedly tested his vital capacity during the past year and has always found it to be about 4,000 c.c. In fact, the character of Dr. L.'s tracing shows his respiratory excursion during the attack to be quite like the respiratory excursions found in dogs when an equal tracheal stenosis to inspiration

and expiration is employed. After the attack was over, there was not the slightest evidence of any kind for bronchitis or any modification in the extensibility of the lung.

REGIONAL EXPIRATORY DYSPNEA

At a stage of the investigation when the relation between bronchiolar hypertonus and pulmonary emphysema seemed very elusive, a patient came into Lakeside Hospital who presented a group of symptoms that I had never before seen.

CASE 10.—This man had an aneurysm of the aorta involving the latter portion of the ascending and the first portion of the transverse arch. The first part of his aorta showed no evidence of dilatation. All the physical signs and the roentgenograms confirmed the diagnosis of an aneurysm which lay in front and above the left bronchus and showed no evidences of contact with the right bronchus. In all cases of obstruction of the bronchus from aneurysm which had come under my observation, there was an equal obstruction to inspiration and expiration, and there never had been in former cases any difference in degree of obstruction when the patient was seated or recumbent. This man, however, showed a very curious phenomenon. When he was in the upright position, there was no demonstrable stenosis to the left bronchus, but when he was on his back, there were decided evidences of stenosis to this bronchus, and during expiration it was much greater than during inspiration. The man suffered no pain and no great discomfort when he was going about. His complaint was that when he lay down he had an uncomfortable, "stuffy" feeling over the left side of his chest.

Physical examination revealed very characteristic signs of aneurysm of the arch of the aorta. When he was in the upright position, the respiratory excursions of the two sides of the thorax were nearly equal, but when he was lying down, the left side became distinctly larger than the right, and the respiratory excursion of the entire left side was very much less than on the right. Palpation revealed comparative immobilization of the ribs of the left side during inspiration in this position, and over the left hypochondrium there was an absence of the piston thrust from the left leaf of the diaphragm, whereas the right side of the diaphragm had a perfectly normal and very active excursion. The costal margin of the left side moved very slightly in an outward direction during inspiration, and percussion revealed a decidedly lower position of the left lung in the axillary line.

When the patient was upright, the respiratory sounds on the two sides of the thorax were equally loud, but when he lay down, those on the left side were only faintly audible. There was also much less tactile fremitus on the left side.

When he was seated, his vital capacity was 3,711 c.c.; lying down, 2,545 c.c.—a difference of 1,166 c. c., which is a far greater disparity than one will find in any other condition, for few persons will on lying down show a lessening of more than 250 c.c. in their vital capacity.

The pulmonary emphysema of the left side when the patient was recumbent was due to the relation between the aneurysm and the left bronchus. In this position the weight of the aneurysm compressed the left bronchus, but during inspiration the lifting of the thoracic cage permitted a freer flow of air into the right lung than that allowed out of the left lung during expiration. He was able to compensate for the impairment in ventilation of his left lung by a very moderate increase in ventilation of the right, and therefore had no air hunger. When the man was upright, there was during expiration no demonstrable sign of compression of the left bronchus.

On comparing this case with Case 4, in which there was an expiratory stenosis of the trachea from an aneurysm of the aortic arch, it will be apparent why this latter patient acquired an emphysema of his left lung when he was lying down. One can readily see that the essential difference between the two cases lies in the fact that the patient last referred to had a very decided expiratory dyspnea involving the left lung but none involving the right, whereas in the former patient, although he suffered from severe expiratory dyspnea, both sides of the lung were equally involved because the expiratory compression was applied to the trachea. This suggested the idea that pulmonary emphysema may be traceable to an excess of expiratory obstruction over inspiratory obstruction; and that clinically we find a marked pulmonary emphysema attending the process because the expiratory dyspnea is unequally distributed throughout the bronchial tree, whereas under the influence of histamin our experiments failed to show any emphysema simply because the hypertonus was equally distributed.

The patient with an expiratory dyspnea confined to the left bronchus had a great increase in the residual air of his left lung, which reduced the total capacity of his lungs by 1,166 c. c. This was accomplished without air hunger or hyperpnea or an active expiration, which is the very essential criticism above presented and must be met by a satisfactory theory for emphysema caused by bronchiolar hypertonus. If we conceive of these gross relations of expiratory dyspnea between the two lungs being applied to the terminal bronchioles throughout the bronchial tree, we then have a theory of emphysema from clinical bronchiolar hypertonus which conforms to the facts of clinical experience.

The physical signs produced by an aneurysm of the transverse arch compressing the left bronchus were very readily reproduced experimentally in the dog by procuring expiratory dyspnea confined to one lung with no obstruction to either bronchus during inspiration.

Experiment 6.—A rubber cork was used, through the middle of which was passed a metallic tube, with a diameter three-fourths that of the cork itself. This cork was just large enough to fill a bronchus of the dog employed. Over one end of the cork was spanned a small strip of rubber dam, and the cork was so inserted into the right bronchus that this end lay in the distal position. During inspiration there was no obstruction to the entrance of air into the right lung, but during expiration there was very pronounced obstruction. Under a pressure equal to 80 mm. of water, the minute volume flow of air through this valve measured 1,200 c.c., which would just about balance the elastic retraction of the dog's lung. Figure 7 shows the animal's thorax when it was comfortably breathing atmospheric air. The disparity in the elevation of the two leaves of the diaphragm was quite like that in our patient with aneurysm when he occupied the horizontal position. When the animal was made to rebreathe a high concentration of carbon dioxid, this disparity was very considerably increased.

If we consider the factors attending pulmonary emphysema as a result of bronchiolar hypertonus, we shall see that the following must be considered: (1) There is always dyspnea, but it is not necessarily so pronounced as to cause great discomfort. (2) The process is not accompanied by hyperpnea. Even in the very severe cases, the minute

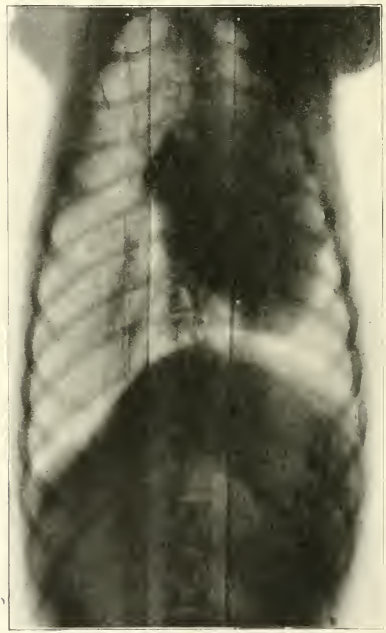

Fig. 7.—Experiment 6. Thorax of dog in which an aneurysm of the transverse arch was produced experimentally.

volume of air is not increased more than 25 per cent. (3) An active expiratory phase is not essential for the production of emphysema.

An unequally distributed expiratory dyspnea would satisfy all these criticisms, as shown in our patient with expiratory dyspnea restricted

to the left side, and the dog with expiratory dyspnea restricted to the right side. From our experimental and clinical observations, therefore, it seems reasonable to suppose that in the acute cases an unequal distribution of the expiratory dyspnea is essential for the production of emphysema. In the chronic atrophic cases also it is known to be unequally distributed.

This study does not pretend to offer a satisfactory solution of the problem of pulmonary emphysema. As in massive collapse of the lung, which is also dependent upon some effect on lung motility, our present knowledge of physiology is not sufficient for a satisfactory explanation. This study does, however, reveal the inadequacy of the commonly accepted theory of emphysema, and justifies the suspicion that an unequal distribution of expiratory stenosis throughout the bronchial tree is the essential factor.

SUMMARY

1. Though active expiratory compression of the lung is rarely employed, the vigor with which the expiratory muscles can compress the lungs is greater than that with which the inspiratory muscles can distend them. Therefore, the air inspired within a given time can be expired within the same time, provided the resistance in the trachea or the branches of the bronchial tree is the same in inspiration as in expiration.

2. When the tracheal or uniform bronchial resistance to expiration exceeds that to inspiration, the residual air in the lung is increased only when hyperpnea attains such a degree that the respiratory need will not allow adequate time for the volume of the expired air to equal that of the inspired air.

3. Compression of the lungs in expiration does not produce a vicious cycle of increasing resistance to expiration.

4. Neither hyperpnea nor an active expiration is essential for the production of emphysema.

5. Prolongation of expiration in emphysema does not measure the degree of expiratory resistance, but indicates the patient's respiratory tolerance of prolongation of the expiratory phase. It is only in the extremity of respiratory needs that active expiration is employed to overcome expiratory resistance.

6. In bronchiolar spasm severe enough to demand an active expiration, the inspiratory and expiratory phases have the same duration and the volume flow within each phase is constant.

7. That an excess of expiratory over inspiratory resistance should produce emphysema, the excess must be unequally distributed in the bronchial tree.

A STUDY OF MICROLYMPHOIDOCYTIC LEUKEMIA

WITH THE REPORT OF A CASE *

SOLOMON FINEMAN, M.D., M.A.

MINNEAPOLIS

PART I

In 1915, Citron [1] reported a case of leukemia which from the blood picture and clinical findings, was diagnosed as "micromyeloblastic leukemia." The postmortem histologic study carried out by Pappenheim and Citron showed that the bone marrow was entirely normal. However, the cells of the follicles, as well as the cells of the interfollicular tissue of the lymph nodes and spleen, contained a slightly enlarged, eccentrically placed, perfectly round nucleus which resembled very closely the nucleus of a "myeloblast." The largest forms, however, were not as large as those found in "myeloblastic leukemia."

While the blood showed a definite myelogenous picture, it was evident that the "myeloblasts" and "micromyeloblasts" of the blood were not coming to any extent from the bone marrow because the bone marrow was normal (Pappenheim and Citron). On the other hand, there was clear evidence that an actual proliferation in situ of the follicular as well as of the interfollicular tissue was taking place, and, furthermore, that there was an actual metaplasia of lymphocytic cells into "micromyeloblastic" cells. Citron's conclusion, therefore, was that the "micromyeloblastic" cells of the blood were being generated in the follicles and interfollicular tissue of the lymph nodes and spleen and that these "micromyeloblastic" cells were passing from the follicles into the blood stream. Citron regarded his case as being of utmost significance in that it was the first case on record which would seem to prove that the dualistic doctrine of the origin of white blood cells, namely, the complete independence of the origin of myeloid and lymphoid blood cells, did not always hold true.

Citron's case was one which anatomists and hematologists had long been seeking. It offered partial evidence in contradition to the statements made by Naegeli, Schridde, Meyer, Hyneke and Ziegler [2] and other dualists that "myeloid tissue" has never been observed proliferat-

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* A thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts.

1. Citron, J.: Ueber zwei bemerkenswerte Fälle von (akuter) Leukämie, Folia haematol. **20**:1, 1915.

2. Naegeli, Schridde, Meyer and Hyneke, and Ziegler: Quoted by Ehrlich, P., and Lazarus, A.: (Rewritten by A. Lazarus and O. Naegeli, and translated by H. Armit). Anemia, New York, Rebman Co., 1910, p. 148.

ing in the germinal centers of spleen or lymph node follicles; that in all cases showing "myeloid infiltration" of the spleen or lymph nodes the follicles are passive or atrophied.

This case shows not only a proliferation of the lymph node follicles but what is of utmost significance, a proliferation of "micromyeloblasts" and "myeloblasts" in the germinal centers of these proliferating follicles. Although a necropsy was not permitted, we were fortunate in obtaining a lymph node during the patient's life. This lymph node was fixed in Helly's fluid immediately after excision, so that the material studied was obtained under ideal conditions.

In brief, we had a case of leukemia in which the blood contained enormous numbers of cells, which ordinarily would be called "the rare micromyeloblasts." The blood picture would lead one to make a diagnosis of myelogenous leukemia. Clinically, however, we had evidence pointing to lymphopoietic activity, namely, a mediastinal tumor, as revealed by percussion and roentgenograms, a very marked enlargement of lymph nodes over the entire body, and a markedly enlarged spleen.

That the lymphopoietic organs were very active was proven by the sections of lymph node, which showed that the blood cells referred to as "micromyeloblasts" were in reality proliferating right in the lymph follicles and germ centers of the node, and could be traced entering the circulation from the lymph node.

I believe, therefore, that our case offers strong evidence that the unitarian theory of the origin of white blood cells, which will be discussed later, is the correct one.

REPORT OF CASE

History.—Service of Dr. E. T. F. Richards. Patient, a girl, aged 17, single, American of Swedish descent, came to University Hospital Jan. 20, 1919.

Present Complaint.—Weakness and rapidly enlarging masses in the neck and axillae.

Family History.—Negative.

Social and Occupational History.—Negative.

Past History.—She has been well up to four weeks ago (December, 1918). She had measles at the age of 6; no sequels; scarlet fever at 15; no sequels; tonsillitis, acute, at 16; lasted four days; could not swallow without pain. No enlarged glands at that time. Felt fine after attack subsided.

Head: *Eyes.*—She has had "eyestrain" for the past four months (October, 1918, to January, 1919) and wore glasses, with relief; vision is good. *Ears.*—Negative. *Nose.*—Occasional "cold"; otherwise negative. *Mouth and Throat.*—Teeth filled during summer of 1918.

Cardiorespiratory: Negative.

Gastro-Intestinal: Negative.

Genito-Urinary: Negative except occasional nocturia.

Catamenia: Began at 15; negative.

Venereal: Negative on direct and indirect questioning.

Neuromuscular: Negative.

Skin: Negative.

Habits: Good. Weight: Best in summer of 1918, 135 pounds; now apparently 120 pounds.

Present Illness.—Patient was well until November, 1918; felt "fine and had red cheeks." Beginning in November, 1918, and especially toward the latter part of the month, she began to complain of being tired, especially so after coming home in the evening. Neither the patient nor her mother noticed any paleness at that time nor enlarged masses. Mother did notice, however, that the patient became very fretful and irritable.

Dec. 23, 1918, the patient came home from work and complained of feeling very tired and of having a severe headache and pain in her knees. Mother thought she had "influenza." Patient did not go back to work on account of weakness. Also at that time she noticed a beginning pallor of the face. The pain in the knees subsided after a few days, but the weakness and pallor became progressive. Patient did not go to bed, however, for two weeks. At the end of that time, in the early part of January, she noticed "lumps" in her neck, especially behind and below the ears. Her hearing became impaired, and once, when she blew her nose, she noticed blood on her handkerchief. A physician was called and diagnosed the case as "mumps."

Two days after the appearance of the masses behind and below the ears, the patient noticed a "lump" under the right jaw. This lump enlarged at first and then decreased in size. Three weeks after onset, about January 14, patient noticed "lumps" in both axillae, but none elsewhere. From that time on the swellings gradually enlarged and the mother began to notice a definite progressive paleness.

Patient denied having fever, hemorrhages and sweats. She "caught cold" about four days before entering the hospital and developed a nonproductive cough. On entrance she had no headache; she could read; nasal breathing was free. She had no pains; her appetite was good; bowels were regular, and she slept well.

Physical Examination.—Temperature, 100.6 F.; pulse, 146. Patient in bed; has dry nonproductive cough; voice hoarse; looks very anemic; development and nutrition, good; no edema, cyanosis or jaundice. Neck and sides of face appear swollen with irregular shaped subcutaneous masses.

Head: *Sinuses and Mastoids.*—Tenderness over frontal sinuses and mastoids and over left antrum. *Eyes.*—Eyegrounds show extensive fresh hemorrhages in both retinae and disks; disk margins indistinct but not choked. Sclerae have a slightly yellowish tinge. Conjunctivae are very pale. Visual fields appear to be normal. *Ears.*—Moderate deafness; with watch, right ear, 3½ inches; left ear, one-half inch. Bone conduction greater than air conduction R. and L. *Nose.*—Negative. *Mouth.*—Lips show extreme anemia and capillary pulse is detectable. Gums are also extremely anemic; gingivitis is present. The gums are tender and bleed on pressure. Teeth are very crowded, especially in the upper jaw where one tooth protrudes in abnormal position. Few teeth are carious. Mucosa of mouth is very pale. The palate is very high and arched. The tonsils are very large, glistening, pearly in appearance, so large that they almost occlude the entire pharynx. The tongue is coated.

Glands: Chains and matted masses of glands are felt in these regions: anterior and posterior auricular; submaxillary; anterior and posterior cervical, left and right subclavicular; over both apices anteriorly and posteriorly; over the trapezii; in the axillae and in the inguinal regions. These are all bilateral. They vary in size from that of a small pea to that of a hen's egg. Some are round; some are oval and many are matted. They are hard and not tender to pressure; are freely movable and not attached to the skin. The size of the face is shown in Figure 1. A comparison is made of the size of the glands from day to day in Table 1 and Figure 2.

Chest and Lungs: *Anteriorly.*—Inspection, negative, except that chest comes down rather slowly with expiration. Palpation, negative. Percussion, abnormally wide supracordial dulness (Fig. 3). Auscultation, generalized "cog-wheel" breathing; exaggerated, tubular over area of supracordial dulness. Vocal

fremitus and whispered voice increased over same area. Posteriorly.—Inspection, small masses over both trapezii. Palpation, negative. Percussion, diminished resonance for 5 cm. to right and left of vertebrae on levels I to VI D. Auscultation, cog-wheel breathing, generalized. Tubular breathing from I to VI D. for 5 cm. to right and left. Vocal fremitus and whispered voice increased over spine from I to VI D. for distance of 5 cm. to the right.

Breasts: . Negative.

Spine: Increased whispered voice and dulness to sixth dorsal vertebra. Costovertebral angles, negative.

Heart: Inspection, negative; palpation, negative; percussion, cardiohepatic angle obtuse; absolute dulness increased (Fig. 3).

Fig. 1.—Photograph of patient Feb. 14, 1919. Note large preauricular nodes. See Figure 2.

Measurements

Intercostal Space	Right, Cm.	Left, Cm.
2	3	4
3	2	6
4	3	7
5	4	8

Auscultation Sounds.—Second pulmonic [illegible] attenuated. First sound at the apex is accentuated. *Murmurs.*—Systolic murmur, short, transmitted but slightly into axilla, heard at apex, tricuspid and aortic areas and clearest immediately to the left of the sternum. Blood vessels, negative. Pulse, rapid; sharp rise and fall. Blood pressure: systolic, 130; diastolic, 40.

Abdomen: Inspection, negative; palpation, spleen palpable 7 cm. below costal margin in midclavicular line. No notch felt; freely movable with respiration; no tenderness; liver not enlarged. Percussion, splenic dulness same as on palpation. Liver dulness 12 cm. in midclavicular line.

Extremities: Upper, negative, except extreme anemia of nails. Lower, old traumatic scar on left thigh, otherwise negative

Sensation: Normal. Reflexes: Negative, except that right knee jerk was very sluggish and the left was not obtainable. No cloni; Babinski, Gordon or Oppenheim signs. Vibration Sense: Present over all bony prominences. Rectum, negative.

Laboratory Data on Entrance.—Urine: trace albumin; sp. gr., 1.010; acid; few leukocytes and few hyalin casts; Bence-Jones body negative. Guaiac test repeatedly negative. Sputum: negative. Stool: negative repeatedly for blood with guaiac test.

Blood: hemoglobin, 29 per cent. (Dare); red blood cells, 1,900,000; white blood cells, 99,000. Differential count (Table 4 and Fig. 4).

Phenolsulphonephthalein excretion, 66 per cent. in two hours. Blood Wassermann negative.

Blood Chemistry: Sugar, 0.105 per cent.; creatinin, 1.40 mg.; urea nitrogen, 10.50 mg.

Blood culture negative.

Mosenthal test negative. For metabolic studies with excreta in urine and feces see Tables 2 and 3. Electrocardiograph tracing: negative.

PROTOCOL

All white and red cell counts and hemoglobin determinations were done by Dr. Swan Erickson and myself. We used the same set of pipets throughout, and on numerous occasions checked each other and followed as closely as possible the same technic throughout the patient's stay in the hospital. In referring to spleen and liver measurements, we mean measurement in the midclavicular line below the costal margin.

Jan. 21, 1919: Hemoglobin, 29 per cent. (Dare). Red blood cells, 1,900,000; white blood cells, 99,000.

January 22: White blood cells before roentgen-ray treatment, 44,000. Roentgen-ray treatment over glands of chest and neck.

January 23: Glands diminished to from one-fourth to one-sixth of their previous size. Mediastinal width 8 cm. Tonsils only half as large. White blood cells, 9,600.

January 24: White blood cells, 4,800.

January 25: Transfusion of 200 c.c. blood; no reaction; clinical improvement marked.

January 27: Glands, smaller than on January 23. Tonsils only about one-sixth of former size. Spleen, 3 cm. Mediastinal dulness diminished.

January 30: Right and left posterior auricular glands enlarging; hearing diminishing. White blood cells, 33,000 at 11 a. m.; 50,000 at 6 p. m.

January 31: Glands enlarging again; spleen 7 cm. White blood cells, 50,000.

February 1: White blood cells, 8000; spleen, 4 cm. Mediastinal dulness, 5.5 cm. Transfusion of 300 c.c. blood.

February 3: White blood cells, 9,000.

February 4: Distinct swellings in front of right and left ears. Tonsils enlarging; some of other glands enlarging. White blood cells, 26,800 at 11 a. m.; 49,000 at 6 p. m.

February 5: White blood cells, 70,300. Difficulty in breathing present; restless; hearing poorer. Tonsils markedly enlarged; lacked 1 cm. of meeting in midline. Spleen 7 cm. All glands definitely enlarged.

February 6: White blood cells, 90,000; no reticulated cells; platelets, 90,000 per cubic millimeter.

February 7: White blood cells, 72,000; axillary lymph gland excised.

February 8: White blood cells, 42,000 at 10:30 a. m.; 68,000 at 7 p. m. Patient's general condition worse in evening; dyspnea; nasal breathing impossible. Tonsils. 0.5 cm. apart. Facial and axillary glands enlarged. Spleen, 7.5 cm. Supracordial dulness, 8.5 cm. in second intercostal space.

February 10: White blood cells, 60,000; patient's general condition the same.

February 11: White blood cells, 89,000.

February 12 and 13: Practically no change in patient's general condition. White blood cells, 108,000.

February 14: White blood cells, 108,000 at 9:30 a. m.; 68,000 at 2 p. m. The third roentgen-ray treatment was given at 2:30 p. m. over the neck, tibia and femurs. Patient dyspneic; dilated veins over temples. Mass of glands on right side of face, 8 cm. in diameter; left, 7 cm. These masses are palpable from back of the ears to the angle of the eye. They are very prominent. The tonsils and uvula practically obstruct nasopharynx. Nasal breathing impossible. Spleen, 9.5 cm.

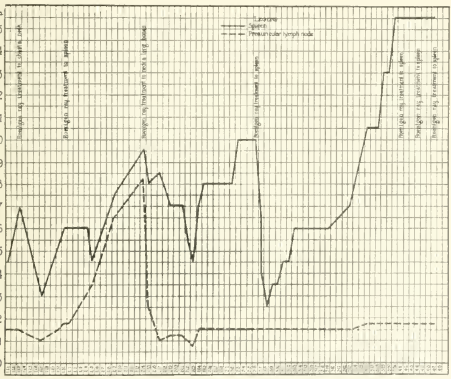

Fig. 2.—Shows variations in size of preauricular lymph nodes and spleen in relation to roentgen-ray therapy. Scale in centimeters shown on left. Splenic tumor measured below costal margin in midclavicular line.

February 15: Masses in front of both ears are barely visible. Patient breathing freely through nose. White blood cells, 29,300 at 10:25 a. m. Clotting and bleeding time, 5 minutes each.

1:30 p. m.: transfusion of 400 c.c. Felt stronger immediately after transfusion. Facial glands still smaller; not visible, just barely palpable as flat masses about 2 cm. in diameter. Tonsils about 1.5 cm. apart. Spleen, 7.5 cm.

February 17: White blood cells, 10,000. Facial mass on right side not palpable at all; on the left just barely palpable. Tonsils about 2.5 cm. apart. Patient "feels fine." Hemoglobin and red blood cells approximately the same as on entrance. Onset of epistaxis and appearance of numerous petechiae on both legs, from 2 to 3 mm. in diameter.

February 18: White blood cells, 20,000.

February 19: Condition worse. Hemoglobin, 26 per cent. (Fleischl); red blood cells, 1,860,000; white blood cells, 140,000 at 3 p. m.; 208,000 at midnight. Headache all day; constant dull abdominal pains; slow epistaxis all day. Complained of dimmed vision. Numerous fresh petechial hemorrhages on legs with several large bluish areas from 2 to 3 cm. in diameter. Edema of feet. Pressure over sternum, skull, humeri, ulnae, radii, femurs and tibiae elicited exquisite pain. For the first time numerous mitotic figures were observed in the blood in wet and dry preparations.

February 20: Condition worse. Hemoglobin, 21 per cent. (Dare); red blood cells, 1,344,000; white blood cells, 242,000. Glands seemingly not enlarged. Transfusion of 200 c.c. Pulse weak and irregular, thready; rate, 160. Fifteen minims benzol by mouth. Blood chemistry: sugar, 0.117 per cent.; creatinin, 0.75 mg.; urea nitrogen, 9.188 mg.

February 21: Eight minims benzol by mouth in the morning. White blood cells at 9:30 a. m., 62,000; at 1 p. m., 44,000. Blood culture negative. Blood of patient injected into rabbit's ear vein. Nitrogen intake, 9.6 gm.; output, 16.8 gm. in urine. Blood chemistry: blood sugar, 0.099 per cent.; creatinin, 0.60 mg.; urea nitrogen, 9.96 mg.

February 22: Spinal puncture, 20 c.c. clear fluid under pressure; Nonné negative; cell count, 3 per cubic millimeter. Colloidal gold test negative; Wassermann +. General condition good. White blood cells, 6,800. Lymph nodes in general smaller. Bone tenderness diminished. Several epistaxes during day.

February 23: Condition further improved; patient smiling, cheerful, laughed, insisted on being allowed to sit up in chair. Vision definitely impaired; could barely see large newspaper headlines, and small type not at all. Glands and spleen somewhat smaller.

February 24: Condition worse; headache; anxious expression; lips seemed paler; spleen and some of glands enlarged somewhat. White blood cells, 10,000.

February 25: Spleen still further enlarged; glands about the same. White blood cells, 44,000; platelets, 92,000.

February 26: White blood cells, 82,000; 23 minims benzol by mouth.

February 27: White blood cells, 76,000; 23 minims benzol by mouth.

February 28: White blood cells, 34,200; hemoglobin, 13 per cent. (Dare); red blood cells, 900,000; felt fine; asked for second helpings of her meals. Benzol discontinued.

March 1: White blood cells, 22,000.

March 2: White blood cells, 61,000. Condition worse; epistaxis in morning; glands and spleen about the same.

March 3: White blood cells, 105,000 at 1 p. m. Condition worse; severe headache. White blood cells, 176,000 at 7 p. m. Profuse epistaxis in the morning. Lymph glands about the same. Spleen 10 cm. and reached to umbilicus; not tender and no rub felt. Liver, 7 cm.; pulse, from 140 to 170; gallop rhythm. Mitotic figures observed in both wet and dry preparations of blood. Transfusion of 160 c.c. followed by hypodermic of morphin sulphate, ⅙ grain, and atropin sulphate, 1/150 grain.

March 4: White blood cells, 95,000 at 2 p. m.; 106,000 at 7 p. m.

March 5: White blood cells, 75,200 at 10:30 a. m. Transfusion at 1:45 p. m., 150 c.c.

March 6: White blood cells, 26,300 at 1:30 p. m. Roentgen-ray treatment to spleen at 3:30 p. m.

March 7: White blood cells, 4,000 at 9:30 a. m. Transfusion at 10:25 a. m., 200 c.c.

March 8: White blood cells, 2,300. Spleen by noon just barely palpable. General condition worse. Sight poor; eyegrounds show numerous fresh hemorrhages.

TABLE 1.—Comparative Data from Day to Day Regarding White Cell Count, Changes in White Count Observable on the Same Day; Roentgen-Ray Treatment; Number of Stem Cells Per C.Mm.; Number of Mitotic Figures Per C.Mm., Transfusions, Fluctuations in Size of Splenic Tumor, Tonsils, Facial Glands and General Condition

Date	White Blood Cells	White Blood Cells Later on in Day	Roentgen Ray Treatment	Stem Cells	Mitotic Figures	Transfusion, C.c.	Spleen,* Cm.	Tonsils,† Cm.	Face Glands, Cm.	General Condition
1 21	99,000	.....	.....	1,386	..	...	4.5	0.5	1.5	Fair
1 22	40,000	.....	Chest-neck							
1 23	9,600	.....	.....	.....	..	...	7	...	1.5	Good
1 24	4,800	.....	.....	271	..	...	...	2		
1 25	5,000	.....	.....	.....	..	200	...	...	...	Good
1 26										
1 27	5,400	.....	.....	.....	..	...	3	3	1	Good
1 28	6,900									
1 29	13,800									
1 30	33,000	50,000	.....	900	..	...	...	...	1.5	Good
1 31	51,600	.....	Spleen	.....	..	...	6	...	...	Fair
2 1	8,000	.....	.....	540	..	300	6	2	1.75	Good
2 2	9,400	.....	.....	.....	..	...	...	...	1.75	
2 3	12,300									
2 4	26,200	49,700	.....	.....	..	...	6	1	3	Good
2 5	70,200	.....	.....	.....	..	...	4.5	0.75	3.5	Bad
2 6	90,000	.....	.....	15,804						
2 7	72,000	.....	.....	.....	+					
2 8	40,200	68,000	.....	2,160						
2 9	65,000	.....	.....	.....	..	...	7.5	0.5	6.5	Bad
2 10	60,000									
2 11	89,000									
2 12										
2 13	108,000									
2 14	108,000	64,000	Neck-bones	31,605	..	...	9.5	0	8	Bad
2 15	29,300	.....	.....	.....	..	400	8	1.5	2.5	Good
2 16	10,300	.....	.....	618						
2 17	10,800	.....	.....	.....	..	...	8.5	2.5	1	Good
2 18	20,000	.....	.....	4,150						
2 19	140,000	208,000	.....	.....	+	...	7	2	1.25	Bad
2 20	242,000	.....	.....	96,840	+	200	7	2	1.25	Bad
2 21	62,000	44,000	.....	8,000	..	...	7	...	1.25	Fair
2 22	6,800	.....	.....	11	..	...	5.5	2.5	1	Fair
2 23	8,500	.....	.....	.....	..	...	4.5	...	0.75	Good
2 24	10,400	.....	.....	.....	..	...	7	2	1.5	Fair
2 25	44,000	.....	.....	.....	..	...	8	...	1.5	Fair
2 26	82,000	.....	.....	45,592	..	...	8	...	1.5	Fair
2 27	76,400	.....	.....	.....	..	...	8	...	1.5	Fine
2 28	34,200	.....	.....	6,498	..	...	...	...	1.5	Fine
3 1	22,000	.....	.....	.....	..	...	...	...	1.5	Fine
3 2	61,000	.....	.....	.....	+	...	8	...	1.5	Fair
3 3	105,000	176,000	.....	50,336	+	160	10	...	1.5	Bad
3 4	95,000	.....	.....	.....	+	...	...	...	1.5	Fair
3 5	75,000	.....	.....	.....	+	150	...	...	1.5	Fine
3 6	9,000	.....	Spleen	.....	..	...	10	...	1.5	Fine
3 7	4,000	.....	.....	.....	..	200	4	...	1.5	Fair
3 8	2,300‡	.....	.....	153	..	...	2.5	...	1.5	Fair
3 9	3,400	.....	.....	.....	+	...	3.5	...	1.5	Fair
3 10	5,600	.....	.....	.....	..	150	3.5	...	1.5	Fair
3 11	5,600	.....	.....	.....	..	...	4.5	1	1.5	Fair
3 12	8,800	.....	.....	.....	..	...	4.5	...	1.5	Fine
3 13	8,100	.....	.....	.....	..	...	6	...	1.5	Fine
3 14	7,000	.....	.....	.....	..	...	6	...	1.5	Fine
3 15	7,900	.....	.....	.....	..	...	6	...	1.5	Fine
3 16	9,600	.....	.....	.....	..	...	6	...	1.5	Fine
3 17	7,000	.....	.....	.....	..	...	6	...	1.5	Fine
3 18	6,000	.....	.....	.....	..	...	6	...	1.5	Fine
3 19	6,900	.....	.....	.....	..	200	6	...	1.5	Fine
3 20	5,900	.....	.....	.....	..	...	...	...	...	Fine
3 21	6,000	.....	.....	160	..	...	...	...	...	Fine
3 22	12,700	.....	.....	.....	..	...	...	...	...	Fine
3 23	17,000	.....	.....	.....	..	...	7	2	1.5	Fine
3 24	17,300	.....	.....	.....	..	...	...	...	...	Fine
3 25	25,500	.....	.....	.....	..	...	...	...	...	Fine
3 26	34,000	.....	.....	.....	..	...	10.5	...	1.75	Fine
3 27	80,000	.....	.....	.....	+	...	10.5	...	1.75	Fair
3 28	115,000	.....	.....	.....	+	...	10.5	...	1.75	Bad
3 29	247,000	178,000	.....	32,505	+	300	13	2.5	1.75	Bad
3 30	260,000	295,000	.....	.....	..	...	13	...	1.75	Fair
3 31	334,000	.....	.....	.....	+	...	15.5	...	1.75	Fair
4 1	480,000	.....	Spleen	.....	+	300	15.5	...	1.75	Bad
4 2	500,000	.....	.....	75,890	+	...	15.5	2	1.76	Fair
4 3	485,000	.....	.....	.....	+	...	...	...	1.75	Good
4 4	578,000	.....	Spleen	.....	+	...	...	...	1.75	Fair
4 5	545,000	.....	.....	.....	+	200	...	...	1.75	Fair
4 6	541,000	.....	.....	.....	+	...	16.5	...	1.75	Fair
4 7	646,000	.....	Spleen	2,584	+	...	15.5	...	1.75	Bad
4 8	.....	.....	.....	.....	..	...	....	...	....	Died

* Splenic tumor palpable below the costal margin in the midclavicular line.

† Approximate distance between the tonsils.

‡ Lowest white count recorded.

March 9 to 21: The next thirteen days the white cell count and the patient's general condition simulated a lull before an impending storm. The white count varied from 5,000 to 9,000. The patient felt fairly well and even insisted on getting out of bed. We gave her her eighth and ninth transfusion of 350 c.c. of blood in all. Epistaxis occurred frequently. Blood culture was again negative. The glands remained stationary. The tonsils enlarged somewhat and the spleen measured 7.5 cm. March 13. From then on to March 21 the spleen remained stationary.

March 11: White blood cells, 5,600. Basal metabolism, +20 per cent.

March 14: White blood cells, 7,000. Basal metabolism, +7 per cent.

March 22: White blood cells, 12,000. General condition same.

March 23: White blood cells, 17,000. Complained of poor vision; facial glands enlarged slightly. Spleen 8.5 cm. Basal metabolism, +29 per cent. Patient restless.

March 24: White blood cells, 17,300; felt fine; sat up in chair. Spinal fluid: normal pressure; Nonne negative; cell count, 1 per cubic millimeter; colloidal gold test negative; Wassermann negative.

March 25: White blood count, 25,000. General condition good.

March 26: White blood cells, 34,000. General condition good; sat up in chair; facial glands little more enlarged. Mediastinum 7.5 cm. on percussion. Spleen, 10.5 cm. on palpation.

March 27: White blood cells, 80,000. Condition worse; felt miserable; sat up very little; complained of dull abdominal pain; pulse very rapid and heart had gallop rhythm.

March 28: White blood cells, 115,000. In bed all day; anxious expression; ankles and feet edematous; suppuration set in under nail of left big toe; hearing diminished; missed third menstrual period.

March 29: White blood cells, 247,000 at 10 a. m. At 10:38 a. m. transfusion of 300 c.c. White blood cells, 185,000 at 1:45 p. m. Spleen, 15 cm. and beyond umbilicoxyphoid line. White blood cells, 178,000 at 4:10 p. m. Liver, 6 cm. Abdominal pains severe. Ankles and feet more edematous.

March 30: White blood cells, 260,000 at 11 a. m.; 295,000 at 5 p. m. Spleen larger (Fig. 5).

March 31: White blood cells, 334,000. Severe abdominal pain—upper half. Pressure over spleen and sternum gave exquisite pain. Spleen still larger. Fluid in flanks. Edema of lower extremities increased. Dulness at base of left lung posteriorly, probably due to enlarged spleen. Pneumonia not demonstrable.

April 1: White blood cells, 480,000 at 10 a. m. Tonsils enlarged, 2 cm. apart; nasal breathing free. Transfusion of 300 c.c. Roentgen-ray treatment of spleen, three minutes only on account of poor condition of patient. Edema of right hand, wrist and sacrum. Patient very stuporous and complained of severe pain over the spleen.

April 2: White blood cells, 500,000. Condition slightly improved.

April 3: White blood cells, 485,000. Condition still better; talkative and bright.

April 4: White blood cells, 578,000 at 2:30 p. m. Roentgen-ray treatment at 1:30 p. m. over spleen. Liver, 10 cm.; tender. Basal metabolism, +29 per cent.

April 5: White blood cells, 545,000 at 4 p. m. Transfusion of 200 c.c. at 11 a. m. Patient felt better; sat up one hour in bed.

April 6: White blood cells, 541,000. Condition worse.

April 7: White blood cells, 646,000 at 2 p. m. Roentgen-ray treatment at 1:30 p. m., 9 minutes to spleen. Frequent severe epistaxis during day, with several emeses of clotted blood. At night breathing became stertorous and at midnight the patient could be awakened only with great difficulty. When awake, she was rational.

April 8: At 12:15 a. m. patient cried out several times, with inspiratory gasps. Pulse at that time was very rapid but of good quality. Death occurred a few seconds later of respiratory failure.

DISCUSSION

1. *Hemoglobin and Red Blood Cells.*—The hemoglobin and red blood cell count remained low throughout and both progressively diminished, in spite of twelve transfusions, a total of 2,760 c. c of blood.

2. *White Cell Count.*—The white cell count showed some extraordinarily sudden, unaccountable fluctuations. The rise or fall of the white cell count during twenty-four hour periods would sometimes be so great that we were obliged to make three or four counts in twenty-four hours to check our findings.

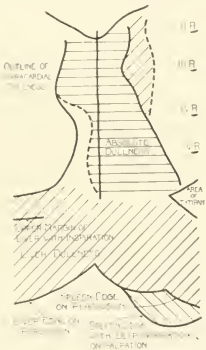

Fig. 3.—Showing percussable mediastinal dulness on entrance to hospital Jan. 21, 1919.

On entrance to the hospital the patient's white cell count was 99,000. In twenty-four hours, before any treatment was instituted, the count fell to 44,000, followed by a further fall after roentgen-ray exposure of the lymph nodes of the neck and mediastinum.

From then on the white cell count kept oscillating between counts as low as 2,300 and as high as 646,000 on the day of death. By making blood counts several hours apart on the same day we were able to demonstrate the following:

January 30: rise of 17,000 white cells in 7 hours.
February 8: rise of 28,000 white cells in 8½ hours.
February 14: fall of 44,000 white cells in 4½ hours.
February 19: rise of 68,000 white cells in 9 hours.

March 3: rise of 71,000 white cells in 6 hours.

March 29: fall of 62,000 white cells in 3 hours.

The rapidity with which a rise or fall of the white cell count would occur in this case was astounding. Thus, we see a rise from 10,500 cells February 17, to 242,000 cells February 20, and just as rapid a fall to 6,800 cells February 22. We see another sudden rise from 22,000 cells March 1, to 176,000 cells March 3, and just as sudden a fall to 2,300 cells March 8. Up to March 8, some of the white cell count fluctuations seemed to occur entirely spontaneously. At times, however, it seemed to us as if the transfusions and roentgen-ray exposures had an immediate effect in causing a drop in the white count. Figure 6, showing the daily blood counts and therapy, would seem to indicate that such was the case.

March 22, the white cell count began to rise with lightning-like rapidity and rose from 6,000 to 646,000 cells in the next seventeen days. From the beginning of this last rise in the white cell count, transfusions, and roentgen-ray exposures had practically no effect on the count, and the patient died with the highest count demonstrable during her stay at the hospital.

On looking over the blood chart (Fig. 6) one is struck by the seemingly periodic exacerbation of the white cell count rise, each period lasting from five to six days. It is of interest to note here that with each rise in the white cell count, the patient's general condition became definitely worse. As a matter of fact, we could usually note a beginning rise in the white cell count by the change in the patient's general condition. During the periods of low count she would be happy and feel so well that she would insist on being permitted to sit up in a chair. As soon as the white cell count would begin to rise, the patient would stay in bed and complain usually of headache and abdominal distress, and she would have an anxious expression.

Krjukow [3] describes a case of "microlymphoidocytic" leukemia in which there were sudden fluctuations in the white cell count, associated with rapid fluctuations in the size of the spleen.

3. *Mitotic Figures.*—A very interesting finding, with counts over 80,000, was the presence of numerous mitotic figures in the blood. These cells, in all stages of mitosis, were easily demonstrable in both the 1 per cent. acetic acid solution, and in the dry stained blood preparations. The higher the count the greater would be the number of mitotic figures. At one time we demonstrated as many as fifteen cells in mitosis in a single field under the low power lens of the microscope and a No. 10 eyepiece.

3. Krjukow, A.: Ueber einen Fall von akuter Microlymphoidozyten Leukämie. Folia Haematol. **15**:328, 1915.

Gordon Ward[4] describes a "peculiar case of acute leukemia," which from his description might very well have been a case of microlymphoidocytic leukemia, in which he observed as many as thirty-seven mitotic figures per cubic millimeter of blood. Krjukow noted in his case numerous mitotic figures in the blood during the periods of splenic enlargement.

In an attempt to determine whether these mitotic cells, which in all probability were being forced out from the rapidly proliferating lymphatic tissue into the blood stream, would continue the process to completion in vitro, Dr. Swan E. Erickson and I made a study of these cells in 1 per cent. acetic acid solution, physiologic solution of sodium chlorid, $1\frac{1}{2}$ per cent. sodium citrate in physiologic sodium chlorid solution, $1\frac{1}{2}$ per cent. sodium citrate in water, stock blood serum

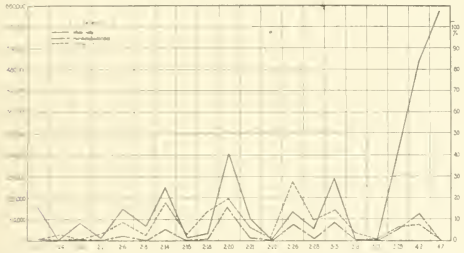

Fig. 4.—Shows relation between the total daily white cell count, total daily microlymphoidocytes, and daily percentage of microlymphoidocytes. Only data obtained during low and high count days are here recorded.

of Groups 2 and 3, and also in patient's own serum, which was of Group 4. We used a warm stage and kept the cells under observation in the above mentioned solutions at body temperature for as long as thirty-six hours. We did not observe a single instance of continuation of the process of mitosis in vitro.

4. *Differential Counts.*—The differential counts gave interesting findings (Table 4). The percentage of the various cells was calculated on a basis of from 300 to 700 cells. The percentage of polymorphonuclear neutrophils varied from as low as 0.4 per cent. to 33.66+ per cent. The total number of polymorphonuclear neutrophils was not directly proportional to the relative percentage. For example, with the lowest

4. Ward, G.: A Peculiar Case of Acute Leukemia, Clin. J. **48**:93 (Aug.) 1919; abstr. Folia haematol. **20**:158 (Nov.) 1920.

count of 2,300, the percentage of polymorphonuclear neutrophils was 19.33+ per cent., and the total number of polymorphonuclear neutrophils per cu. mm. was 445. With the highest count of 646,000 the percentage of polymorphonuclear neutrophils was only 1.4 per cent. with an absolute number of 9,044 polymorphonuclear neutrophils per cu. mm. The highest percentage of polymorphonuclear neutrophils, namely, 33.66+ per cent., was present with a total of 6,000 white cells per cu. mm. The number of polymorphonuclear neutrophils per cu. mm. in the normal blood is about 6,000. In this case even with counts as high as 242,000, the total number of polymorphonuclear neutrophils per cu. mm. was only 3,388. Only shortly before death did the absolute number of polymorphonuclear neutrophils go up above the normal, as follows:

March 29: Total white cells, 247,000; polymorphonuclears, 14,820. April 2: Total white cells, 500,000; polymorphonuclears, 9,150. April 7: Total white cells, 646,000; polymorphonuclears, 9,044.

5. *Nucleated Red Blood Cells and Myelocytes.*—Nucleated red blood cells and myelocytes were present in small numbers. These probably were an irritation phenomenon due to the extreme anemia, which at its lowest point gave a hemoglobin percentage of 13 on the Von Fleischl-Miescher instrument, and a red count of only 900,000.

6. *The "Micromyeloblast."*—The most interesting cell was the so-called "micromyeloblast" of Naegeli and Schridde, or the "microlymphoidocyte" or "stem cell" of Pappenheim. The total number and relative per cent. of this cell was practically directly proportional to the total count (Fig. 4). With the rise in total white cell count our patient was always clinically worse and the disease could be said to have assumed a more severe aspect. Coincidentally with the increase in the severity of the disease, the "micromyeloblast" would increase in number and percentage, a finding which is similar to the findings of Panton and Tidy [5] in a series of three cases.

With a white cell count of 2,300, the total "micromyeloblast" count was 153. With a white cell count of 500,000, the "micromyeloblast" count rose to 75,800. On the day before death, the total white cell count was 646,000, but the "micromyeloblast" count was only 2,548, probably an exhaustion phenomenon.

7. *Therapy.*—Our therapy consisted of a high carbohydrate diet, roentgen-ray exposure and transfusions. Benzol was tried on two occasions, but in amounts so small and for so short a period of time that its effect can safely be discounted. We have already mentioned the peculiar sudden fluctuations in the white cell count, associated with an

5. Panton, P. H., and Tidy, H. L.: Some Atypical Cases of Leukemia, Folia haematol. **17**:398, 1913.

improvement in the patient's general condition during the periods of low count.

Haughwout and Azuzano[6] report improvement in forty-eight hours following the administration of benzyl benzoate. They suggest, however, that this may be a normal fluctuation of the disease.

The roentgen-ray treatment varied a great deal in its effect on the enlarged spleen and lymph nodes, and on the white cell count. Seven treatments were given by Dr. Frank S. Bissel. The white cell count diminished after each treatment, with the exception of the treatments given a few days before the patient's death, at which time the count rose from 6,000 to 646,000. It must not be forgotten, however, that

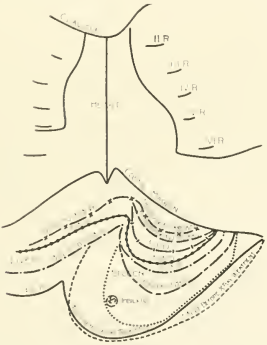

Fig. 5.—Composite tracing of spleen and liver from March 9 to April 6. Note gradual enlargement of both. Compare with Figure 20 showing gradual diminution of splenic dulness.

on six occasions there occurred diminutions in the count, varying from 44,000 to 236,000 cells, without roentgen-ray treatment.

The transfusions also had a varied effect on the patient. They were twelve in number and we gave a total of 2,760 c.c. The hemoglobin and red cell count gradually diminished. In the beginning it seemed as if the transfusions might be a factor in lowering the white cell count and improving the patient's general condition. The

6. Houghwout, F. G., and Azuzano: Notes on the Treatment of a Case of Lymphatic Leukemia with Benzyl Benzoate, New York M. J. **110**:180 (Aug.) 1919.

last few transfusions seemed to have had no effect whatever on the patient. With the first few transfusions there were very severe reactions. We were able to eliminate these reactions practically entirely by the use of small doses of morphin and atropin, given immediately after the transfusions.

An interesting finding during the last few days of the patient's life was the peculiarly changed morphology of the red blood cells. Whereas at the beginning the great majority of cells were very pale and irregular in size and shape, toward the end of the patient's life, the majority of cells appeared like perfectly normal red blood cells. Our impression was that these were functionating transfused cells, and that the patient was practically living on the transfused blood. Ashby [7] has shown that transfused red blood cells may functionate in the recipient for thirty days.

8. *Temperature Curve.*—The temperature varied between 96.6 and 104 F. A rise in the temperature was usually associated with a rise in the white count, enlargement of the spleen, lymph nodes and tonsils, and a marked increase in general malaise. The whole picture would suggest an exacerbation of an infective process.

9. *Blood Culture Studies.*—Blood studies on culture mediums and by injection into rabbits were negative. Baar and Kornitzer [8] and several other authors report positive cultures in the blood of leukemic patients. These, however, were usually found just antemortem and were probably due to secondary infections. To date no one has succeeded in transfering human leukemia to laboratory animals. Ellerman and Bang [9] could produce anatomic and hematologic leukemic lesions in healthy hens by injections of cell free Berkefeld filtered organ emulsions of a leukemic hen. Hirshfeld and Jacoby [10] observed spontaneous leukemia in hens and were successful in transmitting the disease through five generations. Schmeisser [11] also observed spontaneous leukemia in fowls and was successful in transmitting it into other fowls. Ellerman [12] claims that a myeloid type of leukemia may occur in one generation

7. Ashby, W.: Some Data on Range of Life of Transfused Blood Corpuscles in Persons Without Blood Diseases, M. Clinics N. America **3**:783 (Nov.) 1919.

8. Baar, V., and Kornitzer, E.: Ein positiver Bakterienbefund bei einem Fall von chronischer myeloischer Leukämie (Myeloblasten Leukämie), Wien. klin. Wchnschr. **32**:857, 1919.

9. Ellerman and Bang: Experimentelle Leukämie bei Hühnern, Zentralbl. f. Bakteriol. **46**:4, 1908.

10. Hirschfeld, H., and Jacoby, M.: Zur Kenntniss der übertragbaren Hühnerleukämie, Berl. klin. Wchnschr. **46**:159, 1909.

11. Schmeisser, H. C.: Spontaneous and Experimental Leukemia of Fowls, J. Exper. M. **22**:820, 1915.

12. Ellerman, V.: Untersuchungen über das Virus der Hühnerleukämie, Ztschr. f. klin. Med. **74**:43, 1914.

and a lymphatic type in the next, and that this is highly suggestive that both forms are due to the same infective agent.

10. *Metabolic Studies.*—A. The urine and stool chemistry were studied by Drs. Egerer-Seham and Frances Ford. We could not demonstrate any definite relation between our blood and clinical findings and the chemical findings. Tables 2 and 3 give the findings of only a few days on which high fluctuations in white cell count and splenic dimensions occurred.

In Krjukow's case the diminution of splenic enlargement was associated with an increased excretion of ureates.

TABLE 2.—Chemistry of Twenty-Four Hour Specimens of Urine

Date	White Blood Cells	NaCl, Gm.	N, Gm.	Urea N, Gm.	NH_3, Gm.	Inorganic Total Phosphates, Gm.	Creatinin, Gm.	Uric Acid, Gm.
1/20/19	99,000	4.69	4.89	....	....	....	....	....
1/24/19	4,800	5.73	5.93	....	....	....	....	....
2/19/19	206,800	0.70	1.86	1.09	0.25	....	0.17	0.10
2/22/19	6,800	4.84	7.21	3.82	0.22	....	1.81	1.03
3/2/19	61,000	2.66	5.87	2.49	0.74	0.07	1.90	1.02
3/3/19	176,000	2.31	6.24	2.97	1.04	0.53	1.13	0.88
3/4/19	106,000	3.78	6.09	3.11	0.85	1.78	1.84	0.99
3/7/19	4,000	3.22	9.82	4.77	0.88	2.59	2.21	2.87
3/8/19	2,300	2.39	6.33	3.02	1.00	2.20	1.76	3.66
3/9/19	5,600	2.41	7.14	3.98	0.87	0.81	1.34	1.88
3/24/19	17,000	1.43	2.01	1.00	0.37	0.05	0.50	0.16
4/1/19	480,000	4.08	4.66	3.68	0.48	0.08	0.46	0.25
4/2/19	500,000	1.06	3.70	1.62	0.56	....	0.52	0.42

TABLE 3.—Chemistry of Total Twenty-Four Hour Feces

Date	White Blood Cells	Inorganic Phosphates, Gm.	Total Phosphates, Gm.
[illegible]/7/19	76,400	0.53	2.10
[illegible]/28/19	54,200	0.75	1.11
[illegible]/1/19	22,600	0.66	1.14
[illegible]/3/19	176,000	0.53	1.58
[illegible]/4/19	106,000	1.78	2.58
[illegible]/16/19	9,600	0.53	0.76
[illegible]/24/19	17,300	0.05	0.16

Ordway [13] reports that radium applications over the spleen in leukemia increase the protein and phosphate constituents of the urine.

B. Blood chemistry studies did not yield data that could be correlated in any way with the white cell count variations.

C. Basal metabolism studies were as follows:

March 11: +20 per cent.; white blood cells, 5,600

March 14: + 8 per cent.; white blood cells, 7,000

13. Ordway, T.: Metabolism in Leukemia and Carcinoma During Radium Treatment, J. A. M. A. **73**:860 (Sept. 3) 1919.

March 23: +29 per cent.; white blood cells, 17,000
April 3: +41 per cent.; white blood cells, 485,000

11. *Blood in Feces and Urine.*—Feces and urine showed no chemical or microscopic blood at any time.

12. *Spinal Fluid.*—The first specimen gave a positive Wassermann, but was otherwise normal. Fluid obtained at a subsequent puncture was normal.

13. *Kidney Function.*—The phenolsulphonephthalein excretion, Mosenthal test and blood chemistry (sugar, urea nitrogen, and creatinin) gave normal values.

14. *Spleen.*—At first the spleen did not seem to play much of a rôle in the leukemic process. January 21 it was palpable about 3 cm. below the costal margin in the midclavicular line. From January 21 to March 3 marked fluctuations in the size of the spleen occurred. It was rather a peculiar effect or coincidence that roentgen-ray exposure of the mediastinal, facial and neck lymph nodes was followed by marked diminution in the size of the spleen, followed, however, each time by an enlargement of the spleen greater than on each previous occasion (Figs. 2, 5, 7 and 20).

March 6, the spleen was palpable in the midline of the abdomen and 10 cm. below the costal margin in the midclavicular line. It was again exposed to the roentgen rays, and again, either as a result of the roentgen-ray exposure or simply as a pure unexplainable coincidence, it had reduced in size in forty-eight hours to such an extent that it was just barely palpable (Fig. 20). In this connection it is of interest to note that the white cell count fell coincidently to 2,300 per c.m.

March 8, the spleen began to enlarge again very rapidly (Fig. 5) and by March 31 it was 5 cm. beyond the midline and 16 cm. below the costal margin in the midclavicular line. This rapid enlargement took place in spite of three exposures to the roentgen ray (Fig. 2). The white cell count also did not seem to be influenced by the roentgen-ray exposures and rose from 2,300 to 646,000 on the day of death (Fig. 6).

15. *Lymph Nodes.*—On entrance to the hospital the lymph nodes of the face, neck, axillae, groin and mediastinum were markedly enlarged. Photographs (Figs. 1 and 8) taken before and after roentgen-ray exposures show a remarkable difference in the size of facial lymph nodes. Here, again, it is an open question as to whether these changes were caused by the roentgen-ray therapy or whether they were simply a part of the peculiar unexplainable fluctuations of the lymphopoietic system. Figure 2 shows the relative fluctuations in the size of the facial lymph nodes.

A comparison of Figures 3 and 11 shows a definite diminution in the size of the mediastinal shadow. This diminution occurred within

forty-eight hours after roentgen-ray exposure of the chest. Plates 9 and 10 showed the same thing.

16. *Tonsils.*—The tonsils also seemed to take a very active part in the leukemic process. With rises in the white count and enlargement of the lymph nodes or spleen, they too would enlarge, so much so, that not only would nasal breathing become impossible but even mouth breathing would be very difficult. Roentgen-ray exposure over the face and neck seemed to produce a definite diminution in the size of the tonsils so that the patient could breathe with ease through the nose and mouth (Table 1).

17. *Liver.*—At first the liver was not palpable. Toward the end, it also enlarged and could be palpated 10 cm. below the costal margin in the midclavicular line.

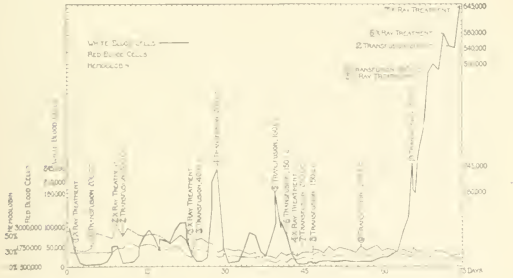

Fig. 6.—Curve of daily white cell count, red cell count and percentage of hemoglobin.

CLINICAL SUMMARY

1. In spite of the twelve transfusions of a total of 2,760 c. c. blood, the patient's hemoglobin percentage and red blood cell count steadily diminished. With a hemoglobin of 15 per cent., on the Von Fleischel Miescher instrument, and a red count of 900,000, the majority of red blood cells were full sized, round, stained well and had every appearance of normal cells. It seems probable, therefore, that the functioning transfused red blood cells prolonged an illness, usually acute and of very short duration.

2. The white cell count showed extraordinary sudden fluctuations. A fluctuation of 70,000 cells in six hours occurred March 29. The blood chart (Fig. 6) shows fourteen additional sudden fluctuations.

3. A study of the blood chart (Fig. 6) shows an apparent rhythmical occurrence of these fluctuations, a seemingly definite cyclic change of from five to seven days' duration.

4. Numerous beautiful cells in all stages of mitosis were demonstrable in the blood, both in the 1 per cent. acetic acid solution and in the dry stained smears.

5. Injection of the patient's blood into a rabbit was negative.

6. Morphin and atrophin, administered after transfusions, eliminated practically all reaction.

7. We could not demonstrate a definitely beneficial effect from roentgen-ray therapy over lymph nodes, spleen and long bones. At first, the spleen diminished in size when roentgen-ray therapy was applied to the chest and lymph nodes or long bones. Whether this was purely coincidental or whether it had any relation to the roentgen-ray therapy, we do not know. One exposure over the spleen was associated with a very pronounced diminution in the size of the spleen, Subsequent roentgen-ray exposures had no effect whatever.

Irradiation of the facial, cervical, axillary and mediastinal lymph nodes by the roentgen ray was followed by marked diminution in their size. Whether this was a direct result of the therapy, or simply coincident with it, is an open question. It is of interest to note that cervical and facial roentgen-ray irradiation was followed by a marked diminution in the size of the tonsils.

8. Enormous rapid fluctuations in the white cell count occurred, which could not be accounted for by therapy.

9. A marked rise in the white cell count was usually preceded and accompanied by a rapid enlargement of the spleen or of some group of lymph nodes.

10. The clinical picture of more or less rhythmically varying white blood cell counts, clinical improvement during the periods of low white cell count, and diminution in size of the lymph nodes or spleen, suggest the possibility of an infectious etiology of the disease.

11. The biopsy of a lymph node showed that at least a great number of "micromyeloblasts," a cell definitely myeloid according to the dualist view, were being generated in the germ center of the lymph node follicles and were passing out from the lymph node into the blood stream. Such a possibility has always been denied by the dualists.

12. Clinically, our case had all the earmarks of a lymphatic leukemia. The blood, however, showed in great numbers a cell, the so-called "micromyeloblast," which is believed by the dualists to originate in the myeloid tissues. To date, the dualists deny the possibility of such a cell originating in the germ center of a lymph node follicle.

A lymph node obtained under the very best possible conditions offers very good evidence in flat contradiction to the dualistic view.

This case is reported, because it offers strong evidence in favor of the unitarian theory of the origin of blood cells.

PART II

MORPHOLOGIC STUDY

Modern hematologists are divided into two strong groups, the so-called unitarians or monophyletists, on the one hand, and the dualists and polyphyletists on the other hand. The bone of contention between these groups is the so-called "stem cell."

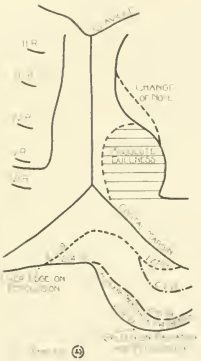

Fig. 7.—Composite tracing showing increase in size of spleen from January 27 to February 14. Slight diminution in size twenty-four hours after roentgen-ray treatment over spleen.

The dualists and polyphyletists consider the lymphopoietic and myelopoietic tissues as two separate tissues, entirely distinct from each other and never interchangeable. They contend that all the cells produced in lymphopoietic tissues come from their own specific stem cells, the "lymphoblasts," and in the same manner all cells produced in myelopoietic tissues come from their own specific stem cells, the "myeloblasts." They claim to be able to demonstrate a difference between "lymphoblasts" and "myeloblasts."

The unitarians or monophyletists deny the specificity of "lymphopoietic" and "myelopoietic" tissues. They present admirable evidence that under certain conditions myeloid cells may be produced by "lymphopoietic" tissues, and, vice versa, lymphoid cells may be produced in "myelopoietic" tissues. Pappenheim and his followers [14] claim that all blood cells spring from a single stem which they call "lymphoidocyte." While some unitarians do not admit that there is a morphologic difference between the "myeloblasts" and the "lymphoblasts," other observers grant such a possibility, but deny the specificity of the mother tissues from which these cells come.

Among the chief exponents of the unitarian theory are Pappenheim,[15] Grawitz,[16] Weidenreich,[17] Maximow,[18] Downey,[19] Ferrata,[20] Du Toit,[21] Arnold,[22] Neumann,[23] May,[24] and Danchakoff.[25] Among the chief exponents of the dualistic and polyphyletic theories are

14. Pappenheim and Hirschfeld: Ueber akute Myeloide und Lymphadenoide Makrolymphozytäre Leukämie an der Hand von zwei vershiedenen Fällen, Folia haematol. **5**:347, 1908. Pappenheim, A.: Atlas der menschlichen Blutzellen, Jena, 1905-1912. Morphologische Hematologie, Leipzig, Werner Klinkhardt, 1919.

15. Pappenheim, A.: Bemerkungen über artliche Unterschiede, usw., der lymphoiden. Zellformen des Blutes, Folia haematol. **9**: 321, 1909. Clinical Examination of the Blood and Its Technique (translated by R. Donaldson), New York, Wm. Wood Co., 1914.

16. Grawitz, E.: Klinische Pathologie des Blutes, Leipzig, Georg Thieme, 1911.

17. Weidenreich, F.: Die Morphologie der Blutzellen und ihre Beziehung zu Einander, Anat. Rec. **4**:317, 1910.

18. Maximow, A.: Ueber die Zellformen des lockeren Bindegewebes, Arch. f. mikr. Anat. **67**:680, 1906. Ueber embryonale Entwicklung der Blut und Bindegewebezellen bei den Saugetieren, Verhandl. der Anat. Gesellsch, 22, Vers., Berlin, 1908. Experimentelle Untersuchungen zur post fötalen Histogeneses des myeloiden Gewebes, Beitr. z. path. Anat. u. z. Allg. Path. **41**: 122, 1907.

19. Downey, Hal, and Weidenreich, F.: Ueber die Bildung der Lymphocyten in Lymphdrüsen und Milz, Arch. f. mikroscop. Anat. **80**:367, 1912. Downey: The Development of the Histogenous Mast Cells of Adult Guinea-Pig and Cat, and the Structure of the Histogenous Mast Cell of Man, Folia haematol. **16**: 1913. On the Development of Lymphocytes in Lymph Nodes and Spleen, Tr. Minnesota Path. Soc., 1912-1914, p. 91.

20. Ferrata, A.: Le Emopatie, Milano, Societa Editrice Lebraria **1**: 1918. (Reviewed in Folia haematol. **20**: 182, 1920, by Downey.)

21. Du Toit, P. J.: Beitrag zur Morphologie des normalen und des leukämischen Rinderblutes, Folia haematol. **21**:1, 1916.

22. Arnold, J.: Zur Morphologie und Biologie der Zellen des Knochenmarks, Arch. f. path. Anat. u. Physiol. **140**:411, 1895.

23. Neumann, E.: Hematologischen Studien der Leukozyten und Leukämie, Arch. f. path. Anat. u. Physiol. **207**:379, 1912.

24. May: Quoted by Naegeli.

25. Danchakoff, V.: Concerning the Conception of Potentialities in the Embryonic Cells, Anat. Rec. **10**:415, 1916.

The Origin of Blood Cells, Anat. Rec. **10**:397, 1916. The Wandering Cells in the Loose Connective Tissue of the Bird and Their Origin, Anat. Rec. **10**:483, 1916.

Naegeli,[25] Ehrlich,[26] Stockard,[27] Ziegler,[28] Türk,[29] Schriddé,[30] Fischer,[31] Butterfield, Stillman Meyer and Heinecke.[32]

Ehrlich [33] (1880) divided all white blood cells into granulated and nongranulated forms. It is this division which forms the basis of the modern dualistic teaching. He placed the lymphocytes, large mononuclears, and transitional cells among the nongranulated cells. The eosinophilic, basophilic and neutrophilic polymorphonuclears were the granulated cells. He believed the transitionals to be an intermediate form between the mononuclears and the neutrophils. Ehrlich believed that the lymphocytes came from lymphoid tissue, i. e., lymph node and spleen follicles, and that the granulocytes came from myeloid tissue, i. e., principally bone marrow. Today, this teaching, practically unchanged, is accepted by the dualists and the great majority of clinicians.

According to Naegeli's scheme the mesenchyme cell gives rise to the normoblast and this in turn to the normocyte. The mesenchyme cell also gives rise to the lymphocyte of the "quiet zone" of the follicle, this in turn to the "lymphoblast" of the germ center, and the "lymphoblast" gives rise to the small lymphocyte of the blood. The "myeloblast," the "stem cell" of the monocytes, megakaryocytes and polymorphonuclears, also comes originally from the mesenchyme cell. In postfetal life, therefore, all the blood cells come from their own specific "stem cells." He denies all transitions between the myeloid and lymphatic systems. He and other dualists meet the argument that myeloid metaplasia may occur in the spleen and lymph nodes in the absence of myeloid elements in the blood by declaring that lymph nodes and spleen are composed of two types of tissue, myeloid and lymphoid. The lymph node and spleen follicles are supposed to be

26. Ehrlich, P., and Lazarus, A.: (Rewritten by A. Lazarus and O. Naegeli, and translated by H. Armit) Anemia, New York, Rebman Co., 1910, p. 148.

27. Stockard, C.: The Origin of Blood and Vascular Endothelium in Embryos Without a Circulation of the Blood and in the Normal Embryo, Am. J. Anat. **18**:227, 1915. A Study of Wandering Mesenchymal Cells on the Living Yolk Sac and Their Developmental Products; Chromatophores, Vascular Endothelium and Blood Cells, Am. J. Anat. **18**:525, 1915.

28. Ziegler, R.: Experimentelle u. klinische Untersuchungen über die Histogenese der myeloiden Leukämie, Jena, G. Fischer, 1906.

29. Türk, W.: Ueber Regeneration des Blutes unter normalen und krankhaften Verhältnissen, Centralbl. f. Allg. Path. u. Anat. **19**:895, 1908.

30. Schriddé, H.: Die embryonale Blutbildung. Erwiderung an Herrn Prof. A. Maximow, Zentralbl. f. Allg. Path. u. Anat. **20**:433, 1909.

31. Fischer, H.: Myeloische Metaplasie und fötale Blutbildung, Berlin, Julius Springer, 1910.

32. Butterfield, E. E., Heinecke, A., and Meyer, E.: Ueber das Vorkommen der Altmannschen Granulationen in den weissen Blutzellen, Folia haematol. **8**:325, 1909. Butterfield, E. E., and Stillman, R. G.: The Broader Aspects of Hematologic Diagnosis, Am. J. M. Sc. **154**:781 (Dec.) 1917.

33. Ehrlich, P.: Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes, Gesammelte mitteilungen, I Teil, 1891, Berlin.

lymphoid, while the interfollicular tissue of the nodes and splenic pulp are myeloid. They further claim that these two types of tissue are sharply contrasted and are distinct from each other. The myeloid function, however, does not manifest itself normally, but comes into play in anemias, infections, and myelogenous leukemias.

Schriddé [30] derives his lymphocytes from the endothelial lining of lymph vessels, and his myeloid tissue from the endothelial lining of blood vessels. This view, however, is untenable, because Thiel and Downey [34] have shown that in the spleen, where a large production of lymphocytes takes place, there are no lymph vessels.

Fig. 8.—Photograph of patient Feb. 17, 1919, seventy-two hours after roentgen-ray treatment of neck and face. See Figures 1 and 2.

Fischer,[31] a strong supporter of Naegeli's views, admits that myeloid cells may develop from endothelium of blood vessels and from connective tissue cells.

Hirschfeld [35] admits that the spleen and lymph nodes can produce granulocytes. They come, however, not from the specific follicular tissue but from the pulp and interfollicular tissue, probably from the perivascular tissue (Hirschfeld).

34. Thiel, G. A., and Downey, H.: The Development of the Mammalian Spleen, with Special Reference to Its Hematopoietic Activities, Am. J. Anat. **28**:279, 1921.

35. Hirschfeld, H.: Die Unitarische und die dualistische Auffassung über die Histopathologie der Leukämien, Folia haematol. **6**: 1, 1908.

TABLE 4.—Differential White Cell Counts on Twenty Successive Days on Which There Had Been Either a Distinct Rise or Fall in the White Count

	1 1/21/19	2 1/24/19	3 1/30/19	4 2/1/19	5 2/6/19	6 2/8/19	7 2/14/19	8 2/16/19	9 2/18/19	10 2/20/19	11 2/21/19	12 2/22/19	13 2/26/19	14 2/28/19	15 3/3/19	16 3/8/19	17 3/21/19	18 3/29/19	19 4/7/19	20 4/7/19
Polymorphonuclear neutrophils:																				
Percentage	3.2	23.6	7.8	26.75	4.66	4.4	3.6	5.33	9.25	1.4	2.8	6.5	1.8	4.25	0.4	19.33	33.66	6.0	1.83	1.1
Number	3,168	1,132.8	3,900	2,140	4,194	1,760	2,392	549	1,850	3,388	1,736	162	1,476	1,154	704	445	2,020—	14,869	9,150	9,944
Small lymphocytes:																				
Percentage	2.6	19.33	12.2	3.25	3.16	0.6	8.0	8.66	4.25	3.8	0.4	11.5	3.2	9.0	1.4	8.33	1.33	10.83	2.5	8.2
Number	2,574	928	6,100	260	2,844	240	1,464	692	850	9,196	248	782	2,024	3,078	1,404	192	80—	41,570	12,500	52,972
Large and medium lymphocytes:																				
Percentage	89.2	46.0	72.4	52.2	51.0	53.2	9.65	61.66	48.6	35.4	52.8	74.16	28.1	44.0	30.2	52.33	49.0	57.16	65.0	81.8
Number	88,308	2,167	36,240	4,180	46,891	21,280	6,777	6,449	9,700	85,693	32,736	5,014	23,288	15,049	53,102	1,294	2,940	142,420	325,000	328,428
Mononuclears:																				
Percentage	.....	.....	0.4	0.25	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.5	1.8	.....	0.33	.....	0.16	
Number	.....	.....	200	20	.....	.....	.....	.....	.....	.....	.....	.....	.....	171	3,168	.....	20—	.....	800	
Transitionals:																				
Percentage	0.8	2.66	1.4	2.5	0.5	0.6	0.33	1.0	0.6	0.2	0.6	0.16	.....	0.75	0.2	2.0	.....	0.33	0.16	1.0
Number	792	127.7—	700	200	470	240	213	108	700	184	372	11—	.....	257	352	40	.....	815	800	6,460
Eosinophils:																				
Percentage	0.2	0.33	0.8	0.25	0.16	.....	0.5	.....	1.0	.....	.....	0.16	0.2	0.25	.....	.....	.....	0.66	0.16	
Number	198	16.2+	400	20	144	...	323	.....	200	.....	.....	11—	161	86	.....	.....	.....	1,630	800	
Basophils:																				
Percentage	...	0.33	0.4	0.75	0.16	.....	.....	0.33	.....	.....	.....	.....	.....	.....	.....	.....	0.66	0.66	0.16	0.2
Number	.....	16.2	200	60	144	.....	.....	33	.....	.....	.....	.....	.....	.....	.....	.....	154	40—	408	1,292
Metamyelocytes:																				
Percentage	0.8	0.66	1.0	4.5	0.83	0.8	.....	0.33	0.25	0.2	0.6	0.16	0.4	1.25	.....	2.33	2.66	0.5	0.16	0.4
Number	792	31.7—	500	360	747	320	.....	33	50	484	372	11—	338	428	.....	54	160	1,295	800	2,584
Myelocytes:																				
Neutrophils—																				
Percentage	1.0	0.33	.....	2.75	0.5	0.2	0.66	.....	1.0	.....	0.2	0.33	0.2	2.25	0.2	3.0	9.33	0.66	0.5	0.8
Number	1,584	16.2	.....	220	450	80	426	.....	200	.....	124	22	161	770	352	60	20—	1,630	2,500	5,168
Eosinophils—																				
Percentage	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.2	.....	.....	.....	.....	0.16		
Number	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	161	.....	.....	.....	.....	800		
Basophils—																				
Percentage	0.2	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.6	0.16	.....	.....	0.2	0.33				
Number	198	.....	.....	.....	.....	.....	.....	.....	.....	.....	372	11—	.....	.....	352	8—				
Micromyeloblasts: lymphoblocytes: or stem cells:																				
Percentage	1.4	5.66	1.8	6.75	17.66	5.4	49.0	6.0	20.75	40.0	18.0	0.16	55.6	10.0	28.6	6.66	1.66	13.16	15.16	0.4
Number	1,386	271.7	900	540	15,894	2,160	31,605	618	4,150	96,800	8,060	11—	45,592	6,108	50,336	153	100	32,505	75,80	2,584
Mitotic figures:																				
Percentage	.....	.....	.....	.....	0.66	0.2	.....	.....	.....	.....	0.6	.....	0.4	.....	.....	.....	.....	.....	0.5	0.4
Number	.....	.....	.....	.....	594	80	.....	.....	.....	.....	372	.....	328	.....	.....	.....	.....	.....	2,500	25,840
Degenerated cells:																				
Percentage	0.2	1.0	1.0	.....	20.5	34.6	28.16	16.66	.....	19.0	28.4	5.66	0.6	18.75	37.0	5.0	10.33	4.5	13.66	5.4
Number	198	48	900	.....	18,450	13,840	18,163	1,710—	.....	45,980	15,068	385—	7,572	6,413	65,129	115	620	11,115	68,300	34,884
No. of cells counted:																				
Percentage	100.0	99.95	100.0	100.0	99.94	100.0	.....	99.97	100.0	.....	100.0	99.95	100.0	100.0	100.0	99.97	99.99	99.96	99.95	100.0
Number	500	300	500	400	600	500	.....	300	400	.....	500	600	500	400	500	300	300	600	500	500
Nucleated R. B. C.:																				
Percentage	3.0	0.66	1.4	1.25	0.16	0.6	.....	.....	1.25	0.4	0.6	0.5	1.2	1.5	1.2	1.66	0.66	1.0	.....	0.6
Number	2,970	79.6	700	100	144	240	392	.....	250	968	372	34	984	513	2,112	38	40	2,470	.....	3,876
Total W. B. C. count	99,000	4,800	50,000	8,000	90,400	40,000	64,500	10,300	20,000	42,000	62,000	6,800	82,000	34,300	176,000	2,300	6,000	247,000	500,000	646,000

Stockard [18] adopts the extreme polyphyletic view. The fixed mesenchymal cells of the embryonic body, even before they begin their migration are already specialized to such an extent that differentiation can take place in one direction only.

Pappenheim and his pupils [14] hold a moderated monophyletic view. The "histioidocyte" a tissue cell gives rise to the "lymphoidocyte." The lymphoidocyte is the only stem cell and gives rise to megakaryocytes, monocytes, polymorphonuclears, lymphocytes and red blood cells. The lymphocytes are fully differentiated cells and can not change into granulocytes.

Ferrata,[20] and his pupil Neigreiros-Rinaldi, accept a modified monophyletic view, similar to the one proposed by Pappenheim. They believe that all the blood cells come from a single stem cell, which they call the "hemocytoblast," they do not believe that fully differentiated lymphocytes are capable of differentiating into granulocytes or red blood cells.

Ferrata considers the connective tissue as a diffuse hemopoietic organ. This tissue gives rise to the "hemohistioblast" (resting-wandering cells of Maximow; clasmatocyte of Ranvier [36]). In the early embryo this cell differentiates into the primitive transitory hemocytoblast, and this, in turn, to the primitive red blood cell of the embryo (megalocytes); while in the adult, lymphoid and myeloid hemocytoblasts (functional differences only) and monocytes are the products of its differentiation.

Grawitz,[16] Weidenreich,[17] Danchakoff,[25] and Maximow,[18] hold the extreme monophyletic view. They believe that all blood cells may come from fixed tissue cells, such as reticular cells, fixed cells of omentum and messentery, as well as from the widely distributed clasmatocytes. These may give rise to free lymphoid cells, and these lymphoid cells may occur anywheres in the body of the adult.

Fully differentiated lymphocytes derived from these lymphoid cells may, according to some authors, dedifferentiate into the more primitive type of lymphoid cell, which, in turn, might differentiate into other forms of white cells, or these fully differentiated lymphocytes might metamorphose into other forms of leukocytes without dedifferentiation. Grawitz believes that lymphocytes can change into granulocytes in the circulating blood.

Weidenreich [17] and Downey [19] do not recognize the term "lymphoblast." They have shown that all the types of lymphocytes are concerned in regeneration and differentiation from one type to another. The reticulum of lymphoid tissue, wherever found, serves as a mother tissue. All types of lymphocytes may be derived from it, and these,

36. Ranvier, L.: Des Clasmatocytes, Arch. d'Anat. micr. **3**:122, 1900.

in turn, may become transformed into other types of lymphocytes. Therefore, no one type of lymphocyte can be recognized as being more highly differentiated than any other type. They claim, therefore, that one cannot speak of a "stem cell" of the lymphocyte in the same sense that one can speak of the "stem cell" of the myeloid cells.

Lymphocytes are not in any sense of the word a final product. Downey,[36] Weill,[37] Weidenreich,[15] and other observers have shown that all forms of lymphocytes can differentiate specific leukocyte granules, thereby becoming granular leukocytes.

Such widely differing opinions indicate the unsettled state of many hematologic questions. These questions regarding the relationship of the blood cells depend primarily on the various theories of postfetal regeneration. Is Naegeli [38] correct, for instance, in assuming that the "myeloblast" is a specific myeloid cell which is in no way related to the lymphatic tissues? He claims that he can differentiate morphologically between the myeloblast and large lymphocyte (lymphoblast). Pappenheim [14] claims that Naegeli's myeloblast is not a stem cell but is the cell which he terms the leukoblast, a cell already partly differentiated along myeloid lines.

The following points are usually considered by the dualists as differentiating between "myeloblasts" and "lymphoblasts."

1. *Character of Chromatin Arrangement.*—Naegeli [39] (1907) describes very poor chromatin content as characteristic for lymphoblasts. Klein [40] (1910) finds that the chromatin content is not characteristic of the cell. He shows lymphoblasts which are identical with du Toit's [21] and Pappenheim's lymphoidocytes and with Naegeli's myeloblasts.

2. *Number of Nucleoli.*—Naegeli (1907) claimed that nucleoli of the "lymphoblasts" are one or two in number, and of myeloblasts from two to four in number. Pappenheim,[41] Klein,[41] Butterfield [42] and others have shown that this is not true. Naegeli himself admitted later [2] (1912 and 1919) that this does not hold true in pathologic blood.

3. *Altmann-Schridde Granules.*—The dualists believed that they occurred in lymphoid cells and were absent in myeloid cells. Türk

37. Weill, P.: Ueber die Bildung von Leukozyten in der Menschlichen und tierischen Thymus des erwachsenen Organismus, Arch. f. mikro. Anat. **83**:305, 1913.

38. Naegeli O.: Blutkrankheiten und Blutdiagnostik, Leipzig, 1919, Dritte auflage.

39. Naegeli: Quoted by Du Toit.

40. Klein: Ueber die groszen einkernigen Leukozyten des Leukämieblutes, Folia haematol. **10**: 1, 1019.

41. Pappenheim and Klein: Quoted by Du Toit.

42. Butterfield: Quoted by Damarus.

(1912)[43] has shown that these granules are not specific for lymphoid cells.

4. *Oxydase Reaction.*—The dualists claim that the oxydase reaction, the staining of the oxydase grandules with the indophenol blue dye, is positive in myeloblasts and negative in lymphoblasts.

Hyneke,[44] Decastello,[45] Blühdorn, Jochman,[46] Glaus[47] and Dunn[48] report cases in which the so-called "myeloblasts" did not give the oxydase reaction. Klein[49] showed that ordinary lymphocytes may give a positive reaction.

Schultze[50] found that the myeloblasts of the normal marrow usually did not give the reaction while the pathologic myeloblasts in the blood and in the organs usually do give the reaction.

According to Menten[51] the reaction is not specific for myeloid cells. She found that lymphocytes may give a well marked reaction. She also found that all tissues with the exception of bone give this reaction, so that it is by no means specific for blood cells.

Forman and Hugger[52] found "large mononuclears" both with and without the indophenol oxydase granules.

Boéchat,[53] Belz,[54] Steffan[55] and Krjukow[3] claim that the reaction may be absent in myeloblasts.

Naegeli himself wavers on the question of the specificity of the oxydase reaction. In his book[38] (p. 211) he makes the statement "the oxydase reaction is present in normal myeloblasts and generally in pathologic myeloblasts, but in some of these the reaction may be not so strong and less diffuse."

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43. Türk, W.: Vorlesungen über klinische Haematologie, Wien. u. Leipzig, W. Braumüller, 1912, Pt. 2, p. 131.

44. Hyneke, K.: Zur Monocytenfrage, Folia haematol. **13**:345, 1912.

45. Decastello: Quoted by Hyneke.

46. Jochman and Blühdorn: Ueber akute Myeloblasten Leukämie, Folia haematol. **12**:1, 1911.

47. Glaus: Quoted by Kahle, H.: Ueber ein Hämogonien und Leukozyten erzeugendes Angiosarkom in zirrhotischer Leber, Arch. f. path. Anat. u. Physiol. **226**:44, 1919.

48. Dunn, J. S.: The Use of the Oxydase Reaction in the Differentiation of Acute Leukemias, Quart. J. M. **6**:293, 1913.

49. Klein: Quoted by Neumann.

50. Schultze, W. H.: Zur Differentialdiagnose der Leukämieen, München. med. Wchnschr. **56**:167, 1909.

51. Menten, M. L.: A Study of the Oxydase Reaction with *a*-naphtha-paraphenyldiamene, J. M. Res. **40**:433, 1919.

52. Forman, J., and Hugger, C. C.: Nature of Mononuclear Cells Seen in Exudate of Lobar Pneumonia Accompanying Typhoid Fever, Am. J. M. Sc. **155**: 317 (March) 1918.

53. Boéchat: Ueber akute Myeloblastenleukämie mit teilweise chloromatösen Charakter, Frankf. Ztschr. f. Path. **13**:489, 1913.

54. Belz, L.: Ueber Leukämie mit besonderer Berücksichtigung der Akuten Form, Deutsch. Arch. f. klin. Med. **113**:116, 1914.

55. Steffan, M.: Ueber einen Fall akuten Myeloblasten Leukämie und über die Beziehungen Leukämie-Sepsis, Folia haematol. **21**:59, 1916.

Pappenheim and Dührer's[56] conclusion regarding the oxydase reaction is, that it does not indicate an absolute unfailing histogenetic difference between two heterogenous cell races. It is clear, therefore, that the opinion of many of the observers is against the specificity of the oxydase reaction and against any of the other differential points usually picked on by the dualists for the differentiation of lymphoblasts and myeloblasts.

Du Teit[21] says that morphologically we cannot differentiate between "lymphoblasts" and "myeloblasts."

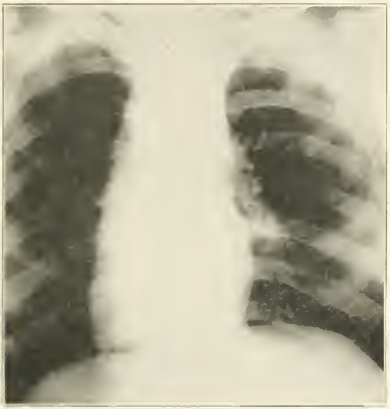

Fig. 9.—Roentgenogram of chest, Jan. 21, 1919.

Krjukow,[3] referring to his case of microlymphoidocytic leukemia, says: "It seems to me that the most skilful dualists could not possibly differentiate our microlymphoidocytes from true micromyeloblasts, except, perhaps, by the use of the various methods that the dualists are wont to use."

Hirschfeld[57] could not see any morphologic difference between myeloblasts and germ center cells.

56. Dührer and Pappenheim, A.: Ein weiterer Fall von akuten Mikrolymphoidozyten leukämie, Folia haematol. **16**:143, 1913.

57. Hirschfeld, H.: Die Unitarische und die Dualistische Auffassung über die Histopathologie der Leukämien, Folia haematol. **6**:382, 1908.

Damarus,[58] Wolf and Türk[59] and Butterfield[60] can see no morphologic difference between the stem cells of lymphocytes and granulocytes.

Weber[61] describes a case of leukemia in which "the conclusion was unavoidable that the lymphoid cells which permeated the various tissues of the body were of the same kind as the lymphoid cells which during the patient's life constituted by far the greatest portion of the white cells of his circulating blood. I thought at the time that the cells in question were probably to be regarded as lymphoblasts but

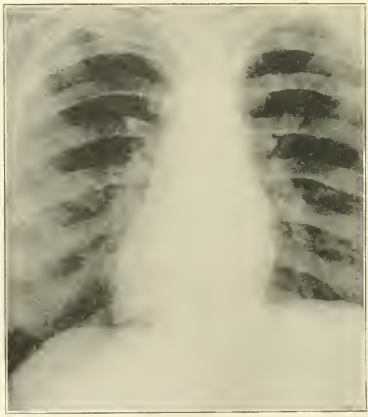

Fig. 10.—Roentgenogram of chest, Jan. 31, 1919, ten days after roentgen-ray treatment of mediastinum. Compare with Figure 9.

from the fact that a few of the cells gave a positive oxydase reaction and from a comparison with Case 4, I now think that they were probably myeloblasts."

58. Damarus: Der gegenwärtige Stand der Leukämiefrage, Folia haematol. **6**:337, 1908.

59. Wolf and Türk: Quoted by Damarus.

60. Butterfield, E. E.: Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz, Leber und Lymphdrüsen, Deutsch. Arch. f. klin. Med. **92**:336, 1903.

61. Weber, F. P.: Acute Leukemia and So-Called Mediastinal Leukosarcomatosis (Sternberg), with the Account of a Case Accompanied by Myeloid Substitution of the Hilus Fat of the Kidneys, Quart. J. M. **12**:212 (April) 1919.

Similarly Chosrojeff [62] reports a case of "micromyeloblastic leukemia" in which he found in the blood all transition forms from myeloblasts to small lymphocytes and "were it not for the oxydase reaction, one could not tell what type of leukemia he was dealing with."

Walter Schultze,[50] a dualist, admits that the morphologic differences between myeloblasts and lymphoblasts, described by Schriddé, are so slight that the majority of hematologists cannot differentiate the two types of cells.

We have shown so far that "lymphoblasts" cannot be differentiated from "myeloblasts" either by morphology, that is cytoplasm, nuclear chromatin arrangement, nucleolar content, Altmann-Schriddé granules,

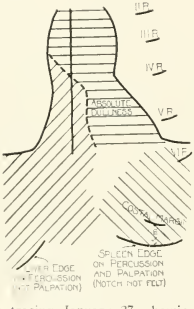

Fig. 11. — Percussion tracing January 27, showing diminution in size of mediastinal dulness. Compare with Figure 3.

or by the oxydase reaction. The dualists trace all the white blood cells from these two stem cells and claim that the lymphopoietic and myelopoietic tissues derived from these two mother cells are entirely distinct, and that lymphoid tissue cannot produce myeloid cells and, vice versa, that myeloid tissue cannot produce lymphoid cells. In the presence of a vast amount of recently accumulated evidence to the contrary, both experimental and clinical, it becomes doubtful whether there exists such a cell as is usually described by the dualists as a "lymphoblast."

The following points are evidence against the dualistic and polyphyletic theories.

62. Chosrojeff, B. P.: Myelosis aleucemica acuta micromyeloblastica, Folia haematol. **20**:33, 1915.

1. Downey and Weidenreich have demonstrated that cells such as are described for the germ centers may be found in the interfollicular tissue, in the spleen pulp, and in the lymph vessels. They have also shown that morphologically and genetically the lymphocytes of the cortex and medulla of lymph nodes are identical, and that follicles with germ centers may arise anywheres in the node.

2. Weidenreich describes these same cells in the chyle of the thoracic duct.

3. Dominici has shown that in certain infections, in man and in the laboratory animals, neutrophilic and eosinophilic myelocytes and normoblasts may develop in the spleen and lymph nodes from lymphocytes.

4. Sacerdotti [63] and Frattin, by tying off and cutting the blood vessels of one kidney in dogs have produced true bone and bone marrow in the pelvis of the kidney.

5. Maximow [64] reproduced these same results and found that these granulated and red blood cells of the bone marrow came from typical lymphocytes of the blood.

6. Downey and Weidenreich [19] have shown that the lymphocytes of the germ center are extremely irregular in size and form and that only a very few of them conform to the descriptions given by Naegeli, Türk, Pappenheim and others.

7. Naegeli himself at one time (1900) describes the lymphoblasts as being very rich in chromatin and at another time (1909) as being very poor in chromatin. They are very young lymphocytes related to the mature lymphocytes by innumerable transition forms. In children they may be found at times in normal blood, and are especially prone to occur in infectious leukocytoses (Naegeli [65]).

8. Weidenreich and Weill [37] claim that lymphocytes may differentiate into neutrophil and eosinophil leukocytes.

9. Downey [66] has shown that lymphocytes may differentiate into histogenous mast cells. Weidenreich and Downey [19] have shown granulated myelocytes developing from the lymphocytes of the spleen. They have also shown granulated cells in mitosis in the spleen.

10. Dominici [67] has observed myelocytes in lymph follicles.

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63. Sacerdotti, C., and Frattin, G.: Ueber die heteroplastische Knochenbildung, Virchows Arch. f. path. Anat. **168**:431, 1902.

64. Maximow, A.: Experimentelle Untersuchungen zur postfötalen Histogenese des myeloiden Gewebes, Beitr. z. path. Anat. u. z. allg. Path. **41**:122, 1907.

65. Naegeli: Blutkrankheiten und Blutdiagnostik, Leipzig, 1919.

66. Downey, H.: The Development of the Histogenous Mast Cells of Adult Guinea-Pigs and the Structure of the Histogenous Mast Cell of Man, Folia haematol. **16**:70, 1913.

67. Dominici: Quoted by Hirschfeld.[37]

11. In a case of eosinophilic polymorphonuclear hyperleukocytosis recently reported by Giffin,[68] Downey has found eosinophilic myelocytes in the germ centers of the follicles of the lymph nodes and spleen.[69]

12. Hertz,[70] using pyrogallol, has produced myeloid metaplasia of the spleen pulp with a hyperplasia of the splenic follicles. This is contrary to the usual statement that myeloid metaplasia is accompanied by reduction in the size of the follicles, which is used as an argument in favor of the supposed antagonism between pulp and follicles.

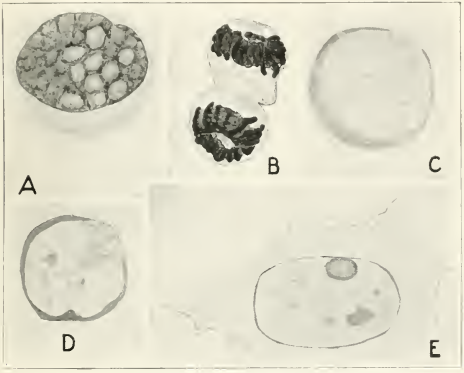

Fig. 12.—The cells in A and B are drawn with 1.9 mm. objective and No. 8 eyepiece; magnified ×2 actual appearance. A. Microlymphoidocyte (stem cell) (micromyeloblast) in blood. B. White cell in mitosis in blood stream. C. Microlymphoidocyte or stem cell in section. Objective 1.5 mm.; ocular No. 8; magnification ×8. D. Stem cell or microlymphoidocyte in section Objective, 1.5 mm.; ocular, No. 8; magnification, ×8. E. Reticulum cell in section. Objective, 1.5 mm.; ocular, No. 8; magnification, ×8.

13. Downey has demonstrated eosinophilic myelocytes in the germinal centers of lymph nodes of rabbits, the subjects of experimental hemorrhages in which there were no myelocytes in the blood so that the development of these myelocytes must have taken place in loco.

68. Giffin, H. Z.: Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly. Am. J. Med. Sc. **158**:618, 1919.

69. Unpublished observation.

70. Hertz: Quoted by Krjukow.[3]

14. Roman[71] has observed germ centers containing myelocytes.

I have attempted to bring out the following points.

1. Hematologists are divided into two main camps—the dualists, or polyphyletists, and the unitarians.

2. The dualists and polyphyletists believe that the blood cells and blood forming organs are divided into two main distinct divisions, the myeloid and lymphoid. These two never change from one into the other either in the tissues or in the blood.

3. The unitarians believe that all blood cells come from the "lymphocyte" found in the bone marrow, spleen, lymph nodes and other tissues of the body, or, according to Pappenheim and his followers, from the "lymphoidocyte," which, in the adult, is confined to the marrow.

4. The dualists claim that they can differentiate between the "lymphoblast" and "myeloblast." They regard the oxydase reaction as being of prime importance for such differentiation.

5. The unitarians claim that such a differentiation is impossible; that the "lymphoblast" as a cell per se does not exist; that the "lymphoblast" is given various descriptions by various authors; that Naegeli himself makes contradictory statements regarding this cell; that the "lymphoblast" may be found anywhere in lymphoid tissue and not only in the germinal centers, as claimed by the dualists, and that the oxydase reaction, the main stay of the dualists, is not a specific test for the myeloblast.

6. A vast amount of experimental evidence is accumulating, which is in favor of the unitarian theory.

We now wish to call attention to histologic and hematologic evidence in which we consider to be in favor of the unitarian theory, reported to date in the literature on leukemia.

Dr. Downey has been kind enough to permit me to study the blood from a recent case of leukemia in which all the transition stages between the lymphoidocyte (myeloblast of Naegeli) and lymphocyte were present.[72]

Fleischmann[73] reports a case of monocyte leukemia (second case on record) in which in June, 1913, he found 65 per cent. mononuclear leukocytes and 19 per cent. small and large lymphocytes. In November, 1913, a bone marrow puncture gave polymorphonuclears, small lymphocytes and "mononuclears" identical in morphology with those found in the blood. Shortly before death, the "mononuclears" dropped

71. Roman, B.: Zur Kenntniss der myeloischen Chloroleukämie, Beitr. z path. Anat. u. z. allg. Path. **55**:61, 1913.

72. This case is not yet reported in the literature.

73. Fleischmann, P.: Der zweite Fall von Monocyten leukämie, Folia haematol. **20**:17, 1915.

to 25 per cent. and there appeared, in the blood, myelocytes, 12½ per cent., promyelocytes and "myeloblasts." At the necropsy there was found myeloid change everywhere. Among the myeloid cells were cells which corresponded to the blood monocytes. The follicles were shrunken in the spleen and the lymph nodes. Fleischmann concludes the report by suggesting the possibility that the monocytes changed into myeloid elements under the influence of some pathologic stimulus.

Pappenheim,[74] Walz,[75] and Dennig[76] have reported cases which hematologically were cases of lymphatic leukemia. Yet, in these cases

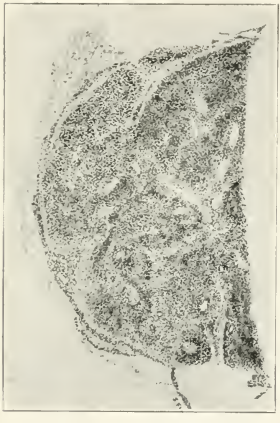

Fig. 13.—Axillary lymph node ×8, showing one distinct follicle with a germinal center.

the spleen and lymph nodes were not involved, but the bone marrow had become lymphoid.

Krjukow[3] (1915) reports a case of microlymphoidocytic leukemia in which the blood showed all transition forms from the stem cell to the mature granulocyte, yet the pathologico-histologic changes were

74. Pappenheim, A.: Ueber Lymphämie ohne Lymphdrüsenschwellung, Ztschr. f. klin. Med. **39**:171, 1900.

75. Walz: Quoted by Damarus.

76. Dennig, A.: Ueber akute Leukämie, Munchen. med. Wchnschr. **47**: 1297, 1900.

those of a lymphatic leukemia. The bone marrow showed only slight activity. The pulp of the spleen and some lymph nodes showed slight myeloid metaplasia. The thymus was hyperplastic and the spleen and lymph nodes showed typical lymphatic leukemia changes. He concludes that the myeloid elements of the blood were coming from the lymph nodes and spleen. He also states that the most skilful dualist could not differentiate morphologically between micromyeloblasts and his micro-lymphoidocytes. He is loath to conclude from this that the myeloid cells of the blood were coming from lymphoid cells and so decides that he has here a case of "mixed leukemia," with a prevailing "lymphatic component." He also concludes that in acute leukemias even the presence in the blood of myelocytes and promyelocytes and stem cells does not necessarily diagnosticate a myelogenous leukemia.

St. Klein [77] (1910) reports a case in which the blood showed all the transition stages between the lymphoidocyte (myeloblast) and the ordinary lymphocyte. The histologic studies showed a lympholeukemic involvement of all the lymphoid tissues.

Türk [78] reports a case of mixed cell leukemia which changed into a lymphatic leukemia.

Hirschfeld [57] has found in cases of mixed cell leukemia hyperplasia of the lymph follicles and a myeloid metaplasia in the rest of the lymph nodes. He has also found in a true case of lymphatic leukemia clumps of myelocytes in the spleen and lymph nodes.

Veszpremi,[79] Glinski,[80] Walter Schultze, Pappenheim,[81] Hirschfeld [82] and Wechselmann describe cases of acute lymphatic leukemia in which there was no proliferation or atrophy of the follicles of the spleen or of the lymph nodes or of both with marked proliferation of the splenic pulp and interfollicular tissues in some of the cases. Hematologically these cases were the same as any ordinary acute lymphatic leukemia, yet histologically we find the proliferation where it should occur in myeloid cases (Hirschfeld [57]).

Hertz [83] (1909) reports a case of lymphatic leukemia in which 15 per cent. of myelocytes appeared before death. Sections of lymph nodes showed lymphatic proliferation as well as neutrophilic granulated

77. St. Klein: Quoted by Du Toit.

78. Türk: Quoted by Hirschfeld.[57]

79. Veszpremi, D.: Beitrage zur Histologie der sogenannten "akuten Leukämie," Arch. f. path. Anat. u. Physiol. **184**:220, 1906.

80. Glinski, L. K.: Zur pathologischen Anatomie der akuten Lymphämie, Arch. f. path. Anat. u. Physiol. **171**:101, 1903.

81. Schultze and Pappenheim: Quoted by Hirschfeld.

82. Wechselmann, W., and Hirschfeld, H.: Ueber einen Fall akuter myeloider makrolymphozytärer Leukämie mit eigentümlichen Zelleinschlussen. Ztschr. f. klin. Med. **66**:349, 1908.

83. Hertz, A.: Zur Frage der gemischten Leukämie, Wien. klin. Wchnschr. **22**:1030, 1909.

myelocytes and erythrocytes. In the bone marrow, follicle like aggregations of lymphocytes were present, besides the myelocytes and myeloblasts. The spleen pulp was myeloid, while the follicles were atrophied.

Chosrojeff [62] (1915) reports a case of "micromyeloblastic" leukemia in which the blood showed all transition forms between the "myelo-

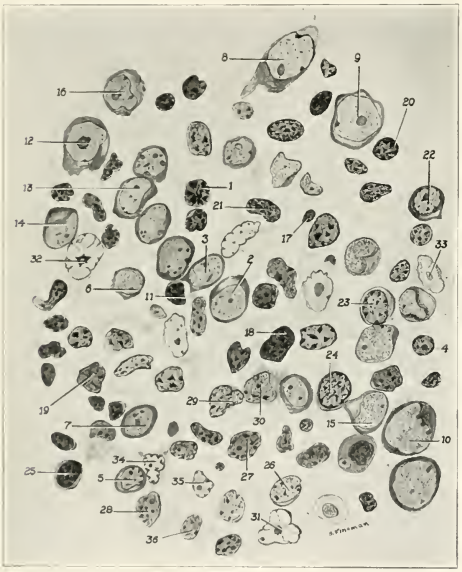

Fig. 14.—Germ center of follicle shown in Figure 13. Objective: Zeiss apochromatic 1.5 mm.; ocular, Zeiss compensating No. 8. Note the numerous stem cells in this germ center.

blast" and the small lymphocyte. He bases his diagnosis on a positive oxydase reaction and says, "were it not for this reaction one could not tell what type of leukemia he was dealing with."

Herxheimer [84] (1913) reports a case of mixed leukemia. The blood contained 69.8 per cent. small lymphocytes and 25.4 per cent. "myeloblasts." The bone marrow showed mostly lymphocytes with a few islands of "myeloblasts." The spleen showed a hyperplasia of follicles, which consisted of large and small lymphocytes. The pulp showed a hyperplasia of its lymphoid constituents and a profuse scattering of "myeloblasts." The lymph nodes showed a hyperplasia of follicles and occasional "myeloblasts." In the bronchial nodes the "myelob'asts" predominated. The mediastinum showed compact parts consisting largely of lymphocytes and loose areas containing many "myeloblasts." The "myeloblasts" were diagnosed by means of the oxydase reaction.

The author regards this positive oxydase reaction as the best indication of the dualistic origin of the myeloid and lymphoid cells.

From these cases the following is evident:

1. The blood may show all transition forms from the "myelob'ast" (lymphoidocyte) to the ordinary lymphocyte (Downey).

2. A monocytic leukemia blood and bone marrow picture changed to a myeloid picture (Fleischmann). The necropsy showed myeloid proliferation everywhere. Among the myeloid cells some monocytes were present.

3. The blood picture was one of lymphatic leukemia (Pappenheim and others). The bone marrow had undergone a lymphoid change and nodes and spleen were normal.

4. The blood showed all transition forms from the "micromyeloblast" to the granulocyte (Krjukow). These "micromyeloblasts" were coming from lymphoid tissue, "from the myeloid parts of these organs."

5. The blood showed all transition stages between the "myeloblast" and the ordinary lymphocyte (Klein). The tissues showed only lymphoid proliferation.

6. A mixed cell leukemia changed into a lymphatic leukemia (Türk).

7. Clumps of myelocytes were present in the spleen and lymph nodes in a case of lymphatic leukemia (Hirschfeld). In a case of mixed cell leukemia, both myeloid and lymphoid proliferation were present in the lymph nodes.

8. Cases of acute lymphatic leukemia showed atrophy of the follicles of the spleen or of the lymph nodes or of both, and a proliferation of the interfollicular tissue and spleen pulp in some of the cases, tissue which according to the dualists is myeloid in nature (Veszpremi and others).

84. Herxheimer, G.: Ueber einen combinierten Fall von Lymphätischer und Myeloblastenleukämie, Zentralbl. f. allg. Path. **24**:897, 1913.

9. A case of lymphatic leukemia in which numerous myelocytes appeared before death (Hertz). The bone marrow showed lymphocytes in follicle arrangement and the spleen pulp showed myeloid proliferation with atrophy of the follicles.

10. In the blood all transition forms from the "myeloblast" to the lymphocyte were present (Chosrojeff). The diagnosis of "myeloblast" is made on the strength of the oxydase reaction.

11. In a case of mixed leukemia (Herxheimer) the bone marrow showed mostly lymphocytes with a small number of "myeloblasts." The spleen, lymph nodes and mediastinal tumor showed hyperplasia of lymphoid and myeloid cells. Here, too, the diagnosis of "myeloblast" was based on the oxydase reaction.

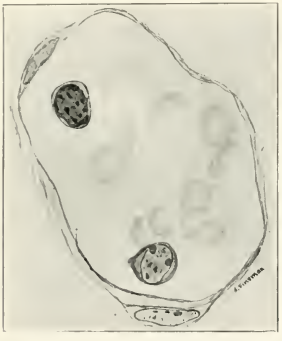

Fig. 15.—Small blood vessel in the lymph node, showing in the lumen a lymphocyte above and typical stem cell below. Objective Zeiss 1.5 mm., apochromatic; ocuar, Zeiss No. 8 compensating.

All of the above evidence is more or less of an indirect nature.

Meyer, Heinecke, Ziegler, Naegeli and other dualists claim a biologic antagonism between the follicles and interfollicular tissues. They claim that no one has ever observed myeloid tissue in the germinal centers of the spleen or lymph nodes.

In 1912, Pappenheim [85] made the statement that the unitarian theory will receive great support, and Lydtin,[86] in 1913, declared that the

85. Pappenheim, A.: Bemerkungen zur Frage der akuten Myeloblastenleukamie und Leukosarcomatose, Wien. klin. Wchnschr. **25**:163, 1912.

86. Lydtin, H.: Ein Fall von Micromyeloblasten leukämie, Folia haematol. **15**:316, 1913.

dualistic theory will receive a serious blow at the moment that a case would be found in which the so-called "myeloblasts" could be shown to originate from lymphatic tissue, that is, from the follicles and follicular cords. In other words, when in the blood the cell morphology will be that of a "myeloblastic" leukemia, while the tissues will show lympho-leukemic changes, i. e., follicular hypertrophy and presence of myeloblasts within the lymph follicles.

Hirschfeld (1908) says that so far researches have shown that although the spleen and lymph nodes can produce granulocytes, yet they come not from the specific follicular tissue but from the pulp and interfollicular tissue.

Naegeli (1910) makes the statement that under no circumstances has it ever been proven that the germinal center of the lymph nodes can act as the site of origin of myeloid cells.

In 1915, Citron published his case of which he says, "It is the only one to date which shows in a seemingly certain and irreproachable manner, that the dualistic division does not always hold true; that not in all cases in which a myeloid metaplasia takes place is it necessary to conclude that a substitution of the lymphatic tissue has taken place by extra parenchymatous myeloid tissue; that in some cases a direct autocellular change of lymphatic follicular lymphocytes into myeloid cells may take place. Citron bases this statement on the following findings.

1. The blood showed a monotonously uniform picture of the so-called "myeloblasts" of Naegeli or "lymphoidocytes" of Pappenheim.

2. The bone marrow was normal.

3. In the lumina of the blood vessels of the spleen and lymph nodes the cells were exactly the same as those which permeated these organs.

4. The splenic pulp and interfollicular tissue of the lymph nodes consisted of cells similar in all respects to the cells of which the follicles were composed.

5. No signs of follicular atrophy were present.

6. No evidence of myeloid metaplasia of the interfollicular tissue was present.

7. The nuclei of the cells of the follicles and of the interfollicular tissue were not those of lymphocytes but of "myeloblasts."

8. These "myeloblasts" could be seen entering the circulation from the hyperplastic lymph follicles.

HEMATOLOGIC AND HISTOLOGIC FINDINGS

A. Blood.—The differential counts are shown in Table 4. The various interesting findings of the blood have already been referred to

in the clinical discussion of the case. I wish again, however, to call attention to the presence of numerous "stem cells" (lymphoidocyte of Pappenheim; myeloblast of Naegeli). These cells were present in the blood during the entire stay of the patient in the hospital. They were extremely variable in size. Some were as large as a large lymphocyte, others were smaller than a red blood cell. In the differential counts we included all sizes under the headings "lymphoidocytes," "myeloblasts," "micromyeloblasts" or "stem cells." As seen in smears stained in Wright's stain, the cells (Fig. 12A) are morphologically identical with those described by Pappenheim. Their cytoplasm is basophilic, and scant in amount. The majority of cells did not contain

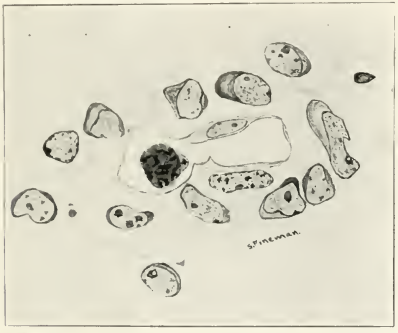

Fig. 16.—Portion of lymph node capsule. Stem cells in majority. Mitotic figure in a small blood vessel. Cell 1, forming part of vessel wall, is an endothelial cell. Cell 2, immediately below, is a connective tissue cell. Objective 1.5 mm., Zeiss apochromatic; ocular No. 8, compensating, Zeiss.

azure granules. The structure of the nuclei forms the diagnostic feature of these cells. The chromatin forms a very fine, evenly distributed sievelike meshwork, in contrast to the large clumped chromatin blocks which characterize the nucleus of the lymphocyte. Nucleoli, in variable numbers, are usually present. The staining of the chromatin sievelike network of the stem cell is much lighter than that of a lymphocyte. With the slightest overstaining the typical appearance of the stem cell becomes altered and differentiation from the lympocyte is difficult.

The oxydase reaction was positive in the polymorphonuclear leukocytes but negative in all other cells. As already pointed out, the

failure of the stem cells to show the oxydase granules is of no significance one way or another. Citron and others refer to cases unquestionably myeloid in character in which this reaction was negative.

Naegeli (1912 and 1919) wavers on the specificity of the oxydase reaction. He says that the oxydase reaction is positive in normal myeloblasts and for the most part in pathologic myeloblasts.

Hyneke, Decastello, Dunn, Jochman and Blühdorn declare that the oxydase reaction need not be positive in unripe myeloid cells.

Boéchat and Belz claim that the reaction may be absent.

Klein has shown that even lymphocytes may give a positive oxydase reaction.

Menten has shown that lymphocytes and many tissues give a positive reaction, so that the reaction is not only not specific for myeloid cells, but is not even specific for blood cells.

Morphologically, the cells in our case were identical with those the dualists call "myeloblasts" and "micromyeloblasts." If the blood alone were examined, the diagnosis from the dualists' point of view would be acute micromyeloblastic leukemia. I will endeavor to show that these "micromyeloblasts," probably the majority of them, certainly a great many of them, were coming from the follicles and germinal centers of the lymph nodes.

In the blood numerous transition forms between these "micromyeloblasts" and lymphocytes were found. I have already pointed out that the slightest overstaining alters the appearance of these cells. Transition forms, however, were found in well stained smears, side by side with the typical "micromyeloblasts." I believe that these transition forms are another bit of evidence showing the relation of "micromyeloblasts" to lymphopoietic tissues.

The number of the "micromyeloblasts" varied roughly with the total white cell count. Table 4 shows these variations. Figure 4 shows three curves expressing the relation between the total white count, the total "micromyeloblast count" and the relative percentage of these cells. The rise in total number of these "micromyeloblasts" was invariably associated with an exaggeration of all clinical symptoms, and an enlargement of either the spleen, lymph nodes or tonsils. It would appear, therefore, that the increase of these cells in the circulation was closely associated with the increased activity of the lymphopoietic tissues.

The numerous mitotic figures in the circulating blood led us to suspect the possibility of multiplication of these cells in the blood. Our experimental work, while not conclusive, leads me to believe, however, that such probably was not the case.

It is not my intention to prove or disprove that "myeloblasts" and "lymphoblasts" are identical cells. I do wish to show, however, that

in this case, great numbers of cells were circulating in the blood, which were morphologically identical with "micromyeloblasts," cells which ordinarily are known to be derived from the bone marrow. We have good evidence that a great many of our "micromyeloblasts" were being generated in the lymphopoietic tissues and were passing out from these tissues into the blood circulation.

Myelocytes were not found on some days, but there were as many as 3 per cent. on other days. No promyelocytes were seen. Nucleated red blood cells were present in small numbers. The appearance of

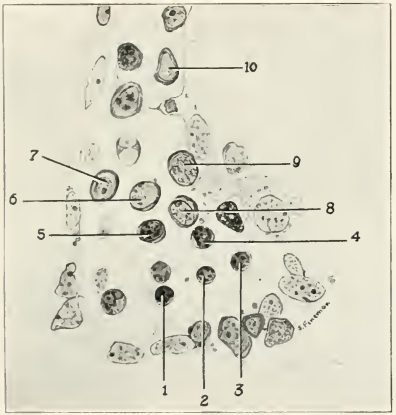

Fig. 17.—Lymph sinus, showing both lymphocytes and stem cells. Objective, 1.5 mm.; Zeiss apochromatic; ocular, No. 8; compensating; Zeiss.

the myelocytes and nucleated red blood cells may be considered as the result of the irritation of the bone marrow due to the severe anemia.

B. Lymph Node.—The lymph node was obtained by biopsy and was immediately fixed in Helly's fluid. The Dominici and methyl green pyronin stains were used. The appearance of the node with a magnification of eight times is represented in Figure 13. With low power, the usual markings of a lymph node are almost obliterated. The structure of the medulla is not as dense as that of the cortex. The follicles of the cortex are not clearly discernible, with the exception

of an occasional one. In examining a hundred sections, only six slides were found showing a single clear follicle containing a germinal center. The remainder of the cortex shows a merging of the follicles with the interfollicular tissue.

The peripheral sinus is filled with cells. The lymph sinuses surrounding the trabeculae are practically all filled with dark staining cells, and the same holds true for the plexus of sinuses throughout the entire node. The medullary cords do not stand out prominently but fuse more or less with the rest of the tissue. The blood vessels contain red blood cells, which are rather indistinct with the low power

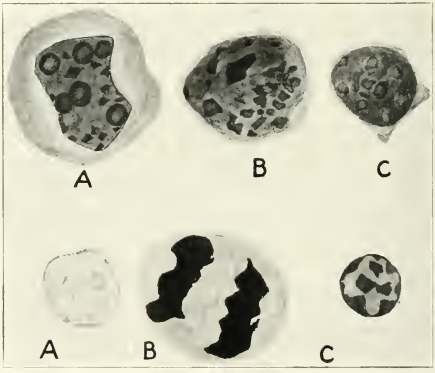

Fig. 18 (Upper).—Objective, 1.5 mm.; ocular, No. 8; magnification, ×8. A. Large lymphocyte with seven nucleoli, in section. B. Medium sized lymphocyte, in section. C. Small lymphocyte, in section.

Fig. 19 (Lower).—Objective, 1.9 mm.; ocular, No. 10; ×8 actual appearance. A. Stem cell, very small, in section. B. Cell in mitosis in the lymph node. C. Small lymphocyte in section.

lens, and white blood cells which show up very distinctly. The capsule is very much thickened and infiltrated. In places it appears to be necrotic. The fatty tissue outside of the capsule is also infiltrated with many dark staining cells. With this low power the Dominici and methyl green pyronin sections show a great many cells which stain paler than the rest.

With the Zeiss apochromatic 1.5 mm. oil immersion lens and the No. 8 Zeiss compensating ocular, it is seen that besides the usual

normal cellular constituents, the entire lymph node is permeated by atypical cells, quite variable in size. Some are larger than the largest lymphocytes to be seen in the node. Others are very small, about the size of a small lymphocyte. The cytoplasm of most of the cells forms a thin ring around the nucleus (Fig. 12c). In a few cells, especially those of the germ center, the cytoplasm projects out in the form of pseudopodia (Fig. 14 Cells 3, 8, 12 and 15). These cells are free and in all probability migratory in nature. The cytoplasm stains basic and is darker than the cytoplasm of the lymphocytes, and has a homogeneous appearance (Figs. 12d and 12e). In some cells the area immediately around the nucleus stains considerably lighter than the peripheral portion. No granules are demonstrable in the cytoplasm of the cells in the sections.

The nuclei, here as well as in the blood cells, form the diagnostic feature of the cell. They are usually eccentrically placed. Some are round, the majority are ovoid, but many are very irregular in shape, especially in the cortical regions, where proliferation seems to be very profuse and the cells are crowded. The nuclear membrane is very thin and hardly to be made out in some cells. The nucleus, as a whole, stains much lighter than the cytoplasm, and can very readily be differentiated from the majority of the nuclei of the lymphocytes which stain considerably darker. Practically all of these atypical cells contain one or more nucleoli. The chromatin arrangement is entirely different from that of the lymphocytes. Whereas the chromatin of the lymphocytes, both large and small, is arranged in blocks, taking a dark stain and usually arranged at the periphery of the nucleus, the chromatin of these atypical cells forms a fine network of tiny particles, which stain very lightly and seem to be linked by fine threads running in every direction through the nucleus. In some nuclei one may observe from one to four very small blocks of chromatin, which stain very lightly and are irregularly placed (Fig. 12d).

The morphology of these cells, therefore, corresponds exactly with the morphology of myeloblasts and micromyeloblasts as decribed by Naegeli, or to the lymphoidocytes of Pappenheim.

Throughout the entire lymph node numerous cells in all stages of mitosis are seen (Fig. 14, Cell 1). The blood vessels show these "micromyeloblasts" in large numbers. They are easily distinguishable from the ordinary lymphocytes. Figure 15 shows a small blood vessel containing a lymphocyte, a "micromyeloblast," and red cells. Occasional mitotic figures can be seen in the lumina of the blood vessels. Figure 16 shows such a figure in a blood vessel.

The lymph sinuses likewise are filled with enormous numbers of these "micromyeloblasts." Figure 17 shows several such cells in a lymph sinus in the cortex of the node. They are here also readily

distinguishable from the large and small lymphocytes. In this figure, cells 6, 7, 8, 9 and 10 are "micromyeloblasts." They are identical with those in the germ center. Cells 1, 2, 3, 4 and 5 are lymphocytes.

The cells of the reticulum proper can easily be differentiated from the lymphocytes and the "micromyeloblasts." The cytoplasm of the reticulum cells is large in amount and stains very lightly. Cytoplasmic processes extend in all directions so that the cell assumes a stellate appearance. The cell membrane is exceedingly fine. In the majority of reticulum cells only part of the cytoplasm is visible, the remainder fading out into the adjacent tissue or being concealed by overlying cells. The nucleus is surrounded by a sharply defined membrane, which in many cells is invaginated and may form long grooves over the surface of the nucleus (Fig. 14, Cells 31, 32 and 34). The nucleus is exceedingly poor in chromatin and appears to be very vesicular. A nucleolus may or may not be present. Occasional small blocks of chromatin may be present. In some cells the chromatin surrounds the nucleolus, in others it is scattered about.

The capsule is thickened and is infiltrated with lymphocytes "myeloblasts" and "micromyeloblasts." Figure 16 shows a small blood vessel of the capsule containing a cell in mitosis. In this figure cell 1 is an endothelial cell; cell 2, a connective tissue cell, and the remaining cells are "myeloblasts." A study of the various cells in the capsule shows transition forms between our "myeloblastic" cells and lymphocytes as well as connective tissue cells. These transition forms are of both large and small cells.

In some places all the cells are flattened and elongated, while in other places actual necrosis is present.

Mitotic figures are also present in the capsule. The "myeloblasts" and "micromyeloblasts" are present in far greater numbers than the lymphocytes. There are also many transition forms between our atypical cells and the lymphocytes, which are recognizable by the fact that in these cells, having all the cytoplasmic and nucleolar characteristics of an atypical cell, some of the chromatin is arranged in the form of dark staining blocks which vary in number in the different cells. The majority of these chromatin blocks are usually to be found at the periphery of the nucleus or abutting the nuclear membrane. Similar transition forms were found in the germ centers of the follicles and will be described in detail under that heading. In the capsule a whole series of cells can be found between our atypical cells and lymphocytes.

We also have evidence indicating relationship between the connective tissue cells of the capsule and our atypical cells. There are typical elongated connective tissue cells, with the clear, pale, almost homogeneous cytoplasmic processes, and vesicular, pale nuclei. The next cell in the series shows a shortening of these processes. Then,

again, a cell may be completely rounded out or oval in shape. These cells take on a more basic stain, which is usually a sign of cell activity, and the nucleus shows more and more the characteristics of our atypical cells.

In the medulla an occasional cord can clearly be made out. The majority of cells in these cords are lymphocytes. However, scattered everywhere among them are our atypical cells. Here, too, mitotic figures are numerous. The rest of the medulla contains a majority of our atypical cells. These are also present in large numbers in the blood vessels and sinuses.

The cortex shows only a very few follicles with germinal centers. In a hundred sections only six were found. Follicles without germinal

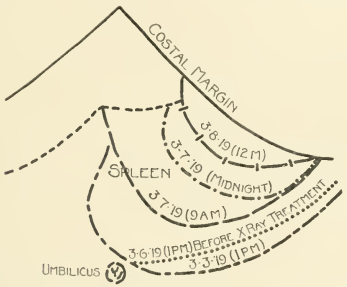

Fig. 20. — Composite tracing showing diminution in size of spleen from March 3 to 8. Roentgen-ray treatment over spleen was given March 6.

centers are more numerous. No signs of follicular atrophy are present. All evidence points toward increased activity. Mitotic figures are numerous. Our atypical cells are present everywhere. Between the follicles they constitute the majority of cells, but they are very numerous throughout the follicle, and are present in large numbers in the very centers of those follicles which do not show germ centers and in the germ centers of the six follicles studied.

Transition forms between our atypical cells and lymphocytes, as well as between lymphocytes and cells of the reticulum, are present throughout the parenchyma of the node.

The germ center of a follicle, as represented in Figure 14, is typical of all other germ centers found.

The "micromyeloblasts" are of about the same size as a small or medium sized lymphocyte (Cell 4). All graduations in size up to the size of a very large lymphocyte are present (Cells 5, 6, 7, 8, 9 and 10). This variation in size is evident throughout the node. With methyl green pyronin the cytoplasm stains an intense red. The red color is more pronounced in these cells than in the cytoplasm of the lymphocytes. In these India ink drawings the red staining cytoplasm is represented by various shades of gray, arranged proportionately to the intensity of the staining reaction. Compare cytoplasm of Cell 11, a lymphocyte, with that of Cell 7, a medium sized "myeloblast." Light staining areas in the cytoplasm (Cell 12), or around the nuclear membrane (Cells 5 and 9) are present. The shape of the cell varies considerably. It may be round (Cell 4) or oval (Cells 2 and 7) or considerably elongated (Cells 13 and 8). Some of the cells are more or less angular, like Cells 9 and 14. Pseudopodia-like cytoplasmic processes are to be seen on some cells, probably indicating their migratory nature (Cells 3, 8, 12 and 15). The cytoplasm appears to be homogeneous and no granules are distinguishable with either the methyl green pyronin or Dominici stains. The cytoplasmic rim varies in size. In the majority of cells it is rather narrow but well defined (Cells 3, 6 and 7). In some cells it is considerably larger (Cells 8, 9, 10 and 12).

The nucleus may be placed eccentrically or centrally. In the majority of cells it is eccentric. The nucleus is large and occupies the greater portion of the cell. It varies greatly in shape. It may be round, oval, or angular (Cells 6, 7 and 9). Bottleneck-like constrictions may occur (Cell 16).

The nuclear membrane is well defined but thin. It may invaginate the nucleus and form folds which may be mistaken in cross section for nucleoli. Cell 10 shows three such invaginations, which could easily be mistaken for nucleoli, since the nucleoli and the cytoplasm both stain red. Careful focusing, however, shows these to be continuous with the cytoplasm.

One or more nucleoli are usually present. These take the pyronin dye and stain red. They may be located anywhere in the nucleus and vary considerably in size. Compare nucleoli in Cells 2 and 9. Small masses of chromatin may surround the nucleoli (Cell 12).

The arrangement and quantity of the chromatin is the chief diagnostic characteristic of the cell. The chromatin and parachromatin are approximately equal in amount. The chromatin, taking a dark greenish violet stain with methyl green pyronin, is in the form of extremely fine dustlike particles, scattered rather uniformly throughout the entire nucleus (Cells 2, 6, 9 and 12). In some cells coarse chromatin masses are entirely absent (Cell 6), while in others, one or more may be present (Cells 7, 10 and 13).

The ordinary lymphocytes are easily distinguishable from our atypical cells. They vary greatly in size (Cells 17 and 18). Their cytoplasm also takes the red stain, but not so intense a red as the cytoplasm of the atypical cells. In the majority of lymphocytes, the cytoplasm forms only a very narrow rim about the nucleus, visible only where the nuclear membrane is invaginated (Cell 19), or only on one side of the cell (Cell 11), or not at all (Cell 18).

The nuclei of these lymphocytes are also characteristic. They stain considerably darker than the nuclei of the atypical cells (Cell 18). Numerous coarse chromatin strands run in all directions. Chromatin blocks, triangular, square, oblong and irregular in shape, are present. These, in many cells, have a tendency to arrange themselves around the nuclear membrane (Cell 20). Nucleoli may be, but usually are not present.

In this germ center (Fig. 14), as well as throughout the parenchyma, many transition forms between lymphocytes and our atypical cells may be seen. Beginning with a cell like Cell 6, which represents a fairly small "myeloblast," we may find a cell like Cell 22. In this cell the nucleolus is surrounded by chromatin, and small masses of chromatin line the nuclear membrane. Two other chromatin blocks are to be seen below the nucleolus. The cytoplasm does not show any changes.

The next in the series would be one like Cell 5. In this cell the chromatin blocks are more numerous and larger. A nucleolus is present. The nucleus is indented in several places. The cytoplasm stains a slightly lighter red.

The next stage is represented by Cell 23. The cytoplasm is definitely less red than in Cell 5. The nucleus still retains the basic character of a "myeloblast." It is lightly stained and fine dustlike particles of chromatin are in evidence everywhere. Here, however, there are eight triangular shaped, dark staining, large chromatin blocks arranged in "radkern" fashion about the nuclear membrane. In addition four more or less large irregular chromatin blocks, and several smaller blocks occupy the central portion of the nucleus. At first sight such a cell has all the earmarks of a lymphocyte. A detailed and careful study and a comparison with typical lymphocytes and "myeloblasts" shows that it is neither one nor the other but a cell which must be placed halfway between the two.

The next cell in the series is Cell 24. In this cell the cytoplasmic rim is considerably narrowed, and is practically invisible in part. The nuclear membrane is thick and is lined all the way around with chromatin strands and blocks. Numerous coarse chromatin blocks and strands are to be seen in the finer chromatin groundwork described

for the "myeloblast." This cell is past the half way mark in the transition series.

Cell 25 is practically a normal lymphocyte. In comparing it with Cell 18, which I consider to be a typical lymphocyte, the only diagnostic differential point is the character of the nucleus. The nucleus of Cell 25 is practically a lymphocyte nucleus. However, it lacks the coarse irregular chromatin strands so frequently found in lymphocytes, and it still shows a rather fine distribution of small chromatin particles all through the nucleus.

Other cells which I consider as transition forms are Cells 26, 27 and 28. And so thoroughout the parenchyma of the lymph node complete series of transition forms are present. Whether the lymphocyte is the mother cell of our atypical cell or vice versa, I do not know. Our evidence is such as to show a relation between the two types of cells.

Another type of cell present (Fig. 14, Cells 31, 32, 33 and 34) is the reticulum cell. This cell varies considerably in size and can very easily be differentiated from the various types of lymphocytes, atypical cells and transition forms. The cytoplasm of this cell takes an extremely light pinkish stain. In most of the cells, as in Cells 31 and 32, no definite cytoplasmic rim can be made out. Cell 34 shows the cytoplasm and the cytoplasmic processes very well. The nuclei of these reticular cells are very vesicular. The nuclear membrane is sharply outlined. The nucleus may be almost triangular in shape, as in Cell 31, or oval shaped, as in Cell 32, or elongated, as in Cell 33. The chromatin content is extremely meager, as in Cells 31, 32 and 33. It usually consists of a few small blocks and a few strands. A rather large nucleolus, staining red, and usually surrounded by some chromatin may be present (Cells 31 and 32). Here, too, there is evidence showing a relationship between our atypical cells and the reticulum cells, as well as a relation between the reticulum cells and the lymphocytes.

A rather incomplete series may be represented by Cells 23, 28, 35 and 36, respectively. The nucleus of a small reticulum cell is shown in Cell 35. Cell 36 shows a beginning formation of chromatin blocks and a darkening of the karyoplasm. Cell 28 shows a small amount of well defined cytoplasm, the nucleolus is prominent and chromatin arrangement and karyoplasm staining are suggestive of a cell between a "myeloblast" and lymphocyte, as well as between a lymphocyte and a reticulum cell. Cell 23 might very well fit in as the next in the series. It has already been described as a transition cell between a lymphocyte and a myeloblast, so that by including it also in our reticulum lymphocyte series I believe to have demonstrated a relation between the reticulum cells, lymphocytes and atypical cells. This relation of reticulum cells to the other two is not as definite as the relation between lymphocytes and the atypical cells. Not enough transition

stages are shown in this one germ center. A study of other parts of the parenchyma reveals much more conclusive evidence.

In comparing our atypical cells with the various cells found in supposedly normal lymph nodes, human and animal, I did not find any cells at all comparable to our "myeloblasts" and "micromyeloblasts." Even germ centers cells, the so-called "lymphoblasts" were not comparable to our atypical cells. In these "lymphoblasts" the cytoplasm takes on a lighter stain, and the chromatin occurs as fairly coarse dark staining blocks. The fine dustlike particles of chromatin scattered fairly uniformly throughout the entire nucleus are lacking.

DISCUSSION

It should be pointed out, that in comparing cells in blood smears with cells in sections we must keep in mind certain morphologic differences which are always present, due to the difference in technic. In making a blood smear, the drop of blood is quickly spread out over the slide and dried. The capillary traction flattens out the cells so that they appear much larger than they actually are. In sections, however, the various cells are exposed to the action of fixing fluids and consequently undergo a certain amount of shrinkage, even with the best of fixing fluids such as Helly's solution. Furthermore, an identical Wright's stain technic cannot be used satisfactorily in sections and blood, so that in comparing blood and tissue cells one must bear this also in mind.

In comparing a normal lymphocyte in the blood with a normal lymphocyte in sections we notice a definite morphological difference. The chromatin of the blood lymphocyte is arranged in a more or less definite network, while in the lymphocytes of sections the chromatin is arranged in coarse blocks and irregular strands. The lymphocytes in the blood vessels of sections also show these coarse blocks and irregular strands. The same holds true for myeloblasts in the blood and in sections. Whereas, myeloblasts in the blood show a beautiful sievelike nuclear chromatin network, in the tissues there is more of a tendency to formation of fine particles with occasional chromatin block formation. This same change is also evident in the myeloblasts in section blood vessels.

The "micromyeloblasts" and "myeloblast" are very frequently mistaken for lymphocytes, because they overstain very easily, thus losing their typical appearance.

The presence of the stem cell (microlymphoidocytes and lymphoidocytes of Pappenheim or micromyeloblasts and myeloblasts of Naegeli) in large numbers in the blood of leukemics is usually associated with an acute and rapidly fatal course of the disease.

A blood picture alone will often lead to a wrong diagnosis. In some cases, for a correct diagnosis, histologic studies must supplement

the blood studies. Krjukoff diagnosed myeloid leukemia from the blood, yet the bone marrow showed only slight activity and he was forced to conclude that his myeloid cells were coming from the "myeloid parts" of lymph nodes and spleen.

Similarly, Citron diagnosed "micromyeloblastic" leukemia, yet he found the bone marrow normal and lymph follicles hyperplastic and proliferating these "myeloid" cells.

The dualists, however, deny the possibility of "myeloid" cells originating from lymphatic tissue. They argue that in lymphatic leukemia the follicles of the lymph nodes atrophy or are, at least, quiescent. They deny absolutely the possibility of "myeloid" cells ever occuring in follicles and especially in the germ centers of follicles.

Citron's case, however, showed the "myeloblasts" of the dualists in the follicles of the lymph nodes and spleen.

Naegeli, referring to Citron's case, belittles the findings because "the patient died as a result of overdosage of benzol." Only one dose of 6 gm. was given by rectum. Boni [87] gave 5 gm. daily for three weeks. Josefson [88] gave 96 gm. in six weeks. Krokiewicz [89] gave in one case a total of 206 gm. No ill results were observed in these cases.

Naegeli also belittles the findings in cases which had excessive roentgen ray therapy.

The patient at the time the axillary lymph node, on which this study is based, was removed had not had any benzol, nor had there been any direct roentgen-ray irradiation of the axillary lymph nodes.

We believe our case to be even more convincing than Citron's for two reasons: The lymph node was obtained in vivo, so that postmortem changes can be ruled out. Whereas, Citron speaks of "myeloblasts" and "micromyeloblasts" in the follicles he does not say that he found them in the germ centers. The germ centers in our cases contained many of these cells.

This case is presented in the belief that it offers evidence in favor of the unitarian theory of Pappenheim and Ferrata. The cell which has been described as a "myeloblast" and which the dualists have assumed to be a specific myeloid cell was found to originate in the germ centers and follicles, as well as in the medullary portion of the node. This case and the case reported by Citron prove, therefore, that the cell in question may be related to lymphocytes as well as to cells of the myeloid series.

87. Boni: Sur une cas de leukémie chronique myeloide traitée par le benzol, Bull. delle clin. (Aug.) 1913; abstr. in Folia haematol. **16**:167, 1914 (Aubertin).

88. Josefson, A.: Benzolbehandlung vid Leukämi, Hygiea, 1914 (abstr. Folia haematol. **16**:167, 1914).

89. Krokiewicz, A.: Die Benzol Behandlung der Leukämie, Przegl. lekarski **52**:582, 1913 (abstr. in Folia haematol. **16**: 169, 1914)

SUMMARY

Morphologic Part 2

1. The blood, at all times, showed numerous stem cells (lymphoidocyted of Pappenheim), (myeloblasts of Naegeli) of all sizes. Our cells, which we shall refer to as atypical cells, had a basophilic cytoplasm and a nucleus in which the chromatin formed a very fine evenly distributed sievelike network. Morphologically our atypical cells were indistinguishable from typical myeloblasts.

2. Very careful staining was essential in bringing out the finer details of these atypical cells.

3. The oxydase reaction was negative in these cells in the blood smears.

4. The diagnosis from the blood alone would be "micromyeloblastic" leukemia.

5. The presence of numerous mitotic figures in the blood stream suggested the possibility of cell proliferation in the blood stream. We could not demonstrate such to be the case.

6. Lymphocytes, normal in appearance were always present in the blood. The contrast between the lymphocytes and the atypical cells was very marked. Numerous transition forms between the lymphocytes and the atypical cells were present in the blood.

7. Some myelocytes and nucleated reds were present. The severe anemia might easily account for these.

8. The biopsy of a lymph node showed these atypical cells proliferating in great numbers in the capsule, interfollicular tissue, lymph cords, lymph follicles and in the germ centers of the lymph follicles.

9. Transition forms between the connective tissue cells of the capsule and these atypical cells as well as between lymphocytes and these atypical cells were present in the capsule.

10. In the interfollicular tissue as well as in the follicles and even in the germinal centers transition forms between these atypical cells and reticulum and lymphocytes were also present.

11. The lymph follicles and lymph cords showed no signs of atrophy, but had all the earmarks of marked activity. Mitotic figures were numerous. The only signs of atrophy or necrosis were found in the capsule.

12. These atypical cells formed the majority of the cells of the parenchyma.

13. These atypical cells constituted by far the majority of the cells in the lymph sinuses and were very numerous in the blood vessels of the node.

14. From the evidence at hand, the conclusion is justified that in all probability the majority of the "myeloblasts" and "micromyeloblasts" of the blood were coming from the lymphoid organs, not only from the portions which, according to the dualists, may give rise to myeloid cells, but from the sanctum sanctorum of the lymphoid tissues, namely, the follicles and germ centers.

I wish to express my sincerest thanks to Professors L. G. Rowntree and S. Marx White for their kind guidance in the preparation of the clinical report, and to Professor Hal Downey who was the first to recognize the significance of the case and under whose direction the morphologic study was carried out.

INTRACUTANEOUS REACTIONS IN LOBAR PNEUMONIA *

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In 1915 Clough [1] reported intracutaneous reactions in lobar pneumonia patients. He prepared his antigen as follows: Cultures used were made from the lungs in cases of fatal pneumonia, with no statement as to type. From twenty-four to thirty-six hour old cultures in 5 per cent. glucose broth plus calcium carbonate were decanted off the carbonate, centrifuged, washed with salt, recentrifuged, the sediment taken up in a few drops of distilled water, dried, weighed, ground for three hours with sterile sand, extracted with 10 c. c. saline for each gram of dried material, incubated for eighteen hours; centrifuged at high speed for several hours until no more sediment came down; used in this form or precipitated with absolute alcohol. One gram of the dried culture residue yielded about 0.15 gm. dried alcoholic precipitate.

He used two methods of inoculation: first, allowing a drop of 1 per cent. solution of his antigen to dry on a scarification as for a von Pirquet tuberculin test; second, injecting a 0.25 per cent. solution intracutaneously, causing a painful inflammatory reaction subsiding after twenty-four hours. There was no appreciable increase in severity or time of the reaction in the pneumonias over the controls. The more dilute solutions gave discrete papules from 0.5 to 2 cm. in diameter with an ill-defined area of hyperemia. The actual measurements of the papules averaged a little larger in the pneumonias, but this was only slight and inconstant. He found no difference in reactivity early, at crisis, or later in convalescence. As to Clough's work, then, it may be said that he used a rather elaborately prepared antigen with practically negative results.

Weil [2] criticizes Clough's antigen for being too strong so that it produced reactions independent of any immunologic response. He used forty-eight hour old cultures on Loeffler's serum medium suspended in distilled water, from 2 to 3 c. c. to a tube, shaken, incubated two hours, and then heated to 60 C. for one hour. In a few early experi-

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* This article is one of a series of studies carried out under the supervision of the Influenza Commission of the Metropolitan Life Insurance Company. The Influenza Commission is investigating the etiology and prevention of the acute respiratory diseases, and the work is being carried on in Boston, New York, Chicago and Washington. The members of the Commission are Dr. M. J. Rosenau, Chairman, Dr. G. W. McCoy, Dr. L. K. Frankel, Dr. A. S. Knight, Dr. E. O. Jordan, Dr. W. H. Frost and Dr. W. H. Park, Secretary.

1. Clough, P. W.: Johns Hopkins Hosp. Bull. **24**:295, 1913.
2. Weil, R.: J. Exper. M. **23**:11, 1916.

ments a Type III organism was used "with success," otherwise Type I was used exclusively. For the test, a sufficient amount of antigen was injected to produce a small wheal, that amount being between 0.1 and 0.2 c. c. All showed an immediate superficial ill-defined blush which was considered merely traumatic. In the negatives this faded within a few hours and nothing more developed. In the positives, within twenty hours a fairly well circumscribed area of erythema had developed with slight infiltration and elevation of the skin surrounding the point of puncture. This may be a true papule, persisting for forty-eight hours or even longer. Weil obtained no reaction during the course of the disease, but "after the subsidence . . . a considerable percentage of cases do present reactions." These exceptionally appeared twenty-four hours after crises, but more commonly later even after two, three or more weeks. The controls "may or may not present a reaction dependent presumably on their previous sensitization by the pneumococcus or an allied organism." A few cases of pneumonia gave no reaction at any time. In summary, Weil obtained positive reaction in a "considerable percentage of cases" after crisis, and in some controls. The reaction which he considered positive reached its maximum within twenty hours, though it might persist for two days or more. He used a relatively simple incubated suspension of pneumococci in distilled water.

Steinfield and Kolmer[3] prepared an antigen in much the same way, except that they suspended in saline instead of distilled water and omitted the incubation. Separate preparations of Types I, II and III were made. The final dilution was such that 1 c. c. contained 2 billion cocci, that is 200 million were injected for a test. They found that at the end of twenty-four hours all tests showed a zone of hyperemia. By forty-eight hours a definite papule had appeared in the positives, with an erythema greater than 1 cm. in diameter and accompanied by slight edema. This reaction persisted for four to five days, and gradually cleared. There was no instance of a pustule formation. In the negatives the erythema had largely cleared by forty-eight hours. Of nineteen cases of clinical lobar pneumonia, six gave positive reactions with one or more antigens. But in none did the type or types found in the sputum exactly correspond with those shown by the skin reaction. For instance, one case showed Type I in the sputum and reacted to Types I and III; another case showed Types I and II in the sputum and reacted to Types II and III, etc. The earliest reaction appeared on the ninth day of the disease, or three days after crisis, and the latest on the thirty-ninth day after onset. "A large number of tests with healthy persons and patients suffering from chronic ailments not involving the chest" were negative. The

3. Steinfield, E., and Kolmer, J. A.: J. Infect. Dis. **20**:344, 1917.

authors conclude that there is no constant relation between the reaction in the skin and the type of organism found in the sputum, and think it probable that the allergic reactions to pneumococcus protein are of a more general character than the agglutination reactions.

In 1918 Weiss and Kolmer [4] report an intracutaneous test with a preparation of "pneumotoxin" as opposed to the "pneumoprotein" of the former tests. Perhaps the most important difference in their antigen over those used previously is that at no time is the product heated to a temperature which would endanger the thermolabile substances. They centrifuged eighteen hour broth cultures of Type I pneumococcus, washed once with saline, took up in 5 c. c. saline and dissolved the cocci in 1 c. c. of a 2 per cent solution of sodium choleate. The total volume was made up to 30 or 40 c. c., centrifuged to remove undissolved pneumococci and 0.2 per cent. tricresol added. The "control fluid" was treated as above, except for the inoculation with pneumococci. The minimal lethal dose for a 250 or 300 gm. guinea-pig was found, and the antigen diluted so that 0.1 c. c contains one twentieth the minimum lethal dose (M. L. D.). This amount was injected intracutaneously for the test. The preparation deteriorated rapidly and was made fresh every day. The authors found the reaction in "all respects similar to that described for the Schick test with diphtheria toxin." Cases just prior to the crisis showed a strongly positive reaction marked by vesiculation. Others showed a definitely circumscribed area of edema and erythema gradually fading, leaving a scaling zone of brownish pigmentation. The "control fluid" and heated "pneumotoxin" remained negative. Pseudoreactions involving the entire arm with diffuse erythema and a definite area of edema never persisted longer than forty-eight hours. Of thirty-eight cases of "acute lobar pneumonia" all reacted positively; of sixteen cases of "lobar pneumonia convalescents" five reacted positively; of five "doubtful" cases ("alcoholism and tuberculosis with possible superimposed pneumonia"), one gave a positive reaction; and of twenty-three controls all were negative.

In summary, they state that the tests with "pneumotoxin" were elicited as early as the fifth day (the earliest under observation) and as late as the thirteenth day of the disease. In general, the test was positive throughout the toxemia.

Further in the paper the authors took up the question of the type specificity of this reaction. The sputum from ten cases which reacted positively to their type I "pneumotoxin" was examined for type organism. Six of these showed Type IV and four showed Type I. They consider that "sensitization to the toxin presumably takes place with its liberation (by action of normal enzymes on pneumococci normally

4. Weiss, C., and Kolmer, J. A.: J. Immunol. **3**:395, 1918.

localized in the lung alveoli) at the time of the prolonged chilling due to exposure." They feel that the method is not as yet of value in serologic type diagnosis.

In these two papers Kolmer shows that his heated saline suspension of pneumococci gives positive reactions after crisis which are not specific for type, and that his unheated bile salt solution of pneumococci gives positive reactions before as well as after crisis which are also not specific for type. It is rather a surprise after having compared this latter reaction to the Schick test in diphtheria, to find that the presence rather than the absence of a reaction is considered specific. The authors' theory of early sensitization against their "pneumotoxin" is certainly open to question when we consider the absence of any sensitization necessary in the case of the positive Schick reaction, and also the lack of specificity in the toxic radicle as shown by Vaughan's work.[5]

EXPERIMENTAL WORK

It was hoped that by the study of a considerable series of pneumonia cases and normal and diseased controls, using antigens made from the various types of pneumococci (homologous and heterologous) prepared in various ways, additional information might be obtained concerning the rôle played by allergy in pneumonia with especial reference to crisis. Furthermore, it was hoped that by varying the method of preparation and dose of antigens prepared from the various types of pneumococci, it might be possible to obtain antigens sufficiently delicate to indicate the type of infection present. If this reaction should prove to be positive in the early stages of the disease, it might furnish an earlier, quicker and simpler means of type determination than can be obtained by the present method of mouse inoculation, thus making it possible to institute specific serum therapy in suitable cases with less loss of time than is at present possible.

Cultures and Their Sources.—The cultures [6] used in the preparation of antigens were:

5. Vaughan, V. C., and Wheeler, S. M.: J. Infect. Dis. **4**:476, 1907.

6. The cultures used were obtained as follows: I A from Dr. F. T. Lord. I B, II A, II B, III A and III B from Dr. G. B. White, State Biological Laboratory, Forest Hills. IV B and IV C from Miss E. A. Beckler, Bacteriological Laboratory, State House, Boston, isolated Dec. 13, 1920. The remaining cultures were isolated in the Pneumonia Laboratory of the Department of Preventive Medicine and Hygiene. The following were obtained from blood cultures taken on patients on the Special Pneumonia Service at the Boston City Hospital on the dates as indicated: I C, Jan. 15, 1921; I D, January 24; I F, Feburary 24; I G, February 18; I H, Feburary 28; I J, March 15; III C, February 15; III D, February 27, and IV E, January 24. The following cultures were isolated from the sputum of similar patients: I E, February 8, and I I, March 22. The following cultures were isolated from the sputum of patients outside Boston as indicated: IV A, Foxboro State Hospital, and IV D, Framingham.

Type I: 10 strains, designated I A, I B, etc.

Type II: 2 strains, designated II A and II B.

Type III: 4 strains, designated III A, III B, etc.

Type IV: 5 strains, designated IV A, IV B, etc.

Methods of Preparing Antigens.—The cultures used were from eighteen to twenty-four hour old growths in 100 c. c. of a 1 per cent. glucose beef infusion broth, neutral to phenolthalein, which was found to correspond to a hydrogen ion concentration of from 8.0 to 8.2. On this medium there was homogeneous clouding of the broth with an abundant sediment in the bottom of the flask. The morphology of the organisms used was typically that of pneumococcus, gram-positive, bile soluble, and the type was repeatedly verified by agglutination with type serum from the New York State Board of Health and the Rockefeller Institute. All growths were examined microscopically for contamination, and serologically to confirm the previous type determinations.

For all the antigens, the first steps were identical. The growth was centrifuged, and the sediment was washed twice with sterile salt solution, centrifuging after each washing. Throughout the work the centrifuge was run at about 3,000 revolutions per minute. The time interval for centrifuging and shaking electrically was one-half hour.

The finished antigen was sealed in ampules containing sterile glass beads so that if desired the suspension could be shaken thoroughly before use to insure uniformity of material. Whenever the antigens were heated to 56 C. special care was taken that the entire ampule was completely submerged in the water bath. Before using the antigens were plated on whole rabbits' blood agar to test sterility, and in the simpler preparations bacterial counts were made according to Wright's method [7] as commonly used in standardizing bacterial vaccines. The ampules were kept on ice until used. No antigen was used more than a week after being put on ice. Both the opalescent supernatant fluid and also the entire opaque suspension of organisms were used. Before using the antigens were diluted with sterile saline solution and doses varying from 10 to 1,000 million bacteria or their equivalent were injected in 0.1 c. c. volume.

With the earlier antigens the strains (except Type IV) were kept separate. Thus a patient with a known Type I pneumonia might be inoculated with four strains of Type I, one strain each of Types II and III, and a polyvalent Type IV, the whole constituting one test. No especial merit was found in this method, the few homologous strains used giving no better results than the heterologous strains, and since it subjected the patients to multiple inoculations, the strains of each

7. Wright, A. E.: Lancet **2**:1556, 1900; **2**:11, 1902.

type were pooled. The Type IV antigen was later omitted since in specific reactions the two nonspecific types furnished ample controls.

Antigen 1.—Cultures I A and I B, II A and II B, III A and IV A, IV B and IV C were used. The sediment after the second washing was taken up in from 20 to 30 c. c. of saline solution and heated to 56 C. for one hour. The ampules were then vigorously shaken, and put on ice.

Antigen 2.—Prepared as Antigen 1, except that it was incubated one week before being used. At the end of that time the sediment formed on standing showed on smear much amorphous gram-negative material including faint staining cocci with individual gram-positive cocci and rare diplococci.

Antigens 1 C and 1 D.—These were prepared as Antigens 1 and 2 from cultures I C and I D. They were used autogenously and on a few other patients.

Antigen 3.—Prepared as Antigen 1 with the following cultures: I A and I B; II A and II B; III A and III B; and IV A and IV C.

Antigen 4.—Same as Antigen 3, except that it was incubated one week.

Antigen 5.—Same as Antigen 4, except that it was incubated two weeks before using.

Antigen 6.—After the second washing with saline solution, the sediment was taken up with distilled water instead of saline solution. Cultures used: I A, I B and I C; II A; III B; IV A, IV C, IV D and IV E.

Antigen 7.—Same as Antigen 6, except that it was incubated one week.

Antigen 8.—After the second washing with saline solution, the sediment was taken up in 10 c. c. of a 10 per cent. bile solution,[8] and incubated for one hour. Attempts were made to obtain suitable animal membrane for separation of the bile salts from the dissolved pneumococcus substances by dialysis, but it was found more feasible to obtain the separation by precipitation of the protein with four volumes of absolute alcohol. This was thoroughly shaken, centrifuged and the sediment again mixed with absolute alcohol. After recentrifuging, the sediment was dried overnight in partial vacuum over sulphuric acid. The residue was weighed, ground with sufficient sodium chlorid to make the final solution physiologic and taken up by adding distilled water drop by drop while grinding until 0.1 c. c. contained 1/150 mg dried sediment.[9] (Later injections up to 1/10 mg. were used.)

8. Bacto-oxgall was used.

9. Gay, F. P. and Minaker, A. J.: J. A. M. A. **70**:215 (Jan. 26) 1918.

This was heated to 56 C. for one hour. For this antigen all the strains of each type were pooled. The cultures used were: I A, I B, I C, I D and I E; II A, and II B; III A, III B and III C.

Antigen 9.—After the second washing with saline solution, the sediment was taken up in a small amount of saline solution and precipitated with four volumes of absolute alcohol. This was centrifuged and taken up a second time in absolute alcohol. After again centrifuging the sediment was extracted by thoroughly shaking with ether. The sediment was dried for one hour in the incubator, weighed, and ground with sufficient salt to make the final solution physiological, and taken up in distilled water, added slowly while grinding. The dilutions were such that the antigen contained 20/150 mg. per 0.1 c. c. This was at first diluted twenty times before using but was eventually used full strength. The antigen was heated to 56 C. for one hour. In this preparation the strains of each type were pooled. The cultures used were: I A, I B, I C, I D, I F, I G, and I H; II A and II B; III A, III B, III C, and III D.

Antigen 10.—The most important difference between this and the foregoing antigens is that it was at no time raised above 37.5 C. The strains of each type used were pooled and were as follows: I B, I C, I D, I G, I H, I I and I J; II B; III C and III D. After the second washing with salt solution the sediment was divided into known amounts and kept on ice. The day of the tests, sufficient of sterile solution of 2 per cent. bile plus 0.25 per cent. tricresol was added to make 0.1 c. c. contain the equivalent of one twentieth of the growth of pneumococci on 60 c. c. of broth.[10] An incubated solution of 2 per cent bile plus tricresol was used as control.

In summary, the first seven antigens were simple suspensions of pneumococci in saline solution or distilled water. Antigens 1, 3 and 6 were not autolyzed in the incubator, while antigens 2, 4, 5 and 7 were incubated one week or more. In antigens 8 and 9 the pneumococci were treated with bile and alcohol, and alcohol and ether, respectively. Thus the pneumococcus protein was subjected to considerable violence. Antigen 10 differed from all the others in that it was never raised above 37.5 C., while the others were all held at 56 C. for one hour. In the bile solution whatever endotoxins the pneumococci contain should be liberated.

Tests.—A "test" consisted of multiple inoculations. In the first seven antigens each strain of the different types was made up separately, with the exception of Type IV strains which were pooled and served

10. Cole, R.: J. Exper. M. **16**:644, 1912; **20**:346, 1914. Avery, O. T., Chickering, H. T., Cole, R. and Dochez, A. R.: Acute Lobar Pneumonia, Prevention and Serum Treatment, Monograph No. 7, Rockefeller Institute for M. Res., 1917. Weiss, C.: J. M. Research **34**:103, 1918.

as a control for the reactions which might be specific for type. Thus, with these antigens, a Type I pneumonia might receive from one to four different strains of Type I antigen, besides one Type II, one Type III and the pooled Type IV antigen. As it was very exceptional to obtain a reaction with one strain and not with all of the same type used (this occurred only in Case 7, which on the thirty-eighth day of the disease responded positively to the homologous strain and negatively to the heterologous strains of Type I), this method was abandoned later, since it subjected the patient to the discomfort of multiple inoculations.

Antigens 8, 9 and 10 were made from pooled strains of each of the fixed types. Type IV was no longer used, since in specific type reaction the two nonspecific type antigens acted as ample controls. Thus with these antigens a "test" consisted of three inoculations, one for each of the three fixed types.

With each new antigen various dilutions of each strain or pooled type were injected in an effort to obtain the titre of the antigen for both the specific type reactions and also for those reactions which did not show type specificity. These titres were, unfortunately, found to be very close to each other, and varied within considerable limits with each preparation and individual.

As stated earlier, tests were performed with both the opalescent supernatant fluid and the whole thoroughly mixed opaque antigen. In general, the supernatant fluid gave fewer reactions that were nonspecific for type, but it was also feared that in the same dilutions it might also elicit specific type reactions with less constancy.

The tests were made on the flexor surface of the forearms. A 26 gage needle was used and 0.1 c. c. was injected intracutaneously. When properly done a bleb appeared which persisted for some minutes; there was pitting at the hair follicles, and no bleeding at the point of inoculation.

Readings.—The tests were read, as a routine, after two, eighteen, twenty-four, thirty, forty-eight and seventy-two hours. Additional readings were made on the positive reactions.

Reactions Appearing with Only One Type of Pneumococcus.—The reactions in this group were at their height in from twenty-eight to thirty-two hours. These showed a deep red, indurated, papular center measuring from 2 to 4 cm. in diameter. Around this there was a somewhat lighter areola measuring up to 8 cm. in diameter. In forty-eight hours the papule still persisted, usually duller in color, the areola had entirely faded and in about half the cases was replaced by a zone of pigmentation. The papule in some cases persisted to the sixth day after the test. In one case there was very fine scaling. In some cases this type of reaction showed nothing after eighteen and twenty-

four hours. In others there was the reaction described below which was fading in twenty-four hours. The reaction to but one type of the antigen used was, in general, specifically positive for the type of infection, and will be referred to hereafter as specific type reaction.

Reactions with Two or More Types.—These reactions were at their height in eighteen hours. They showed no distinct differentiation between central papule and surrounding areola, and were usually indefinite in outline, fading gradually into the surrounding normal skin. The erythema was often mottled and of large dimensions up to 10 or 12 cm. in the longest axis which was always parallel to the long axis of the arm. On fading, unless they later showed specific type reaction, there was no pigmentation or scaling. By twenty-eight hours there remained only a small area about 0.5 cm. across of local redness around the point of inoculation. This reaction was always elicited with more than one of the types of the antigen used and generally with all when all types were used in the same strength. In an individual showing this reaction the number of types in which it appeared seemed, in general, to depend on the strength in which the type antigen was used and in no case on its specificity for the type of infection present. As will be discussed later these reactions were considered as a response to some substance possessed in common by all types of pneumococci or to some property of the antigen not even specific for the entire pneumococcus group. This reaction which was elicited in common by all types of pneumococci will be referred to hereafter as the common reaction.

In an effort to increase the number of specific type reactions, the strength of the antigens was varied with the object of reducing the common reactions to a minimum and yet retain sufficient strength to elicit the reaction to a single specific type.

Special reference must be made to the reactions obtained with Antigen 10 in which the thermolabile toxic substances from the pneumococcus were not destroyed. When used in the strength recommended by Kolmer[4] and in weaker dilutions, severe local reactions were elicited, showing papules becoming pustular with wide zones of erythema and induration up to 12 or 14 cm. in their longest dimension. This was at its height in about thirty hours when the erythema faded, leaving no pigmentation or scaling in any case. The pustule persisted for weeks. This reaction was well marked in both controls and pneumonia cases, the most severe being in a normal control. The control injection of bile and tricresol showed only a small local papule, but none of the violent erythematous and edematous reaction.

Results.—During the course of the work, 124 persons were tested, as follows: (1) Lobar pneumonia, 104 cases; forty-seven had a Type I infection (specific antipneumococcus serum being used in twenty of

these and not used in twenty-seven); eight had Type II infections; seven had Type III pneumonia, one had Types II and III, twenty-nine had Type IV, and in twelve the type was not determined (no atypical Type II cases presented themselves); (2) controls, twenty persons, of whom sixteen were patients showing for the most part acute febrile conditions other than lobar pneumonia, and four were apparently normal. On these 124 persons, 223 tests were performed, divided about equally between the ten antigens. The earliest test was performed on the third day of the disease and the latest on the eighty-first day. The number of tests on each individual varied from one to five.

Of the 104 cases of lobar pneumonia tested, eleven (10.5 per cent.) gave specific type reactions, forty-six (42.3 per cent.) gave a common reaction and fifty-two (50 per cent.) gave no such reaction. Of the twenty controls, none gave a specific type reaction, nine gave a common reaction and eleven gave no reaction.

The eleven cases which gave specific type reactions were distributed among the types of infection as follows:

TABLE 1.—Cases Manifesting Specific Type Reactions

Type of Pneumonia	Number of Cases Tested	Number Showing Specific Type Reaction	Per Cent. Specific
I	47	6	12.7
II	9	2	22.2
III	8	1	12.5
IV	29	2	6.8

This reaction was specific for the type of infection in the patient as determined in the blood or sputum, or both, except with Antigen 9. With this antigen, reactions were elicited in three patients, in each case with the Type II preparation; while with Types I and III preparations the reactions were consistently negative. Of these patients one showed a Type II pneumococcus in the sputum, one a Type I and one a Type IV. In the last two cases blood cultures were persistently negative and repeated examinations of the sputum failed to show a Type II organism. In the Type I patient, the test was repeated with the same antigen five days later and was negative. In the cases of Type I and IV pneumonias, the reaction with Type II antigen was obviously nonspecific as to type of pneumococcus. Although this Type II preparation of Antigen 9 gave frequent negative tests in other cases, it is not unlikely that its apparent specific reaction in one case may be accounted for on the law of chance. Thus all three reactions might well be considered as nonspecific for type, and as a response to some form of protein common to all types of pneumococci, though in that case the Type I and III preparations should also have shown positive reactions, or to some other factor in the antigen rather than

to specific type sensitization in the patient. None of these three patients gave a specific reaction with any of the other antigens used.

Deducting these three reactions from Table 1, we may reconstruct it as follows:

TABLE 2

Type of Pneumonia	Number of Cases Tested	Number Showing Specific Type Reaction	Per Cent. Specific
I	47	5	10.6
II	9	1	11.1
III	8	1	12.5
IV	29	1	3.5

Although the number is small, it may be said that in these tests, no one of the fixed types of pneumonia shows any marked preponderance over the others as regards the ease with which intracutaneous reactions, specific for the type of infection, could be elicited.

The relation between the specific type reactions in Type I cases and treatment with specific antipneumococcus serum is shown in Table 3.

TABLE 3.—SPECIFIC TYPE REACTIONS AND SPECIFIC SERUM TREATMENT

Total of Type I pneumonias tested..... 47
Total of Type I pneumonias with specific reactions..... 6

Treated	Total Tested	Specific Reactions	Per Cent. Specific
With serum	20	2	10
Without serum	27	4	14.8

Thus, instead of finding more ease in eliciting this reaction following specific serum therapy, as might be expected from the report [11] of the earlier appearance of antibodies in such cases, a somewhat smaller proportion of these reactions appeared among cases so treated than among those receiving no serum.

Of the eleven cases showing specific type reactions, seven gave one such test with one or more negatives; three gave two with one or more negatives, and one gave three with one negative test. There was a total of sixteen specific type reactions out of thirty-seven performed on these eleven patients. The earliest specific test was performed on the sixth day of the disease, or the day of the termination of crisis; the latest was on the thirty-eighth day, or twenty-nine days after crisis. The only reaction of this kind obtained before crisis was on the eighth day of the disease, or three days before crisis. This, however, was not specific for the type of organism found in the patient's sputum. Dividing the disease into weekly periods, the specific type reaction occurs as shown in Table 4.

11 Knox, J. H., Moss, W. L. and Brown G. L.: J. Exper. M. **12**:562, 1910.

TABLE 4

Week	1st	2d	3d	4th	5th	6th
Of the disease	1	6	3	2	3	1
After crisis	7	1	4	1	1	.

One reaction occurred before and one during crisis. Thus the largest number of these reactions appeared during the second week of the disease or the first week after crisis. With the crisis a phenomenon of allergy, this is what would be expected since the seven to fourteen day interval is that commonly required for antibody formation (vaccinia [12] and serum disease [13]) after which period there is a gradual reduction in the concentration of antibodies, and since directly after the clinical manifestation, the antibodies may be in their highest concentration,[14] as it is on these antibodies that the antigen must depend for its reaction.

In these eleven cases the various antigens were used as shown in Table 5.

TABLE 5

Number of antigen	1	2	3	4	Ic	5	6	7	8	9	10
Total tests	4	5	3	4	3	6	2	3	1	4	4
Specific tests	0	5	0	3	1	2	1	1	0	3	0

It will be remembered that Antigens 2, 4, 5 and 7 were identical with Antigens 1, 3 and 6, respectively, except that the former were autolyzed in the incubator for a week or more, while the latter were put directly on ice. Thus out of eighteen tests with autolyzed antigens, eleven (61.1 per cent.) gave specific type reactions; while out of nine tests with nonautolyzed antigens only one (11.1 per cent.) so reacted. The superiority of the former type of antigen is well illustrated in Case 11 in which autolyzed antigens gave specific type reactions on the thirteenth and twenty-ninth days, and no such reaction on the twenty-third day. It is very unlikely that in the interval of sixteen days between the positive tests, the patient lost his specific type sensitiveness and regained it again, but rather that the antigen used during this interval was not suitable to elicit such a reaction. In this connection, it is significant that when one case responded specifically on the thirty-eighth day of the disease to an autolyzed antigen of culture I C

12. Rosenau, M. J.: Preventive Medicine and Hygiene, New York., D. Appleton & Co., 1918.

13. Von Pirquet, C., and Schick, B.: Die Serumkrankheit, Leipsig, Deuticke, 1905.

14. Chickering, H. T.: J. Exper. M. **20**:599, 1914. Dochez, A. R.: J. Exper. M. **16**:655, 1912. Ricketts, H. T.: Infection, Immunity and Serum Therapy, Chicago, A. M. A. Press, 1906. Rosenow, E. C.: J. Infect. Dis. **3**:683, 1906. Tunnicliff, R.: J. Infect. Dis. **8**:302, 1911. Wolf, H. E.: J. Infect. Dis. **3**:731, 1906.

(homologous) the identically prepared, but nonautolyzed, antigen gave no reaction.

Of the antigens in which the pneumococci were subjected to considerable violence (Antigens 8, 9 and 10) No. 9 was the only one showing any reaction to a single type and the lack of type specificity of these reactions has already been discussed.

In the light of Weil's [2] work, the common reactions are especially worthy of analysis. Of the 104 cases of lobar pneumonia tested, forty-six (42.3 per cent.) showed the reaction with one or more antigens, and of the twenty controls, nine (45 per cent.) showed such reactions. They were elicited by the various antigens as shown in Table 6.

TABLE 6

Antigens	1	2	3	4	5	6	7	8	9	10
Reactions in pneumonias	5	4	6	7	3	2	0	2	7	17
Reactions in controls	1	3	0	1	0	2	0	2	0	3

The earliest reaction of this type appeared on the sixth day of the disease and the latest on the forty-sixth day. In relation to crisis, one appeared twenty-four hours before, two during, and the remainder after crisis.

These reactions were at their height in eighteen hours, and were fading in from twenty-four to thirty-six hours. They showed no differentiation between central induration and areola. Though a central macule, sometimes just palpable about the point of inoculation, might persist for forty-eight hours or even longer, there was no pigmentation or scaling. Weil describes what he considers a positive reaction to the pneumococcus protein as follows:

> Within the twenty hours following the injection further changes may occur at the site of injection. A fairly well circumscribed area of erythema, with slight infiltration and elevation of the skin surrounding the point of puncture, may develop. If the infiltration is marked, a true papule results. These changes may persist for forty-eight hours or more. . . . The normal individuals, or the diseased controls, may or may not present a reaction, depending presumably on their previous sensitization by the pneumococcus or an allied organism.

It would seem, then, that the reactions obtained by Weil and those described here as common reactions were the same. Weil is not disturbed by similar reactions in controls and feels that they are specific for the pneumococcus protein. When a history of lobar pneumonia cannot be obtained, he feels that an abortive and unrecognized attack may be used as an explanation of sensitization. Another explanation is that suggested by Gay [9] for his "meningococcin" reaction in normals with negative cultures, namely, that the presence of the organisms on the mucous membrane in the past was sufficient to

sensitize. It is impossible to check up Gay's suggestion, because the discovery of a carrier state in the past is beyond present day bacteriologic technic. At least, it can be said that a test in which 45 per cent. of the controls react is of no service diagnostically.

SUMMARY

Of 104 cases of lobar pneumonia, eleven (10.5 per cent.) gave one or more intracutaneous reactions to only one type of pneumococcus used, while forty-six (42.3 per cent.) reacted to two or more types. Of twenty controls none showed the single type reaction, while nine (45 per cent.) showed the multiple type reactions.

These two reactions are sharply differentiated both as to time and character. The reactions elicited to a single type of pneumococcus were (with the exception of those from Antigen 9) specific for the type of organism isolated from the patient. The reactions, elicited by multiple types of pneumococci in 42.3 per cent. of the cases of lobar pneumonia and in 45 per cent. of the controls were not specific for the type of pneumococcus causing the disease. To determine whether they are specific for pneumococcus protein or not a control antigen made from other bacteria should be used.

In 10 per cent. of the cases treated with Type I antipneumococcus serum, specific type reactions were obtained, and in 14.8 per cent. not so treated there were similar reactions. No one of the fixed types showed any marked preponderance of specific type reactions. The longest period over which the specific type reaction was obtained was seventeen days. The largest number of the specific type reactions occurred during the second week of the disease (six cases) and the first week after crisis (seven cases).

With antigens prepared from simple saline suspensions of pneumococci, 61.1 per cent. of the tests, performed on the patients showing the specific type reactions, were positive when the antigen used had been autolyzed in the incubator for a week or more, and 11.1 per cent. of the tests with nonautolyzed antigen were positive.

Of the antigens in which the pneumococci were treated with bile, alcohol, etc., only one gave reactions to a single type and these were probably all nonspecific for the type of infection present.

No reactions comparable to those reported by Weiss and Kolmer with their "pneumotoxin" were obtained with a similar preparation, nor was there any specific absence of reactions as might be expected from an analogy to the Schick test.

CONCLUSIONS

1. Intracutaneous reactions specific for the type of pneumococcus causing lobar pneumonia may be obtained in certain cases.

2. The reaction has not been demonstrated sufficiently early to be of service in directing specific serum therapy.

3. The largest number of reactions occur during the period when, on the assumption of allergy, the highest concentration of antibodies would be expected.

4. The sensitization responsible for the specific reactions may persist more than two weeks.

5. The most satisfactory antigen for obtaining specific type reactions is made by autolyzing saline solution or distilled water suspensions of the various types of pneumococci.

6. A reaction, differing from that which is specific for type in time and character, may be obtained in a considerable number of cases of lobar pneumonia and controls. This appears with more than one of the pneumococcus type antigens and is in no way specific for the type of organism causing the infection. Whether this reaction is specific for a common factor in all types of pneumococcus protein or whether it is in no way specific for the organisms composing the antigens has not been demonstrated.

CLINICAL STUDIES ON THE RESPIRATION

VIII. THE RELATION OF DYSPNEA TO THE MAXIMUM MINUTE-VOLUME OF PULMONARY VENTILATION *

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Failure to obtain the required amount of oxygen or to remove a sufficient quantity of carbon dioxid from the body tissues results in the subjective sensation of dyspnea. The maintenance of a gaseous exchange which is adequate for the needs of the metabolism depends on the coordination of several factors, and insufficiency of any one of these may produce dyspnea, but we proposed here to consider only the subject of the pulmonary ventilation. With the body at complete rest the demand for oxygen is supplied and the excess carbon dioxid is removed when an individual is breathing from 4 to 5 liters of air per minute. Physical exertion requires a greater gaseous exchange and this is met by an increase in the amount of air breathed which is nearly proportional to the rise in metabolism. The degree, therefore, to which the metabolism may be increased by physical exertion without the production of dyspnea will depend, in part at least, on the ability to increase the minute-volume of the respiration so that it keeps pace with the metabolism. Aside from any other factors, the maximum minute-volume which an individual is capable of maintaining thus sets a definite limit to the amount of exercise which he can carry on without dyspnea, and the determination of the maximum minute-volume becomes a point of considerable practical interest. The maximum minute-volume depends, of course, on the ability to increase the rate, and more especially the depth, of breathing, and it is normally subject to variations depending on such factors as the vital capacity of the lungs and physical training, while in pathologic conditions it may be affected by numerous influences. The difference between the amount of air breathed per minute when lying quietly at rest and the amount breathed during the greatest exertion, or the maximum minute-volume, constitutes the pulmonary reserve which enables an individual to provide a greater supply of oxygen and remove larger quantities of

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carbon dioxid from the body when the demand is made. An individual with a large pulmonary reserve may be capable of violent exercise without dyspnea, while a patient with a very small reserve, from any cause, as, for instance, from heart disease, will become dyspneic on slight exertion. Hence the tendency to dyspnea depends, in part at least, on the extent of the pulmonary reserve.

The first experiments to be reported consist of an attempt to determine the maximum minute-volume and the pulmonary reserve in normal young men. The second series of experiments was devised to illustrate the effect on the pulmonary reserve of a decrease in the vital capacity of the lungs, with a consequent diminution of the maximum minute-volume.

THE MAXIMUM MINUTE-VOLUME IN NORMAL YOUNG MEN

To determine the maximum minute-volume which can be maintained during exercise, a study was made of twelve normal, young, male adults. The volume of air breathed was measured by conducting the expired air through a Bohr meter while the subject was riding on a stationary bicycle. During the period of exercise, the subject was instructed to ride hard until he was exhausted, and toward the end of the experiment he was encouraged to "spurt" for thirty seconds. The duration of the experiment varied from two and one-half to fifteen minutes, depending on the endurance of the individual. Dyspnea and muscular fatigue were both factors in making the subject stop riding and it was often difficult to determine which was the more important.

The results of the experiments, which are summarized in Table 1, show that in the twelve normal subjects the average minute-volume during the last one and one-half minutes of the observation, when the exercise was most violent was 60.3 liters. For periods of thirty seconds somewhat higher minute-volumes were often obtained, but these were maintained for so short a time that they are of less practical significance from the present point of view. No observations were made on the minute-volume of these subjects when lying down at complete rest, but general experience indicates that the average would not be far from 5 liters per minute. On this basis, it is clear that the pulmonary reserve is such that the minute-volume during violent exercise may be raised to about twelve times its resting value.

It is of interest to analyze the high minute-volumes in order to find out how they have been produced. There is always an increase in the rate of respiration and this consists of an average rise to 34 per minute during severe exercise. During the last minute and one-half of exercise the lowest rate observed was 26 and the highest 45 per minute, but in eight of the twelve subjects the rate was between 31 and 37. It would appear, therefore, that a rate of respiration of about 35 per

minute is usually attained during severe exertion. The other factor in producing the high minute-volume breathed during exercise is the increase in the depth of respiration. The depth of breathing will, of course, be governed to some extent by the vital capacity of the lungs, but it is quite obvious that when breathing rapidly it is impossible for the volume of each respiration to be equal to the total volume of the vital capacity. In the subjects investigated it was found that the volume of each respiration, during the period when they were breathing their maximum minute-volume, varied between 23 per cent. and 45 per cent. of their vital capacity, with nine of the twelve subjects using between 27 and 39 per cent. In general, therefore, an average of about 33 per cent. of the vital capacity was made use of with each respiration during the period of greatest exertion. It is interesting

TABLE 1.—Summary of Experiments on Twelve Subjects

No.	Subject	Vital Capacity, C.c.	Highest Minute-Volume for 30 Seconds, Liters	Duration of Exercise, Min.	Pulmonary Ventilation for Last 1½ Minutes of Exercise		Percentage of Vital Capacity per Respiration
					Minute-Volume, Liters	Respiratory Rate	Volume per Respiration, C.c.	
1	G. F. H.	7,180	84.00	7	79.0	39	2,050	28
2	A. M. G.	6,200	67.2	4	60.8	26	2,339	38
3	K. T. R.	5,530	60.4	5	58.9	31	1,900	34
4	J. B. M.	5,000	60.0	2½	50.6	37	1,367	27
5	T. E. B.	5,180	63.0	8	58.7	37	1,586	31
6	W. C. R.	5,400	66.0	6½	56.6	45	1,258	23
7	F. C. H.	5,530	84.6	13	80.0	35	2,285	41
8	J. W.	5,080	74.0	15	69.5	35	1,985	39
9	H. C. D.	5,210	54.6	4½	52.6	37	1,422	27
10	W. T. V.	5,180	50.4	5½	47.6	27	1,762	34
11	J. M. Mc.	4,210	66.4	7½	60.6	32	1,895	45
12	F. R. B.	5,080	50.6	8	48.2	31	1,555	31
	Average	.....	60.3	...	....	34	.....	33

that Barr and Peters[1] found that normal subjects and patients with heart disease, made dyspneic by rebreathing carbon dioxid, were able to use between one-third and one-half the volume of their vital capacity at each respiration. If one accepts the usual figures associated with the maximum minute-volume in this group of subjects, of a rate of 35 per minute and a volume per respiration equal to 33 per cent. of the vital capacity, it is possible to compute with fair approximation the theoretical maximum minute-volume of any individual if the vital capacity is known. Thus, if the vital capacity is 4.600 c.c., the maximum minute-volume is $\frac{4600}{3} \times 35$, or 53.7 liters. Figures obtained in such a manner, have, of course, only a relative value, and there will necessarily be considerable individual variation from such theoretically derived maximum minute-volumes depending on the extent to which the individual under consideration is able to increase the rate and depth of

1. Barr, D. P., and Peters, J. P., Jr.: Am. J. Physiol. **54**:345, 1920.

respiration. If the above formula be applied to the twelve subjects of these observations, it is found that the actual minute-volume of air breathed during the minute and one-half of greatest exertion was between 79 and 129 per cent. of the calculated maximum minute-volume, but in nine of the twelve subjects it was between 79 and 98 per cent. of the calculated maximum. The average minute-volume of the twelve subjects is 96 per cent. of the calculated maximum. Accepting the fact, therefore, that such calculations can give only a rough approximation of the truth, it is nevertheless clear that by their use it is possible to determine, with a degree of error that is unimportant for practical purposes, the maximum minute-volume of respiration which any individual can maintain, if the vital capacity of the lungs is known. Since most persons are able to increase the rate of respiration to about 35 per minute, or to the usual maximum rate during severe exertion, it is obvious that the fundamental factor which influences the maximum minute-volume is the vital capacity of the lungs. The clinical significance of these observations will be discussed later.

THE EFFECT OF REDUCTION OF VITAL CAPACITY OF THE LUNGS ON THE MAXIMUM MINUTE-VOLUME OF PULMONARY VENTILATION AND ON THE PRODUCTION OF DYSPNEA

The above observations having called attention to the importance of the maximum minute-volume of the respiration in its relation to bodily activity and the production of dyspnea, and also to the importance of the vital capacity of the lungs in determining the maximum minute-volume, the experiments to be described now were devised as an attempt to illustrate the relation of variations in the vital capacity of the lungs to the production of dyspnea.

It was found possible to cause an artificial reduction of the vital capacity to about one-half the normal value by means of a heavy canvas swathe strapped tightly round the chest, and in two healthy subjects the reaction to exercise was studied both before and after reducing the vital capacity in this way. Observations were made during the fasting state, on the respiration rate, volume per respiration, minute-volume, oxygen consumption, and carbon dioxid production per minute while the subject was lying at complete rest (Period I), standing at rest (Period II), walking sixty steps upstairs on a treadmill in sixty seconds (Period III), and over two consecutive five-minute periods standing at rest immediately after the walk (Periods IV and V). The amount of exercise involved in the walk upstairs was, of course, slight and caused little shortness of breath. In order to increase the exertion and produce more dyspnea a pack weighing 50 pounds was then put on the subject's back and he again walked sixty steps upstairs in sixty seconds (Period VI), this exercise being immediately followed by two five-

minute periods of observation while standing at rest (Periods VII and VIII). In each experiment the subject had been fasting fourteen hours so that the effect of food on the metabolism was eliminated. The expired air was collected in two 100 liter Tissot spirometers by means of a half-mask fitting tightly over the nose and mouth and connected to the spirometers with rubber tubing of large caliber. The oxygen and carbon dioxid percentages in the expired air were determined by analysis with the Haldane gas analysis apparatus. Duplicate analyses

TABLE 2.—SUMMARY OF EXPERIMENTS ON SUBJECT S. G.

Subject, S. G.: Age, 24 years; weight, 68.9 kg.; height, 171.4 cm.; surface area, 1.80 sq. m.

Experiment A: Vital Capacity = 4,600 C.c.

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{3} \times 35 = 53.7 \text{ liters.}$$

Period	Respiratory Rate	Volume per Respiration		Minute-Volume		Oxygen Consumption, C.c. per Minute	CO_2 Production, C.c. per Minute
		C.c.	Percentage of Vital Capacity	Liters	Percentage of Maximum Minute-Volume		
I. Basal.....	8.9	500	9	4.45	8	241	189
II. Standing at rest 5 minutes	11.2	563	12	6.30	12	278	227
III. Walking 60 steps	19.0	750	16	14.30	27 no dyspnea	794	587
IV. Rest of 5 min.	11.4	765	16	8.74	16	428	358
V. Rest of 5 min.	11.8	537	12	6.35	12	261	222
VI. Walking 60 steps carrying 50 pound pack	23.0	792	17	18.20	34 slight dyspnea	913	744
VII. Rest of 5 min.	13.0	1,120	24	14.56	27	655	629
VIII. Rest of 5 min.	13.0	540	12	7.04	13	271	238

Experiment B. Vital Capacity = 2,100 C.c.

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{3} \times 35 = 24.5 \text{ liters.}$$

I. Basal.....	16.9	353	17	6.15	25	250	201
II. Standing at rest 5 minutes	19.3	386	18	7.44	30	281	225
III. Walking 60 steps	28.0	560	27	15.70	64 moderate dyspnea	826	571
IV. Rest of 5 min.	26.2	515	24	13.50	55	553	452
V. Rest of 5 min.	23.1	435	21	10.00	41	348	304
VI. Walking 60 steps carrying 50 pound pack	28.0	696	33	19.50	80 more marked dyspnea	977	743
VII. Rest of 5 min.	21.0	705	34	14.80	60	566	489
VIII. Rest of 5 min.	20.3	490	23	9.83	40	277	276

were done on samples from each period and the results were not accepted unless they checked within 0.03 per cent. of the average for oxygen and 0.02 per cent. of the average for carbon dioxid. The respiratory rate was determined by means of a pneumograph leading to a tambour which recorded the respiratory movements by means of a lever marking on a smoked drum.

TABLE 3.—Summary of Experiments on Subject F. F-S.

Subject, F. F-S.: Age, 25 years; weight, 72.1 kg.; height, 179.2 cm.; surface area, 1.90 sq. m.

Experiment A: Vital Capacity = 4,200 C.c.

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{3} \times 35 = 49 \text{ liters.}$$

Period	Respiratory Rate	Volume per Respiration		Minute-Volume		Oxygen Consumption, C.c. per Minute	CO_2 Production, C.c. per Minute
		C.c.	Percentage of Vital Capacity	Liters	Percentage of Maximum Minute-Volume		
I. Basal	11.8	313	7	3.69	8	202*	145
II. Standing at rest 5 minutes	14.0	420	10	5.87	12	240	202
III. Walking 60 steps	23.0	687	16	15.80	32 no dyspnea	976	717
IV. Rest of 5 min.	16.0	605	14	9.70	20	438	407
V. Rest of 5 min.	14.0	450	11	6.30	13	261	227
VI. Walking 60 steps carrying 50 pound pack	26.0	705	17	18.30	37 slight dyspnea	1110	859
VII. Rest of 5 min.	16.8	625	15	10.50	21	430	443
VIII. Rest of 5 min.	14.5	457	11	6.63	14	284	245

Experiment B: Vital Capacity = 2,550 C.c.†

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{3} \times 35 = 29.8 \text{ liters.}$$

I. Basal	18.4	302	11	5.57	18	224	186
II. Standing at rest 5 minutes	18.2	381	15	6.94	23	285	225
III. Walking 60 steps	31.0	610	24	18.90	64 moderate dyspnea	1090	752
IV. Rest of 5 min.	23.2	510	20	11.90	40	475	407
V. Rest of 5 min.	18.8	430	17	8.08	27	319	266
VI. Walking 60 steps carrying 50 pound pack	35.0	615	24	21.50	72 more marked dyspnea	1200	882
VII. Rest of 5 min.	27.8	530	21	14.70	50	540	518
VIII. Rest of 5 min.	22.4	375	15	8.40	28	303	248

* There was no apparent reason to account for this subject's abnormally low oxygen consumption. He was an active, alert, fourth year medical student with none of the signs or symptoms suggesting hypothyroidism. His basal metabolism on this occasion was —24 per cent. of normal when compared to the standards of DuBois.

† The vital capacity was 2,700 c.c. in the basal period. In periods II to VIII it was decreased to 2,550 c.c. by tightening the swathe. This alteration results in a theoretical maximum minute-volume of 31.5 liters in the basal period and 29.8 liters thereafter.

ANALYSIS OF RESULTS IN TABLES 2 AND 3

Tables 2 and 3 give the results of the two experiments. In both of them Experiment A was performed while the vital capacity was normal, while in Experiment B the vital capacity was reduced approximately 50 per cent. by means of the swathe. In Experiment A, Table 2, when the subject, S. G., was lying quietly at complete rest he was breathing 4.45 liters of air per minute. His maximum minute-volume, computed according to the formula suggested above, is 53.7 liters, so that during this first period he was breathing only 8 per cent. of his maximum minute-volume. In period III, while walking sixty steps in

sixty seconds, he breathed 14.30 liters per minute, or 27 per cent. of his maximum minute-volume and yet experienced no dyspnea. In Period VI, while walking sixty steps upstairs in a minute and carrying a 50 pound pack on his back, the minute-volume rose to 18.20 liters, or 34 per cent. of his maximum minute-volume and slight shortness of breath was noticed. In Experiment B, Table 2, the vital capacity of the lungs was reduced to 2,100 c.c. in the same subject and the calculated maximum minute-volume was thereby diminished to 24.5 liters. Under these conditions, although the subject was only breathing 6.15 liters per minute in Period I, while lying at complete rest, he was, nevertheless, using 25 per cent. of his maximum minute-volume. In Period III, when walking upstairs, he used 64 per cent. and was moderately dyspneic, and in Period VI, when walking upstairs with a pack, he used 80 per cent. of his maximum minute-volume and had marked dyspnea. In general, therefore, there is a striking correspondence between the degree of subjective dyspnea and the extent to which the maximum minute-volume is encroached upon. The actual minute-volumes in the corresponding exercise periods (Periods III and VI) in the experiments with and without the swathe were not very different but the degree of dyspnea was much greater in the experiment in which the vital capacity was reduced, Experiment B, and in which a larger proportion of the theoretical maximum minute-volume was made use of. Exactly the same relationships are found in the case of subject F. F-S. which are given in Table 3. Here, again, the subjective sensation of dyspnea varied, not with the actual minute-volume breathed, but with the extent of utilization of the maximum minute volume or, to express it in another way, with the decrease in the pulmonary reserve.

In both sets of observations shown in Tables 2 and 3 the oxygen consumption was approximately the same in the corresponding periods of Experiments A and B. There is a general tendency to a slightly higher metabolism in the experiments with reduced vital capacity and this is probably due largely to the discomfort incident to the very tight swathe and to the greater exertion associated with more rapid breathing. The minute-volumes for the corresponding periods are almost uniformly higher in the experiments with reduced vital capacity. This depends on the fact that in order to obtain the volume of alveolar ventilation necessary to meet the needs of the metabolism it was easier to increase the rate of respiration than it was to increase the depth. Under such circumstances the "dead space" of the upper respiratory tract becomes an important factor and the total minute-volume of pulmonary ventilation must be increased in order to produce the same volume of alveolar ventilation.

DISCUSSION

The first observations described were made on twelve normal young men who rode on a stationary bicycle until they were forced to stop on account of complete exhaustion. During the last one and one-half minutes of the ride, when the exercise was most violent and the dyspnea great, the average minute-volume of air breathed was 60.5 liters, or approximately twelve times the average minute-volume of such a group of men when they are lying down at complete rest. These figures give a general indication of the normal pulmonary reserve, by virtue of which the individual is able to increase the pulmonary ventilation and keep it adequate to the needs of the body when the metabolism is raised far above its resting or basal value by severe exercise. An analysis of these high minute-volumes shows that they were obtained by increasing the rate of respiration up to an average maximum of about 35 per minute, and by increasing the depth of each respiration up to a volume which approximates one third of the vital capacity of the lungs. On this basis, it was suggested that the maximum minute-volume which can be maintained for more than a very short period can be calculated in any given instance with an accuracy which is sufficient for practical purposes, by multiplying one-third of the vital capacity of the lungs by 35. Such a calculated or theoretic maximum minute-volume has considerable clinical significance for it tells about how far the person concerned is able to increase his minute-volume, and consequently how great an increase of metabolism he can meet with a pulmonary ventilation which will ensure proper aeration of the blood in the lungs. If the minute-volume of respiration can only be raised to three times the volume that a given subject breathes while at rest, then he will not be able to meet much more than a three-fold increase of metabolism, and he will become dyspneic walking slowly upstairs, but if the minute-volume can be raised to six or seven times above the resting value then the subject will be able to carry on most of the activities of a normal life without subjective dyspnea. The maximum minute-volume calculated in this manner is thus a guide to the amount of physical exertion that any individual may be expected to undertake.

The maximum minute-volume that a person can breathe depends on the rate and depth of the respiration. The observations reported appear to show that the highest rate that is compatible with efficient respiration is about 35 per minute, and practical experience indicates that most persons, whether or not they are in normal condition, can raise their respiration rate to this figure. The important factor in producing variations in the maximum minute-volume is thus the vital capacity of the lungs, which determines the possible depth of breathing. This

is, of course, subject to marked changes in normal, and to a greater extent in pathological conditions.

In the second series of observations reported, two subjects were studied while walking upstairs on a treadmill. One set of experiments on each of them was carried out in the normal state, and one set when the vital capacity was reduced to about one-half by means of a tight chest swathe. The wholly artificial condition this produced is not unlike that in a case of pleurisy with effusion and simulates in some degree other conditions, such as heart disease, in which the vital capacity of the lungs is below normal. The calculated maximum minute-volume was, of course, much less in the experiments with the chest swathe than in those in which the vital capacity was normal and it was found that the tendency to dyspnea varied closely with the percentage of the calculated maximum minute-volume that was being used in respiration. When the minute-volume breathed was only 25 per cent. of the maximum, the subject was not conscious of his respiration; when it was 50 per cent. he noticed that he was breathing deeply, and when it was 75 per cent. of the maximum he was frankly short of breath. These experiments, therefore, are of interest in that they bring out the importance of the conception of the maximum minute-volume of the pulmonary ventilation as one of the factors which determine the occurrence of dyspnea in various clinical conditions. This factor can be easily expressed in a sufficiently accurate quantitative manner and it has a broader physiologic significance than has the determination of the vital capacity of the lungs alone, for the minute-volume of pulmonary ventilation bears a close relationship to those fundamental processes of the body which go to make up what is known as the metabolism. The essential cause of the variations which may occur in the maximum minute-volume is an alteration in the vital capacity of the lungs and this may, therefore, be regarded as a practical index of the maximum minute-volume.

POSITION AND ACTIVITIES OF THE DIAPHRAGM AS AFFECTED BY CHANGES OF POSTURE *

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Most studies of the diaphragm are made with the subject standing, sitting or lying prone or supine. Such consideration ignores the fact that in health, as well as in disease, much time is spent lying on the side, and that the position and activities of this muscle and adjoining organs are greatly changed by shifts of posture. Although the literature is not without more or less detailed reference to these changes, their magnitude and clinical importance are popularly underestimated. As they affect directly physical signs, and as convenience or necessity frequently demands examination of a patient lying on one or the other side, it follows that an understanding of the action of the diaphragm in lateral positions of recumbency possesses an interest of practical value.

The relaxed diaphragm, in health, assumes a height and position dependent on forces exerted from below as well as from above. Recumbent on the back or face, gravity operates on the viscera in such a direction as to affect the diaphragm least. In this position the organ arches high into the chest. When standing or sitting, gravity comes into action on the thoracic organs above and the abdominal viscera below in such a manner as to push and draw the diaphragm downward. Its level is lower in the sitting position because of relaxed abdominal walls and consequent opportunity offered the viscera to sag forward as well as downward.

While a number of normal subjects form the basis of this discussion, in order to reduce the problem to its simplest terms, effort has been made to present an average specimen. Such a process is not without acknowledged error, in that wide variations from a so-called average present themselves. However, as variations in different types, in respect to the points under discussion, are of degree rather than kind, the error is not of a serious nature.

In our studies of normal chests, a fixed point, arbitrarily selected on the first lumbar vertebra, has been utilized. Variations in height of the diaphragm are measured on a line drawn from this point parallel

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to the vertebral column. In a state of normal inspiration, the distances above the marker of the right and left domes respectively are:

Standing: 6.5 and 5 cm.
Sitting: 5.5 and 3 cm.
Prone on abdomen: 12 and 9 cm.

It is thus seen that the right dome is 5.5 cm. and the left dome 6 cm. higher when the subject is reclining than when he is sitting. In all three positions, the excursion during normal, mixed breathing is about equal on the two sides and varies from 1.5 to 2.5 cm. in extent.

With assumption of the right prone position, the upper or left leaf of the diaphragm descends, opening to a considerable extent the left costophrenic angle, while the dependent or right leaf takes a higher level, at the same time increasing the extent of costophrenic contact. During quiet breathing, the excursion of the dependent half of the muscle is greater than that of the upper, the ratio being approximately 2 to 1. Recumbency on the left side reverses conditions, the right half of the diaphragm assuming a lower level, and exhibiting less excursion than the dependent left half. The explanation of these changes is simple on a purely mechanical basis. Both thoracic and abdominal viscera, especially the latter, because of their great weight and mobility, sag toward the dependent side, thus opening the upper costophrenic angle and straightening the upper diaphragm. In this position, the effect of equal contraction of the halves of the muscle will differ on the two sides. The dependent half, being highly arched, will descend, whereas the upper, approaching more nearly a plane, will tend rather to antagonize the intercostal muscles. In other words, the upper half works to a better mechanical, but poorer respiratory advantage than does the dependent half.

NEIGHBORING ORGANS

The effects of lateral recumbency on the positions and activities of adjacent organs are manifold. However, we here confine our remarks to three, namely: (1) the position of the heart; (2) marginal sounds or râles; (3) breath sounds at the bases.

1. The Heart.—In all positions the roentgenograms on which our results are based were taken at a distance of five feet from the plate. By actual measurements the dimensions of the negative do not vary more than 1 cm. from those of the subject, so that errors in detail are comparatively slight. The cardiac shifts in position are noted in figures which represent the distance of the apex from the midline of the spine. In some instances, the apex is near to or remote from the spine because of lateral tilting of the cardiac axis. In others, a

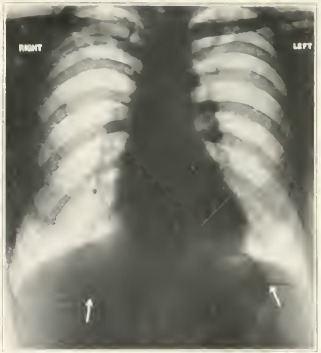

Fig. 1.—Subject sitting, end of normal inspiration, showing low position of diaphragm.

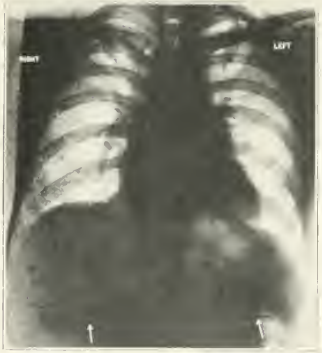

Fig. 2.—Same subject lying prone on abdomen, end of normal inspiration. Note high position of diaphragm.

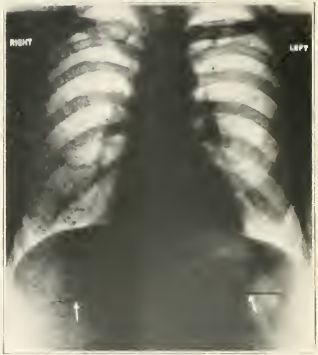

Fig. 3.—Same subject standing, showing position of diaphragm intermediate between Figs. 1 and 2.

Note: The "marker" shown in all of the photographs consists of a flexible wire, held in position by adhesive tape, at the level of the top of the first lumbar vertebra.

sagging mediastinum allows the entire cardia to fall toward the dependent side. Rotation is a third factor in the production of variations in heart shadow. Finally, two or more of these factors may be found combined.

The distance of the apex from the midline, in the average chest used for detailed illustration, in the sitting position is 8 cm.; prone on the abdomen, it is 10; both measurements taken at the end of a normal inspiration, a difference of 2 cm. effected by simple shift from a vertical to horizontal plane.

At the end of normal expiration, with the subject on the right side, the apex is 6 cm. from the midline. At the same respiratory phase, prone on the left, it is 12.3 cm., a total difference, allowing for slight error of oblique rays of about 6 cm. The difference in the same positions, at the end of full inspiration is much less marked, being only 1.5 cm. This is as one would naturally expect because of the firm pericardiophrenic attachment and the consequent straightening of the mediastinum incidental to descent of the diaphragm.

The distance of the left border of the heart from the midline at the end of normal inspiration, with the subject standing, is 8.5 cm., sitting, 8 cm.; prone on abdomen, 10 cm.; recumbent on the right side, 6.5 cm.; prone on left side, 11.7 cm. That is to say, with the ascension of the diaphragm consequent to a change from the vertical to horizontal position on the abdomen, the apex shifts to the left a distance of from 1.5 to 2 cm. Turning on the left side produces a further movement to the left of a little over 1.5 cm., while recumbency on the right side is accompanied by a shift to the right of 3.5 cm. The left border, then, in the right prone position, is only from 1.5 to 2 cm. to the right of the point which it occupied in the upright position, whereas prone on the left side it is removed from this point by a distance about twice as great. However, the subject having assumed a recumbent position may accomplish a greater cardiac shift by turning upon the right side than by turning to the left.

2. *Marginal Sounds.*—By the term marginal sounds we refer to that group of sounds which is heard over the base of the lung during deep inspiration. They vary in different individuals from dry crepitations or crackles to sounds resembling fine or medium size moist râles. Such sounds may be elicited in almost any normal individual capable of abdominal breathing. They are heard over the edge of descending lung and therefore assume the form of a wave rather than of a fixed line. The vertical length of this wave depends upon the extent of the complimental space and the ability of the individual to obliterate this space by diaphragmatic contraction. It is greatest in the axilla, tapering to a narrower area at the spine behind and ensiform cartilage in front.

Positions of recumbency are especially favorable to the production of marginal sounds because of the high position of the diaphragm and consequent increase in the complimental space. Right lateral recumbency further increasing the right complimental space, amplifies the extent of marginal sounds on the right side. At the same time, by opening the left space, this position diminishes or obliterates the sounds on the upper side. Reversal of position, reverses conditions. The sounds may be produced or dissipated at will by having the subject lie upon one or the other side.

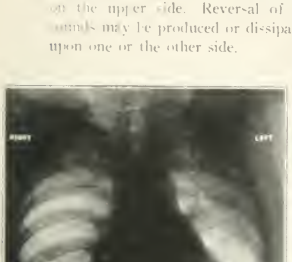

Fig. 4.—Prone on left side, end of normal respiration. Diaphragm high on left side, right costophrenic angle widely open, heart outline far to left

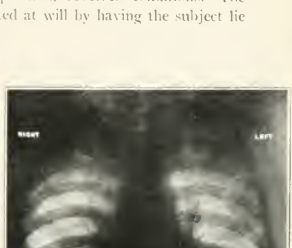

Fig. 5.—Same subject prone on left side, end of full inspiration. Diaphragm levels equal on two sides and heart occupying slight left position.

Note: Showing wide excursion of dependent left diaphragm and wide extent of separation from parietal pleura corresponding to area of marginal sounds on the dependent side. Note the change in axes of heart and position of apex.

(Because of the necessity for economy in reproduction of photographs, the illustrations in the corresponding respiratory phases with the subject prone on the right side, are omitted. Reversal of position however, produces a corresponding reversal of position of the organs. With deep inspiration, there is a corresponding wide excursion of the dependent diaphragm, accompanied with a cardiac shift toward the left.)

The tendency of an individual in deep breathing is always toward over inflation, so that after a number of inspirations the diaphragm becomes for awhile established at a lower level. Its excursion is thereby considerably curtailed and marginal sounds disappear, to recur

only after rest sufficient to permit the lung elasticity to reassert itself. This situation does not arise, or it may be obviated, when the subject instinctively, or as a result of instruction, forcibly exhales sufficiently to prevent over inflation.

In explaining the occurrence of marginal sounds, it is necessary to bear in mind the fact that at their point of audibility, three events are transpiring. The phrenic pleura is separating from the costal; the visceral pleura is gliding downward to replace the phrenic, and finally, air is entering the margins of the lungs.

That the second of these phenomena is not productive of marginal sounds may be assumed from the fact that viscerocostal friction is elsewhere inaudible in the chest. Moreover, marginal sounds are heard only during inspiration.

The view most generally accepted is based on inflation of the marginal air spaces, a theory dependent on complete or incomplete atalectasis of the lung. There are serious objections to such an explanation. In the first place, marginal sounds are heard in almost any normal subject capable of deep breathing. They may be repeatedly dissipated or produced at will by over inflation or strong deflation of the lung. They may likewise be made to appear and disappear by changes of position in lateral decubitus. Most convincing of all is the fact that they occur over a moving line keeping pace with Litten's Shadow and corresponding, not only to the downward moving margin of the lung, but also to the line of cleavage of the diaphragmatic from the parietal pleura.

Explanation for the production of marginal sounds based on separation of the phrenic from the parietal pleura is provided for in two ways. In the first place, other explanations, under close scrutiny, fail to withstand criticism. In the second place, the "peeling off" of the diaphragm from the costal pleura contributes a mechanism unique in pleural contact and, at least, theoretically satisfying. Further, it has been found that varying conditions of moisture and dryness of the pleural surfaces bear a direct relation to the quality and intensity of marginal sounds.

The points we wish to emphasize in connection with marginal râles are: (1) They may be elicited in the normal subject. (2) They are a tribute to the mobility of the diaphragm. (3) They are reversible in position and extent. (4) They are audible at the point of cleavage of the diaphragm from the chest wall and may therefore be heard early or late in deep inspiration according as one listens at the top or bottom of the costophrenic space.

3. Breath Sounds at the Bases.—Auscultation of the back from the seventh vertebra to the base, with the subject prone on the side,

reveals a more intense respiratory murmur on the dependent side. The difference is more marked in the expiratory than in the inspiratory phase. Relative intensification of breath sounds on the lower side is due to two factors; first, the more active ventilation of the lower part of this lung as revealed by the greater diaphragmatic excursion. In the second place, the relative compression and actual relaxation of the lower side furnish conditions favorable to better transmission of sound.

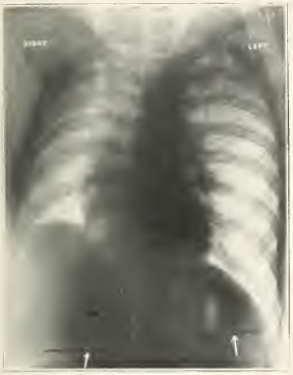

Fig. 6.—Subject prone on right side, end of normal inspiration. Showing high position of right dome of diaphragm, low position of left dome, also wide cardiac and mediastinal shadow to right of vertebral column.

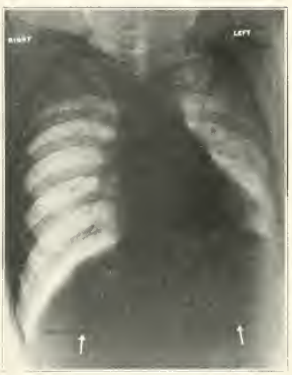

Fig. 7.—Same subject prone on left side, end of normal inspiration. Showing high position of left dome and low position of right. Little cardiac and mediastinal shadow seen to right of vertebral column.

Note the vast difference in levels of diaphragm and position of heart produced by turning from right to left prone position.

Inasmuch as the inspiratory murmur is produced close to the ear, while the expiratory sound is initiated at a point remote from the surface of the lung, it follows that in the inspiratory phase, ventilation is the more important agent, whereas in expiration, conduction probably plays a great rôle in augmenting sounds on the lower side. Accompanying intensification of the breath sounds just referred to, there is an increased intensity of the whispered sound, spoken word and of tactile fremitus.

SUMMARY

To summarize: The diaphragm is highest in the prone position; intermediate, with the subject standing erect; lowest in the sitting posture. Its excursion in these positions is equal on the two sides. Prone on the right side, the right dome is higher than the left and its excursion is in excess in the proportion of 2:1. Reversal of position, reverses the height and excursion of the two sides.

The position of the heart, accompanying changes in position of the diaphragm, is subject to a wide range. The extreme excursion is 6 cm.

Marginal sounds are heard over the healthy lung and are not incidental to or dependent upon pathology in the lung or pleura. They are heard over a broad area on the dependent side in lateral decubitus because of the greater extent of the complimental space. These sounds are heard best during vigorous inspiration following forceful expiration.

In lateral recumbency, the dependent lung is relatively relaxed. Its diaphragmatic ventilation is in excess of that of the upper lung. Breath, voice and whisper sounds and tactile fremitus are all increased as compared with the opposite side.[1]

1. Bushnell, George E.: Some Extra Pulmonary Sounds Which Simulate Râles, Med. Rec. (Jan. 20) 1912, Vol. 81, Page 101-107 inc.; Marginal Sounds in the Diagnosis of Pulmonary Tuberculosis, Med. Rec. (Dec. 21) 1912, Vol. 82, Page 1106.

Gerhardt: Auskultation und Perkussion.

Hoover, C. F.: The Functions of the Diaphragm and their Diagnostic Significance, Arch. Int. Med. **12**:214 (Aug.) 1913.

Morrison: Lancet **1**: (May 6) 1911, Page 1202.

AURICULOVENTRICULAR RHYTHM AND DIGITALIS*

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Auriculoventricular rhythm, a condition in which the A-V node assumes rhythmicity independent of the sinus node, is due to one of two causes; depressed irritability of the sinus node or enhanced irritability of the A-V node. Experimentally both types have been produced, the former by tying off (Engelmann [1]), injuring (Hering [2]), or cooling (Ganter and Zahn [3]) the sinus node, the latter by stimulating the A-V node either directly (Lohmann [4]) or through the left accelerator (Hering;[5] Rothberger and Winterberg [6]). Meek and Eyster [7] reviewed and extended the experimental work. By means of electrodes connected with a string galvanometer and applied direct to the heart they obtained evidence that in A-V rhythm the electrical activity originates in the A-V node.

Clinically, both types of the A-V rhythm have been observed, the type in which the irritability of the sinus node is depressed, characterized by a slow rhythm, and the type in which the irritability of the A-V node is enhanced, characterized by a relatively rapid rhythm. The former, though rare, is much the more common of the two. White [8] distinguishes further between A-V rhythm and simple ventricular escape. In the former the excitation wave arises from the A-V node alone, in the latter from both nodes simultaneously. He bases the distinction on the form of the P wave which is known to be inverted or upright according as the excitation wave arises near the A-V node or near the sinus node. A-V rhythm is, therefore, characterized by an inverted P wave, simple ventricular escape by an upright P wave. Of the two conditions A-V rhythm is much the more permanent.

The accompanying table indicates the variety of the conditions in which A-V rhythm occurs, together with the outcome of the cases. No death occurred as a result of A-V rhythm alone. In the fatal cases the postmortem examination revealed ample causes for death

*From the Cardiovascular Service of the Presbyterian Hospital.

1. Engelmann, Th. W.: Arch. f. Anat. u. Physiol. Physiol. Abth., 505, 1903.
2. Hering, H. E.: Arch. f. d. ges. Physiol. **136**:466. 1910.
3. Ganter, G., and Zahn, A.: Arch. f. d. ges. Physiol. **145**:335, 1912.
4. Lohmann, A.: Arch. f. Anat. u. Physiol., Physiol. Abth., 431, 1904.
5. Hering, H. E.: Zentralbl. f. physiol. **19**:129 (June) 1905.
6. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. **135**:559. 1910.
7. Meek, W. J., and Eyster, J. A. E.: Heart **5**:227. 1913.
8. White, P. D.: Arch. Int. Med. **18**:244 (Sept.) 1916.

quite apart from the A-V rhythm. In the other cases the arrhythmia was either transient or relatively short, with one exception, the case of Williams and James,[9] in which it was observed for fourteen months. During this period the patient improved. It is evident, therefore, that in and by itself A-V rhythm is not dangerous to life. When associated with severe infections or cardiac disease it is the associated disease which determines the prognosis.

The case reported here is of especial interest in view of its relation to digitalis. Such a relation has been reported but rarely. Norrie and Bastedo[10] observed it in a case of heart-block following the administration of digitalis. Cohn and Fraser,[11] also Cohn[12] give a clear description of A-V rhythm as an effect of digitalis. White[13] observed it in a case of auricular flutter in which the administration of digitalis was followed first, as expected, by auricular fibrillation and then by A-V rhythm instead of normal rhythm. Later[8] he recorded two cases of A-V rhythm following digitalis, the first a slow rhythm arising, in part at least, from depression of the sino-auricular node, the second a more rapid rhythm resulting from irritation of the A-V node. Eggleston[14] mentions A-V rhythm as one of the toxic effects of digitalis.

REPORT OF CASE

History.—A woman, aged 47, housewife, was first admitted to the Presbyterian Hospital, March 10, 1920. Her father and mother had died aged 35 and 25, respectively, and four of her brothers and sisters had died in infancy. Marital history included one miscarriage and two stillbirths. At the age of 18 she had an attack of acute arthritis in the left knee. Her symptoms began four weeks prior to admission and consisted of epigastric pain radiating to the left arm, dyspnea and edema.

Physical Examination.—This revealed cyanosis, emaciation and dyspnea. The heart was enlarged and a blowing systolic murmur was heard at the apex. Signs of a moderate amount of fluid in the right chest were present, together with congestion at the bases of the lungs. The liver was much enlarged and there was moderate edema. Blood pressure: 150/98. The roentgenogram showed a cardiac shadow extending 6 cm. to the right and 9.75 cm. to the left of the midline.

The blood Wassermann was negative. Blood urea was 0.78 gm. per liter; phthalein excretion, 19 per cent.

Clinical Diagnosis.—Chronic cardiac valvular disease; mitral insufficiency; cardiac insufficiency; caries of teeth.

Treatment.—She received 45 minims of the tincture of digitalis daily from March 17 to March 25.

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9. Williams, H. B., and James, H.: Heart **5**:109, 1913.

10. Norrie and Bastedo: St. Luke's Hospital, New York M. & S. Rep. No. 2, p. 101.

11. Cohn and Fraser: Internat. Med. Congr., Sec. 6, Pt. 2, p. 258, 1913.

12. Cohn, A. E.: J. A. M. A. **65**:1527 (Oct. 30) 1915.

13. White, P. D.: Arch. Int. Med. **16**:517 (Oct.) 1915.

14. Eggleston, Cary: Am. J. M. Sc. **160**:625, 1920.

Clinical Course.—She was readmitted May 12, 1920, after rapid return of decompensation. Physical signs were essentially the same, cardiac borders somewhat wider but liver not palpable. An irregularity of the pulse was noted. Blood pressure: systolic, 180; diastolic, 120. To the previous diagnosis were added hypertension and chronic nephritis. She was admitted for the third time September 3. For a while she improved gradually, but then developed ascites and was twice tapped. She died October 7 of pneumonia.

In taking the graphic records the galvanometer was standardized so that the introduction of 1 millivolt of current caused a deflection of the string 1 cm.

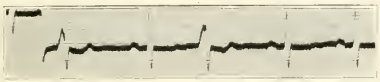

Fig. 1.—May 14, 1920. Lead I. Control record taken before administration of digitalis. Sequential rhythm. P-R interval 0.18. Rate = 80. Two ventricular extrasystoles recorded. Time, 1/25 sec.

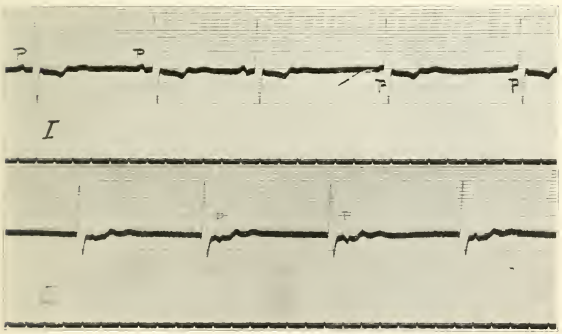

Fig. 2.—June 1, 1920. Lead I. Transition from sino-auricular to A-V rhythm. Lead II. A-V rhythm fully developed. P-R interval has changed from + 0.18 to — 0.18. Rate, 43.5.

The electrocardiograms taken on the first admission were essentially the same as shown in Figure 1. At this time the effect of digitalis was limited to minor changes in the T wave. On the second admission, the effect of digitalis was quite different. Figure 1 presents the control record taken on the third day. The P wave precedes the R wave

by a normal interval of 0.18 seconds, indicating a sequential rhythm, that is, one in which the pacemaker is located in the sinus node. P is of normal contour except that it is inverted in the third lead. The Q. R. S. complex is essentially normal except for a deep notch in Lead III. Frequent extra systoles occur. Digitalis was then given in the form of the tincture, 30 minims a day for five days, and 20 minims a day for two days. Figure 2 is the curve recorded just after cessation of digitalis. It is characterized by a marked bradycardia and a striking variability in the time relation of the P and R waves. Reading from left to right the P wave gradually approaches the R wave until it merges with it. This change is associated with a decrease in rate from 48 to 43. In Lead II the change of the position of P has continued until P appears after R. This wave is a clear example of auriculoventricular or nodal rhythm.

On the third admission no record was taken until after a course of digitalis consisting of 2 c. c. digifolin and 172 minims of the tincture in the course of eight days. This record (Fig. 3) shows essentially the same mechanism as Figure 2; bradycardia and A-V rhythm. Two days later only a single delayed nodal beat was recorded (Fig. 4); sequential rhythm otherwise present, though with a marked variation in shape and rate of P wave. One week later an occasional delayed nodal or A-V beat was recorded and two weeks later a reversion to a more rapid sequential rhythm with occasional extrosystoles of ventricular origin (Fig. 5).

There can be little doubt that the mechanism represented by Figures 2 and 3 is that of A-V rhythm. A possibility to be ruled out is A-V block with complete dissociation. In this case the auricular wave must appear sooner or later in the middle of diastole. This it failed to do in any of the several curves in which A-V rhythm was recorded. It is conceivable also that the abnormal P wave belongs to the following ventricular complex, in other words that there is a P-R interval of over a second. Such a delay in conduction without block is hardly probable.

The gradual transition from normal to A-V rhythm is puzzling. Two explanations have been advanced. According to the first the transition represents a stage during which both nodes are active. The auricle, receiving its stimulus from the sinus node, contracts in the normal way and its contraction is recorded as an upright P wave. The stimulus arising from the A-V node activates the ventricle prematurely. Hence the combination of an upright P wave and a diminished P-R interval. According to the second explanation the pace-maker simply migrates first to the auricular end of the A-V node and then gradually downward through this structure. As most of the delay in conduction takes place in the A-V node this migration is accompanied by all the

changes from positive to negative P-R interval. The auricle, receiving its stimulus from below, would be expected to contract in such a manner as to produce an inverted P wave. Ganter and Zahn [3] and Lewis [15] favor the former explanation, Hering,[2] Weil [16] and Meek and Eyster [7] the latter. In the present case the fact that the P wave remains upright throughout the transition tends to favor the hypothesis of an interference between two nodes, both active.

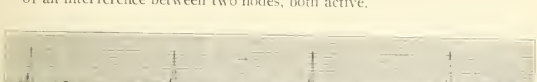

Fig. 3.—Sept. 14, 1920. Lead III. A-V rhythm. P wave merged with ventricular complex. Rate = 38.3.

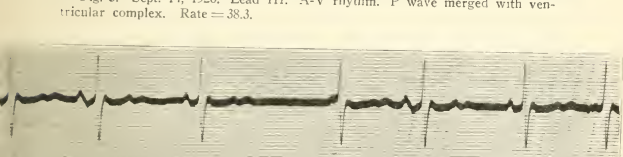

Fig. 4.—Sept. 16, 1920. Lead I. Delayed nodal beat at ×. Sinus arrhythmia. Unexplained variation is form of P wave. Rate = 53.9.

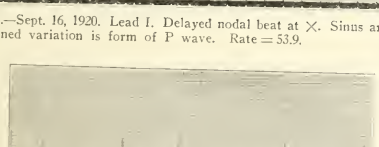

Fig. 5.—Sept. 28, 1920. Lead III. Sequential rhythm. Rate = 67.5. PR = 0.18. One ventricular extrasystole shown. (The inverted P wave was present in the third lead in all records and is of no apparent significance.)

Extracts from the Protocol of the Postmortem Examination.—Necropsy 9075; Dr. Von Glahn: Abdominal cavity 1,000 c.c. clear fluid.

Heart: The pericardial cavity does not contain an excess of fluid. The pericardium is slightly adherent to the anterior surface of the heart by delicate tendinous adhesions. There is a large tendinous patch on the anterior surface of the right ventricle and the vessels of the heart are engorged. The

15. Lewis, T.: Heart **5**:247, 1913.
16. Weil, A.: Deutsch. Arch. f. klin. med. **116**:486, 1914.

epicardium over the right auricle is roughened and the auricle is greatly distended. The heart weighs 420 gm. The right auricle contains postmortem clot and in the appendage and clinging to the wall of the auricle are antemortem thrombi. Just at the opening of the superior vena cava in the auricle the endocardium is quite thickened and opaque over an area about 2 cm. in its greatest diameter. There is also some thickening of the intima of the cava at this point. The foramen ovale is closed. The tricuspid valve shows a little thickening of the cusps but it is quite flexible. The columnae carnae stand out quite prominently. There are seen beneath the endocardium a few yellow areas which appear fatty. The pulmonic valve is thin and delicate. The left auricle contains only postmortem clot. The endocardium is slightly thickened over the entire auricle. The mitral valve leaflets are slightly thickened, but flexible. At the apex of the left ventricle are a few small grayish red thrombi which have softened centers. These are adherent to the wall of the ventricle, in the spaces between the columnae carnae. On the anterior and left posterior leaflets of the aortic valve are small clumps of gray translucent vegetations which break off readily. They are situated over the corpus aurantii. The coronary arteries show a few yellow fatty plaques, without calcification or obvious stenosis of the lumen. The myocardium is grayish red in color with here and there lighter areas due to connective tissue.

Anatomic Diagnosis.—Scars of endocardium of right auricle; cardiac hypertrophy; fibrous myocarditis; acute cardiac valvular disease, aortic; thrombi in right auricular appendage and left ventricle; chronic passive congestion of liver and spleen; ascites; chronic diffuse nephritis; confluent lobular pneumonia; acute fibrinous plenrisy; acute fibrinous pericarditis; arteriosclerosis, slight.

Microscopic Examination.—Serial sections of the sinus and A-V nodes together with the bundle of His and a portion of the branches were made and examined by myself. The sections were from 15 to 17 microns in thickness and every fifth one was examined. The sinus node was situated between superior and inferior vena cava, about 2 cm. from the orifice of the former. It was situated in a sulcus just beneath the endocardium. It measured 5.1 by 10 mm. and was about 1.5 mm. deep. The muscle cells of the node appeared normal. The connective tissue stroma comprised usually about one third, sometimes about one half of the nodal tissue. This amount does not appear in excess of normal. The arteries showed no sclerosis. Beneath the epicardium was a layer of fat infiltrated in the region of the node with cells of which a majority were lymphoid, the rest polymorphonuclear. The infiltration did not extend into the node. Microscopical examination of the sinus node therefore revealed no abnormality except a subendocardial infiltration which did not extend to the node itself.

The auriculoventricular node was found in the auricular tissue near the septal cusp of the mitral valve. It appeared normal as to condition of muscle fibers, arteries and proportion of connective tissue. Its greatest length was 17 mm., greatest width 7.5 mm., and depth 1 mm. The stem showed no abnormalities. The right and left branches were traced continuously to a point 10.5 mm. below the beginning of the node. No abnormalities were found.

As to the cause of the A-V rhythm, three possibilities must be considered: first, an organic lesion in the conduction system; second, an endogenous factor which failed to produce demonstrable pathologic lesions, and third, digitalis. The first was ruled out by the examination of serial sections. The second remains a possibility, though an unlikely one. Arrhythmias, heart block, for instance, can occur without digitalis or pathologic lesions, but the absence of the latter markedly diminishes the probability of an endogenous cause. In the third case, the relation

CLINICAL COURSE OF AURICULOVENTRICULAR RHYTHM

Observer	Diagnosis or Pathology	Outcome	Cause of Death
Belski (9)	(1) Acute rheumatic fever.....	Recovery	
	(2) Typhoid fever.....	Recovery, arrhythmia for 23 days	
	(3) Acute rheumatic fever.....	Lasted 1 day	
	(4) Scarlet fever.....	Recovery, arrhythmia lasted 4 weeks	
		lasted 2 days	
	(5) Acute rheumatic fever.....	Recovery, arrhythmia	
Cowan, Fleming and Kennedy (10)	(1) Acute ulcerative endocarditis; profound inflammatory disturbance in A-V node	Died.....	Endocarditis; pneumonia
	(2) Acute endocarditis; acute inflammatory process involving A-V node	Died.....	Endocarditis
	(3) Acute endocarditis; subacute pericarditis; infiltration of A-V bundle and node	Died.....	Endocarditis; pericarditis
Williams and James (11)	Cardiac arrhythmia; A-V rhythm	Duration 1 year; improved	
Hume (12)	(1) Diphtheria, bronchopneumonia, pleural effusion; A-V node normal	Died.....	Diphtheria; bronchopneumonia; pleural effusion
	(2) Diphtheria, S-A node the seat of an acute inflammation	Died.....	Diphtheria
Weil (13)	(1) Carcinoma of stomach; pericarditis; arteriosclerosis of branch of coronary leading to region of sinus	Died.....	Carcinoma of stomach; pericarditis; arteriosclerosis
	(2) Syphilitic aortitis; thrombosis of left coronary artery	Died.....	Aortitis; aneurysm
	(3) Acute rheumatic fever.....	Discharged from hospital after 11 days	
White (15)	Auricular flutter; auricular fibrillation; A-V rhythm	Discharged from hospital 19 days after admission	
Laslett (15)	Malaise and pain in hip.....	Recovered after few days	
Neuhof (16)	Rheumatic fever.....	Left hospital after 12 days	
Fussell and Wolferth (17)	A-V rhythm; paroxysmal tachycardia	Died.....	Cardiac decompensation
Presbyterian Hospital 46935	Chronic myocarditis; cardiac insufficiency; cardiac arrhythmia; hypertension	Discharged improved after 5 weeks	
Presbyterian Hospital 45232	Acute rheumatic fever; acute rheumatic endocarditis; chronic cardiac valvular disease; mitral insufficiency and stenosis; A-V rhythm resulting in incomplete A-V dissociation with ventricular rate in excess of auricular	Discharged from hospital after 1 month, recovered from acute illness; electrocardiogram normal 1 month after discharge	

between the administration of digitalis and the onset of the A-V rhythm is so striking as to point with considerable emphasis to this last explanation. Electrocardiograms demonstrated sinus rhythm prior to a course of digitalis medication and A-V rhythm just after it; on another occasion A-V rhythm just after a course of digitalis and sinus rhythm after the effect had worn off. The clinical and pathologic observations combine to indicate a causal relation between digitalis and A-V rhythm.

In neither of our cases did stimulation or depression of the vagus nerve by pressure on the vagus nerve and atrophin, respectively, produce any definite effect. This is in accord with the findings of several other observers on the more permanent type of A-V rhythm, and would seem to indicate that the region affected lies within the heart rather than in the extrinsic cardiac nerves.[17]

SUMMARY

Auriculoventricular rhythm is not in itself fatal, but is frequently associated with severe infections or severe acute and chronic cardiac disease.

A case is described in which clinical and pathologic observations combined to indicate a causal relation between the administration of digitalis and auriculoventricular rhythm.

I wish to take the opportunity of expressing my thanks to Drs. T. Stuart Hart and Dr. Warfield T. Longcope for their helpful interest in the work, and to Miss Rose Richter for her advice and cooperation in the preparation of sections.

17. The following references also bear on this subject:
Belski, A.: Ztschr. f. klin. Med. **67**:515, 1909.
Cowan, J.; Fleming, G. B., and Kennedy, A. M.: Lancet **1**:277, 1912.
Hume, W. E.: Heart **5**:25, 1913.
Laslett, E. E.: Heart **6**:81, 1915.
Neuhof, S.: Arch. Int. Med. **15**:169 (Feb.) 1915.
Fussell, M. H., and Wolferth, C. C.: Arch. Int. Med. **26**:192 (Aug.) 1920.

A CASE OF DISSEMINATED MILIARY TUBERCULOSIS IN A STILL-BORN FETUS*

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Every layman knows that tuberculosis tends to cling to families. "The consumptive," says Hippocrates, "is born of a consumptive," and the search for an explanation of this fact has long engaged general interest. The earliest and most obvious explanation assumed an hereditary transmission, but the notion of an inherited tuberculosis, in a mendelian sense, could not, of course, survive the discovery of the cause of the disease. Other notions which have enjoyed more or less vogue at various times are, for example (*a*), germinal transmission by ovum or spermatozoon, such as is known to occur in silkworm pebrine. A certain amount of experimental evidence (which will be discussed in some detail later), supports this view, but the theory is open to criticism on various grounds, among others, that tuberculous infection of either germ cell would probably render it incapable of function, or, at least, lead to the early death of the embryo. (*b*) It is often said that the individual inherits not the disease itself, but a special predisposition to it. But this assumed predisposition has remained so vaguely defined as to represent little more than a form of words. If it is supposed to be a definite mendelian character, it is open to the same objection as the theory of hereditary transmission of the disease itself, and if it is assumed to be specific it runs counter to all we know about immunity; for immune bodies or toxins which might find their way from the maternal into the fetal circulation, would serve to protect the child, by conferring passive immunity or stimulating the production of an active immunity, respectively, unless, indeed, we are ready to believe that every infection is an anaphylactic phenomenon. Only if aggressins alone of the tubercle baccillus should be absorbed by the fetus would there be a specific lowering of resistance to the disease. These, being foreign substances, would tend to be eliminated very rapidly after birth. Moreover, the selective absorption of aggressins alone would probably be the rarest of occurrences. For example, Coca [1] found that anaphylactic sensitiveness is not inheritable in the true sense; but the mother may transmit specific antibodies from her blood to that of the fetus through the placenta. Krause [1a] observed

* From the Henry S. Denison Research Laboratories and the Department of Pathology, University of Colorado School of Medicine.

1. Coca: J. Immunol. **5**:363, 1920.

1a. Krause: Johns Hopkins Hosp. Bull. **22**:250, 1911.

that such maternal transmission occurs, but is always more or less irregular and inconstant, and the amount of immunity decreases with age and weight of the animal; the "inheritance" is probably always one of antibodies. Finally, if the predisposition is merely a nonspecific condition of lowered resistance, it flies in the face of daily experience. Such patients react to other infections just as those normally constituted, and often exhibit marked physical and mental vigor. The stigmata of the tuberculosis candidate can be explained more rationally by regarding them as interferences with growth due to an accomplished infection rather than as earmarks of an inherited constitutional inferiority predisposing to a later infection. (*c*) Probably the most widely accepted notion is that the child of a consumptive family inherits neither the disease itself, nor any peculiar tendency to it, but merely an increased exposure to infection. There is little doubt that this is the effective factor in many cases. (*d*) There is, however, one other possibility, which forms the topic of the present discussion, viz., that the child inherits the disease not in a mendelian sense, but in the sense that constitutional syphilis is inherited; that is, it is infected during intrauterine life. Such infection, in the case of syphilis, we regard as a universal law, in tuberculosis we regard it as rare. Whatever disparity exists (and the disparity, we are inclined to believe, is not so great as is generally thought to be the case), may be explained as being due to the markedly greater invasive tendency of syphilis.

These several explanations of the origin of familial tuberculosis are discussed at greater length, but in the same general tenor, by Sitzenfrey [2] and by Péhu and Chalier.[3]

We are not concerned, in this paper, with minutiae of pathologic anatomy and histogenesis, but only with the epidemiologic, or, as Warthin and Cowie [4] so aptly express it, the sociologic and eugenic significance of prenatal tuberculosis. The cases are now so many that a detailed enumeration of them has become, in a sense, of as little practical importance as such an enumeration of appendicitis cases would be. We have been content to collect without distinction as to source, the cases listed in the bibliographies of Warthin and Cowie,[4] Sitzenfrey,[2] Péhu and Chalier,[5] Lanz,[6] Weber [7] and Chomé,[8] care being taken to eliminate duplicates. The distinction drawn by all previous writers between authentic and non-authentic cases, we have adhered to as

2. Sitzenfrey: Die Lehre von der kongenitaler Tuberkulose, etc., Berlin, 1909.
3. Péhu et Chalier: Arch. d. Méd. d. enf. **18**:1, 1915.
4. Warthin and Cowie: J. Infect. Dis. **1**:140, 1904.
5. Péhu et Chalier: Arch. d. méd. d. enf. **11**:1, 100, 1908; **17**:921, 1914.
6. Lanz: Arch. f. Gynäk. **104**:214, 1915.
7. Weber: Brit. J. Child. Dis. **13**:321, 359, 1916.
8. Chomé: Arch. mens. d'obstr. et de gynéc, Paris **7**:294, 1918.

closely as possible, in view of the fact that, naturally enough, there is no general agreement as to certain of the cases. The four or five cases listed by Warthin and Cowie in the doubtful class, as "probable" or "very probable" we have placed in the list of cases accepted as genuine (where, indeed, they are also listed by others), in the conviction that a truer notion of the actual situation is thus gained. To the total thus obtained we add with greater detail the small number we have found, not included in any of the lists above mentioned, and our own case.

List of Published Cases of Prenatal Tuberculosis

	Authentic	Doubtful
Congenital tuberculosis of fetus and placenta	38	509
Tubercle bacilli but no histologic changes:		
Fetus and placenta	21	10
Fetus only	3	...
Same in fetus with histologic tubercle in placenta	4	...
Tuberculosis of placenta, with bacilli and histologic tubercle	44	...
Bacilli but no histologic tubercle, placenta only	3	...
Total	113	519

To this total of 113 authentic and 519 more or less doubtful cases of prenatal tuberculosis we have been able to add a number of cases.

Leuenberger [9] reports two cases. In the first, the mother suffering from an old tuberculosis of the kidney, ureter and bladder died of acute miliary tuberculosis and tuberculous meningitis in the eighth or ninth month of pregnancy. The placenta showed no macroscopic evidence of tuberculosis, but in sections there were found many typical tubercles, uniform in size and smaller than those in the maternal organs. Tubercle bacilli were found by direct examination in the capillaries of the fetal liver, but there were no histologic tubercles. Guinea-pig inoculation tests of the fetal blood and liver gave positive results. In the second case, the mother died of cavernous consumption following spontaneous abortion. Bacilli but no histologic tubercles were found in the fetal liver. Guinea-pig tests of the fetal blood were positive; of the fetal liver, negative. The placenta likewise contained no histologic tubercles, but bacilli were found in the intervillous spaces, especially at the edges of the white infarcts. A very few bacilli could be traced through the wall into the capillaries of the villi.

Sugai and Monobe,[10] using direct search in sections, found tubercle bacilli in three out of seven placentas from tuberculous mothers. (By the same method they found leprosy bacilli in all of twelve placentas from leprous mothers).

9. Leuenberger: Beitr. z. Geburtsh. u. Gynäk. **15**:456, 1910.
10. Sugai and Monobe: Zentralbl. f. Bakteriol. Orig. **67**:232, 1912.

Chomé [8] reports the case of a mother who died of chronic pulmonary tuberculosis twenty-four hours after delivery at term. The infant had no contact with the mother after birth, and was placed at once in a tuberculosis-free environment. The child was sick from birth, coughed on the seventh day, and when seven weeks old, enormous numbers of tubercle bacilli were found in the stools. At eight weeks it weighed less than at birth. There were râles in the lungs, and inoculation of guinea-pigs with material from feces gave a positive result in six weeks. The intradermal tuberculin test was negative. The child died at three months. At the necropsy there was found miliary tuberculosis of the lungs, with croupous pneumonia in the stage of red hepatization. The peribronchial and mesenteric lymph nodes were large and caseous. The middle ear on both sides contained pus and tubercle bacilli. The miliary tubercles in the lungs contained incredible numbers of tubercle bacilli. The liver contained early miliary tubercles with giant cells and a few bacilli. The spleen was packed with tubercles. The suprarenal medulla was caseous and contained many bacilli. The placenta was not examined. Chomé thinks that intrapartum infection in this case is excluded by the fact that the amnion ruptured only at the moment when the head disengaged. He suggests, as we do, that the lung may be a favorable culture medium for the tubercle bacillus because of the abundance of atmospheric oxygen and blood.

In addition to the above we have found the following titles to which we have not been able to get access: Királyfi's [11] article on congenital tuberculosis has a Magyar text which we cannot read, nor have we been able to find anyone who can translate it for us. Ludwig's [12] article on tuberculosis of the placenta and congenital tuberculosis, and Kerscher's [13] monograph we have not been able to obtain. Kerscher's monograph is the only one whose title gives promise of adding more material.

Our case adds one more clear instance of transplacental infection. The following is a brief abstract from the protocol of the necropsy, which was performed Oct. 24, 1919, by Prof. E. R. Mugrage, to whom we here express our grateful appreciation.

REPORT OF CASE

The body is that of a still-born Mexican female infant, stated to be in the ninth month of gestation. (The record in the University Dispensary shows a nine months' pregnancy.) The body is 45 cm. long and weighs 3,402 gm. Body heat is still present. There are several scars, oval in shape and somewhat depressed, varying in size from a pinhead to 5 cm. in diameter, scattered

11. Királyfi: Orvosi hetil. **49**:568, 1905.
12. Ludwig: Gynäckol. Helvet. **14**:25, 1914.
13. Kerscher: Kasuistischer Beitr., etc., Stuttgart. 1909-1910.

over the anterior aspect of both shoulders, and on the left cheek. The pleural cavities show widespread, firm, bandlike adhesions. The lungs sink in water and are studded with innumerable calcareous nodules. The kidneys are thickly set with small, grayish white nodules uniformly distributed throughout the cortex and medulla. The adrenals are much enlarged and the medulla filled with a large amount of caseous material. Macroscopic lesions are also present in the left ovary, both lateral ventricles, and in the anterior part of the thalamus. The other organs do not contain lesions visible to the naked eye. The fragments of the placenta, which were saved, contain numerous caseous nodules measuring 4 or 5 mm. in diameter.

Microscopic Examination.—(The structure of the tubercles in the lungs only is described. The lesions in the other organs are essentially identical.) The lungs are thickly set with tubercles varying greatly in size and stage of development. The earlier lesions consist of collections of epithelioid cells, which are large and circular at the center of the tubercle, becoming more and more flattened toward the periphery, until at the edge they are long and spindle shaped. Giant cells are rare but occasionally are found. Lymphocytes form a zone about the periphery, and some tubercles are completely infiltrated by small round cells. About the tubercles the air cells are filled with hyaline coagulated exudate, with a considerable number of polymorphonuclear cells. The larger tubercles are caseous at their centers. Many calcareous nodules are also present, probably representing a still later phase of the process.

The spleen and pancreas contain numerous calcified tubercles, and the suprarenal and ovary contain caseous tubercles. The kidney contains many tubercles, frequently caseous. After prolonged search through many sections, a few tubercle bacilli were found in the kidney lesions. They could not be demonstrated in any other organ. The liver is markedly fatty and contains an occasional small tubercle. The floor of the lateral ventricle contains an occasional caseous tubercle. The placenta shows numerous necrotic areas and tubercles with caseous centers.

It is to be regretted that no animal inoculation tests could be made owing to the tissue being fixed prematurely; but the diagnosis is firmly established by the character of the histologic changes, and the finding of tubercle bacilli in the kidney. The fact of still-birth at term precludes intrapartum infection.

History of the Mother.—Mexican, 36 years old, has had five children, four of whom died of influenza in 1918. Denies miscarriages. The examination made at the dispensary previous to confinement revealed no active tuberculosis but one made at the time of delivery by Dr. H. O. Calhoun (to whom we express our sincere thanks) revealed an area of dulness with râles at the right apex. Thirteen months later (November, 1920) she is apparently healthy and well nourished but still has a dull area with râles as before. She raises little or no sputum.

In view of all the difficulties which, except in rare cases, attend the search for tuberculosis in fetus and placenta, and the fact that they are rarely subjected to exhaustive examination unless there is some special reason therefor, this collection of cases is by mere weight of numbers an imposing one; imposing enough to lift prenatal tuberculosis out of the class of medical curiosities and to stimulate consideration of the broader aspects of the question. But if, as is maintained by many, prenatal tuberculosis is inevitably fatal within a few weeks or months after birth, the condition becomes again merely an interesting phenome-

non of little practical importance. The question of its significance in human pathology is intimately bound up with the question as to the validity of the old Baumgarten theory of latency. By the very nature of the case, the theory is hardly susceptible of objective proof or disproof, and can only be approached indirectly. We shall review as briefly as possible the arguments which Baumgarten himself has made familiar, and submit certain further considerations which seem to us not devoid of weight.

The possible common portals of entry are (a) the respiratory tract, by the inspiration of bacilli suspended in dry dust, or, still wet, in droplets of saliva and mucus, coughed, sneezed or otherwise expelled from the mouths and noses of consumptive persons; (b) the digestive tract, by swallowing bacilli reaching the mouth as above, or in food and drink; (c) the tonsils, similarly. Baumgarten [13a] has argued that in the first place, the real or apparent primary localization of the disease in the lungs is absolutely no proof of an aerogenic origin. The relative frequency of pulmonary tuberculosis, as compared to other localizations, is due merely to a special predilection of the organism for the lungs. The extraordinarily tortuous character of the path to be traveled along the bronchi, the defense against entrance afforded by mucin and cilia, and the very slow progress into the lung of any given unit of air, probably render the bronchial tree the most difficult of the routes into the lung. Animals are rarely infected by breathing bacillus laden dust, perhaps due to attenuation caused by drying. Breathing moist bacilli in spray produces a higher percentage of infections; usually caseous pneumonia or bronchopneumonia, rarely bronchiolitis or perbronchiolitis. But the same processes can be produced in typical form by hematogenous infection. On the whole, the droplet method of infection, Baumgarten thinks, has more in its favor that the dry dust method, but this is far from proving that the former is the most common mode of infection under normal conditions.

Feeding experiments are much more successful, especially when the bacillus is administered in small doses over a long period, thus simulating as closely as possible the natural conditions of infection, rather than in only one or two large doses. Moreover, calves, which never become infected by breathing infected dust, etc., do so regularly in the feeding experiment. Necropsies on such animals, performed at successive stages of the process, prove that the (bovine) bacillus may pass the intestinal wall without producing any local lesion, and can be found in the mesenteric glands, even when these are not enlarged. Later the bacilli reach the thoracic organs, usually only the peribron-

13a. Baumgarten: Samml. klin. Vortr., No. 281, 1882; (Inn. Med., No. 74, p. 1955); Deutsch. med. Wchnschr. **35**:1729, 1909.

chial glands, but sometimes the lungs also. Since no direct path from the mesenteric to the bronchial glands exists, the transfer must be assumed to take place via the thoracic duct or portal vein.

Baumgarten insists that these facts can not be transferred unhesitatingly to human pathology. Primary tuberculosis of the mesenteric glands is rare in man, and a primary lesion due to the bovine type is rarer still. Even when the bovine type does reach the glands it grows but meagerly and soon dies out. It is rarely found in other lesions, especially the lungs, and he does not believe that an infection due to the bovine type could lose this character by conversion of the bacillus into the human type, since this would require passage of the strain involved through several human hosts. Human tissue, on the other hand, is a favorable medium for the human type of bacillus, so that these objections do not apply to infection with the latter. In the vast majority of cases of combined pulmonary and intestinal tuberculosis the pulmonary lesion is obviously the older. But just as this fact does not prove aerogenic origin, so involvement of the intestines, even if very common, would not prove that the intestine serves as a frequent portal of entry. If that were the case, the bacillus must be assumed to have passed the intestinal wall and mesenteric glands without injuring them, and this, he insists, the human type, in contrast to the bovine type, does not do.

Baumgarten's argument, however, is open to criticism. His thesis requires that, while postnatal infection through the intestinal tract is looked upon as unable to reach the lung without leaving indications of its passage along the route followed, prenatal infection through the placenta and umbilical vein shall be assumed to be able to do just that. Schmorl and Kockel [14] long ago showed that the bacillus is found more abundantly in the fetal liver than anywhere else in prenatal tuberculosis, and often unaccompanied by histologic changes. Conceivably this might be due to infection having occurred so short a time before the examination was made that no opportunity was afforded for the customary changes to develop. Be this as it may, there is no question that lesions in the liver, other than those obviously arising in the last days or weeks of life, are very rare in pulmonary tuberculosis. Baumgarten's argument on this point therefore cuts both ways.

To the above brief and very incomplete sketch of Baumgarten's argument in favor of latent and prenatal infection we would add the following considerations:

1. There is a general tendency to apply to man the ideas of von Behring [15] regarding the age period of infection in cattle. Quite

14. Schmorl and Kockel: Beitr. z. path. Anat. u. z. allg. Path. **16**:313, 1894.
15. Von Behring: Deutsch. med. Wchnschr. **29**:689, 1903; **30**:193, 1904 abstr. Zentralbl. f. Bakteriol. Refer. **34**:136, 729, 1903.

recently, for example, von Jaksch [16] has complained with some petulance of a failure in certain quarters to apprehend the "fact" that the human animal is insusceptible to tuberculous infection (aside from such purely local manifestations as the anatomist's tubercle) after the age of six years. Griffith [17] puts it somewhat differently when he defines tuberculosis as a disease of childhood. But if we accept the theory that tuberculous infection, either always, or only usually, occurs either before birth, or during the years of infancy and childhood, we cannot escape accepting "in principle," as the diplomats say, the theory of latency; because in the vast majority of cases, manifest symptoms develop only later in life, sometimes very late, and often in connection with some special tax on the vitality, such as measles, whooping cough, pneumonia, pregnancy, etc. Moreover, if an infection acquired during the first weeks or months after birth may remain latent for years, it is hard to see any valid reason why an infection acquired during the last weeks or months before birth should not behave in the same way. Certainly, the struggle for existence is not more difficult or exhausting for the child in utero than for the child not thus protected.

2. The mechanism of latency may be placed on a more solid theoretic basis than that provided by Baumgarten's theory that the bacillus preserves and prolongs its individual life by "slumbering" over long periods. It has been abundantly proved that immune bodies present in the mothers' blood may find their way into the fetal circulation (Coca,[1] Krause [18] and others). Since these are isoimmune bodies, and therefore practically identical with any immune bodies which might be produced by the fetus itself, they would tend to be only very slowly eliminated, and would no doubt protect the child as completely, and over as long a period as an active immunity of equal titre. A partial immunity would tend to prevent active progress of the disease, without, however, being able to destroy the bacillus completely, thus creating a situation analogous to that which we assume to exist, in order to account for the progressively narrowing field of activity ordinarily observed in the later stages of syphilis. Sitzenfrey noticed that the extent of the disease in fetal tuberculosis is roughly directly proportional to the extent and activity in the mother. This is probably usually true, though the cases of Warthin and Cowie, Grulee and Harms,[19] and our case prove that it is not necessarily true. The same rule stated differently may be useful here. Let us put it in this way: the extent and severity of the disease in the fetus is, roughly, inversely proportional to the mother's immunity.

16. Von Jaksch: Zentralbl. f. Inn. Med. **39**:545, 1918.
17. Griffith: New York M. J. **109**:485, 1919.
19. Grulee and Harms: Am. J. Dis. Child. **9**:322 (April) 1915.

3. Numerous researches of recent years prove conclusively that what we term latency is often not latency at all, but defective diagnosis; or more often, no diagnosis at all. We shall mention only a few of the many works in this field. Landouzy [20] reports in detail seven cases of infantile tuberculosis, with necropsy findings, in children varying in age from 6 weeks to 12 months. These occurred in a total of twenty-three deaths, or 30.4 per cent., in a hospital population of 127 children, in a period of 4 months. In another series [21] he reports twenty deaths, fifteen with necropsy, three without necropsy, and two doubtful, in children varying in age from 3 to 24 months. Total deaths for the period were sixty-nine, including eleven incidental to a severe epidemic of diphtheria. The fifteen deaths with necropsy constitute 20.7 per cent of the total, and the largest single item in the list of causes of death. Landouzy, who is a firm believer in the Baumgarten theory of latency, contends very earnestly that tuberculosis, instead of being rare in childhood, "as commonly supposed," is the most important cause of infantile mortality. Klare,[22] in a clinical lecture on tuberculosis in childhood, maintains that practically every one becomes infected by the fourteenth year of life. Griffith [17] collected data showing that, when the diagnosis is based on sensitization tests, tuberculosis is rare in the first three months of life, but increases rapidly up to as high as 83 per cent. of the children examined, at 14 years of age. Under the more rigid criterion of necropsy, the percentage is naturally somewhat lower, viz., 40 per cent. in 848 necropsies at Vienna, 35 per cent. in 332 necropsies at Philadelphia, 38 per cent. in 1,675 necropsies at Paris, distributed as follows:

	Per Cent
Up to age of 3 months	1.82
From 3 to 6 months	18.0
From 6 to 12 months	26.0
From 1 to 2 years	40.0
From 2 to 5 years	60.0
From 5 to 10 years	67.0
From 10 to 15 years	71.0

It is to be noted that the failure to find visible tuberculosis in early infancy does not at all prove that the infection had not already taken place, as is shown by the large number of cases in the table given earlier, of infection without histologic changes. Honl,[23] who gave this condition the name, status bacillaris, suggested that it might be due to retardation of growth of the bacillus, through lack of free

20. Landouzy: Rev. de méd. **7**:383, 1887.
21. Landouzy: Rev. de méd. **11**:721, 1891.
22. Klare: Aertzl. Rundschau **28**:67, 73, 1918.
23. Honl: Bull. intern. de l'Acad. de Sc. de l'Empereur Francis Joseph I, 1894 (cited from Warthin and Cowie).

oxygen. Spolverini [24] studied a series of 900 children, varying in age from 3 to 12 months. Marantic and undergrown children, and children ill with, or recently recovered from, other diseases were not included in the series. The children were first tested by the percutaneous tuberculin method and if this was positive, were examined radioscopically and by the other recognized methods of physical diagnosis. Some children negative on the first test became positive when tested again several months later. In almost every case, when one child of a family gave positive results, other children in the family were also found to be positive. Of the 900 children examined, sixty-three, or seven per cent., were found to be tuberculous. Of the sixty-three positive cases, eight children were from 3 to 4 months old, twenty-two from 4 to 6 months, and thirty-three from 6 to 12 months. He thinks that his results are too low because several of the children were undersized, and probably failed to react because of general ill health.

The term, latency, is usually taken as covering all that period in the progress of the disease from its actual inception to the onset of manifest disturbance of health. The above figures would indicate that this period would be materially shortened, and perhaps reduced to something like a rational period of incubation, if every child, regardless of the apparent state of its health, could enjoy the benefit of an exhaustive search for the disease, by the aid of the most refined diagnostic methods. Latency as a problem might then disappear.

4. It seems to us also that not enough account is taken of possible variations in the virulence of the bacillus. In one of Schrumpf's [25] cases the bacillus recovered from the placenta and fetal tissues was so avirulent that it failed to kill a guinea-pig. The case of Repaci,[26] of a child dying on the twenty-ninth day of life, is doubted by Weber simply because the child lived so long. For the same reason Weber doubts the authenticity of Hamburger's [27] case, in which the child lived nearly eight weeks. But everyone who has employed animal tests for the diagnosis of tuberculosis in adults knows that the animals sometimes live an exasperatingly (when one is waiting to make the diagnosis) long time. Certainly slow progress of the disease is no reason for doubts as to its nature.

Whatever the facts may ultimately prove to be, there is already sound reason for believing that prenatal infection is an important, if not the most important, method of propagating the disease. Nor is

24. Spolverini: Riv. de clin. Pediat. **17**:169, 1919; also Tuberculosi **10**:239, 1918.

25. Schrumpf: Beitr. z. path. Anat. u. z. allg. Path. **42**:225, 1907.

26. Repaci: Osp. d. Bamb. d. Milan **1**:147, 1913 (abstr. Brit. J. Child. Dis. **10**:547, 1913; cited from Weber).

27. Hamburger: Beitr. z. Klin. d. Tuberk. **5**:197, 1906 (cited from Weber).

the mother the only possible source of danger. In the case of the father, animal experimentation and for man statistical studies constitute almost our only weapons for attacking the problem. Friedmann's [28] experiments are classical. He found that when buck rabbits are injected in one or both vasa deferentia with either the human or bovine type of bacilli and mated a few weeks later with healthy females, tubercle bacilli could usually be demonstrated in the seven day embryos. If the injection was made into the testis instead of the vas, the bacilli could likewise be found in the seven day embryos, provided that not too long a time elapsed between the injection and mating. When the interval was too long (four weeks or more) conception did not take place. If the injection was made intravenously, the bacilli could sometimes be found in the six day old embryos. When the interval between injection and mating was four weeks or more, the bacilli were found less readily but could still be demonstrated in a few instances. When the difficulties of the search, a veritable hunting for a needle in a haystack, are taken into account, these positive results become very significant.

Friedmann also analyzed 983 cases of pulmonary tuberculosis with hereditary taint from the records of the second medical clinic of the University of Berlin. Among the 983 cases were 503, or 51.2 per cent., with a history of tuberculosis on the father's side, 323 cases, or 32.8 per cent., with a similar history on the mother's side, and 157 cases, or 15.9 per cent., with such a history on both sides. He quotes the paper of Klebs [29] who found that in a family with a history extending back to the middle of the eighteenth century, many of whose members he had himself known, consumptive males married to healthy females often got consumptive children. Several times he observed that one and the same woman bore consumptive children when married to a consumptive husband, and later, with a healthy husband, bore healthy children. Forty per cent. of the children of consumptive mothers and only 4 per cent. of those of consumptive fathers were healthy, so that tuberculosis in the father is ten times as dangerous for the child as tuberculosis in the mother. Such data are difficult to harmonize with the view that tuberculosis is always or generally contracted after birth, that it recurs in families simply because of greater exposure, or that on the other hand, it is due to any sort of predisposition.

Finally, Friedmann cites from the literature two cases of "proved" congenital tuberculosis derived from the father. Sarwey [30] reported

28. Friedmann: Virchows Arch. f. path. Anat. **181**:150, 1905.

29. Klebs: München. med. Wchnschr. **48**:129, 1901 (cited from Friedmann).

30. Sarwey: Arch. f. Gynäk. **43**:162, 1892; abstr. Schmidt's Jahrb. **240**: 174, 1893.

a case (included in Warthin and Cowie's list as "very doubtful") from Baumgarten's laboratory, of a still-born hemicephalic monster, with missed labor, carried over eleven months, in which there was a tuberculous abscess of the cervical vertebrae. The father had suffered for a long time with cough and a tough expectoration, and the paternal grandfather had died of chronic pulmonary tuberculosis. There was no demonstrable tuberculosis in the mother. Landouzy described the case of a child who died when 24 hours old of tuberculosis. The father was a consumptive and the mother quite healthy. Landouzy [31] reports the following two family histories, which could, he thinks, be duplicated from the experience of any active practitioner. An officer fell sick in 1878, in the midst of apparent sound health, with tuberculosis, which progressed with various complications to his death in 1888. He was married in 1876 to a "superb young girl," 21 years old. He had five children; the first, a boy, born at term in 1876, developed normally and died at eight months of cholera infantum. The second, a girl, born before term (seventh or eighth month) in 1878, died twenty-four hours later in convulsions. This is the case, so far as we can make out, cited by Friedmann as a proved case of paternal transmission. Comment seems superfluous. The third child, born at term in March, 1881, was brought up like the first under the best possible conditions. It died when 6 months old with classical symptoms of tuberculous meningitis. The fourth, a girl, born at term in February, 1882, also died when 6 months old with symptoms of tuberculous meningitis. The fifth, a boy, born at term in 1883, was breast fed and brought up far from the father, in the open country. At 5 months, he fell sick with a purulent otitis media, which ultimately extended to the meninges and was diagnosed by a physician, the uncle of the child, as tuberculous. The mother remains perfectly well fifteen years later, in spite of five pregnancies in seven years and the sorrows and trials of her married life. It will be agreed, he says, that if these children died of tuberculosis, they received the disease from the father, not from the mother. In another family, four children, all brought up carefully and fed exclusively on breast milk, partly from the healthy mother, partly from a healthy nurse, died of tuberculosis at ages ranging from 3 to 12 months. The father, who had no genito-urinary tuberculosis, had a pulmonary process in the first or second stage. He coughed but raised no sputum. Moreover three of the children lived removed from the father from birth. Landouzy mentions an experiment of his own, similar to one of Friedmann's, in which six out of sixteen male guinea-pigs, inoculated with tubercle bacilli, begot tuberculous offspring.

31. Landouzy: Rev. de méd. **11**:411, 1891.

The importance of this matter lies in this, that to the extent that the conclusions outlined are sound, all our present day methods of attacking tuberculosis are merely palliative, designed to prolong the life of the consumptive, but having not the slightest effect on the source of contagion. A year ago one of us (R. C. W.) heard Dr. V. C. Vaughan say, in the course of an impromptu after-dinner talk to a gathering of physicians that thirty years ago he had been wont to prophesy, with the enthusiasm of unbounded faith, "No tuberculosis by 1920." Some contemporaries, less sanguine than himself, thought 1950 a safer estimate. "Now," said Dr. Vaughan, "the years have brought disillusionment and I feel that we shall be lucky if we stamp out tuberculosis in five hundred years." We would not be too pessimistic, but we believe that five times five hundred years may well find us just about where we are today, with a falling death rate, due to an increasing proportion of cures and greater prolongation of life of the consumptive, but with no very great reduction in the morbidity rate, unless indeed we change our methods. It will seem harsh and heartless to many to argue that although it may well be doubted whether if leprosy had been allowed to spread unchecked, it would ever have wrought anything like the havoc caused by tuberculosis,[32] yet general fear and the tradition of centuries sanction a degree of harshness in the control of leprosy, which we would not dream of employing toward the consumptive. It is worth considering whether our methods of control in tuberculosis are not in large measure determined by what we like to call sentiments of compassion, but which really deserve a much harsher name. It could be argued with a good show of reason that methods of control based on education, rather than segregation, constitute a cowardly repudiation of the rights of unborn, uncounted millions.

CONCLUSIONS

1. Prenatal tuberculosis has ceased to be a mere curiosity of the laboratory, and has become a pressing problem of the sanitarian.

2. The facts at hand are significant enough to command the active employment of every agency by which further facts may be elicited.

3. To the extent that the spread of the disease is due to prenatal, rather than postnatal, infection, present methods of control must be revised and amended, even at the expense of those sentiments of compassion and tolerant forbearance by which our present efforts are so notably handicapped.

32. II Kings, v. 1 et seq. "Now Naaman, captain of the host of the king of Syria, was a great man with his master, and honorable, because by him the Lord had given deliverance unto Syria: he was also a mighty man in valor; but he was a leper," etc. Certainly, the picture of this warrior and national hero, living en famille with wife and servants, hardly suggests that leprosy inspired the horror three thousand years ago that it does today.

A CONVENIENT ELECTRODE FOR EXPERIMENTAL ELECTROCARDIOGRAPHIC WORK*

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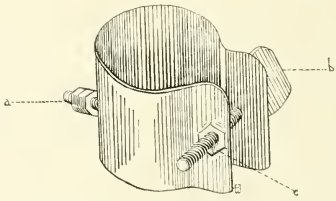
ROCHESTER, MINN.

In undertaking a series of experimental electrocardiographic studies, we found a large number of animals that were not suitable for our work. But before the adaptability of an animal could be determined with the usual experimental electrocardiographic electrode, it was necessary to anesthetize it and make an incision in the skin in order properly to insert the electrodes. This procedure requires considerable time and sometimes results in an infected wound if the animal is not used at once.



(*a*) Attachment for lead wire.
(*b*) Long screw for adjusting diameter of electrode.
(*c*) Nut for screw *b*. It is not necessary to have a nut on each side of the adjustment leads.

To obviate this difficulty we have adopted a very convenient type of electrode, consisting of an adjustable copper plate with an attachment for the lead wires. The width of the cuff is 1¾ inches, and the minimum diameter, after it has been bent roughly to conform to the shape of the leg, is 1 inch. The copper is flexible, and is readily adjusted to a large or small animal by means of a thumbscrew.

The connection of the lead wire to the copper plate is secured by soldering a copper rivet to the outside of the electrode. Care is taken to place the solder only around the edge of the rivet; otherwise it would interfere with conduction. The rivet is then threaded and provided with lugs to hold the lead wire.

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*From the Division of Experimental Surgery and Pathology, Mayo Foundation.

In using this electrode the animal's leg is shaved and the copper cuff snugly adjusted by means of the thumbscrew. No especial attention is given to the cleansing of the skin, although excess dirt should always be removed.

We have found the instrument to be very adaptable in making studies on unanesthetized animals. In a large series of experiments we have not had more than 1,000 ohms resistance, and in all respects this electrode has been an improvement over the type generally used in experimental electrocardiographic work.

BOOK REVIEW

THE HEART AND THE AORTA: STUDIES IN CLINICAL PATHOLOGY. By H. Vaquez, Professeur agrégé à la Faculté de Médecine de Paris, Médecin de l'Hôspital San-Antoine; and E. Bordet, Chef de laboratoire Adjoint à la Faculté de Médecine de Paris. Translated from the Second French Edition by James A. Honeij, M.D., and John Macy, M.A. Pp. 256. 181 illustrations. Yale University Press, New Haven, Conn.

In this book the authors begin with a description and comparison of the various radiographic methods of examining the heart and the aorta, including their personal technic. They consider that there are three reliable methods, teleradiography, orthodiography and teleradioscopy. The latter two furnish identical information and are designated as radioscopy of percision. They point out that teleradiography and radioscopy of percision each have its advantages and that the association of the two methods gives nearly perfect results. If, however, only one is to be used the orthodiographic examination gives more precise information.

In the following chapter the authors describe the normal cardiac shadow in the frontal and oblique positions and consider variations in the physiological form of the heart. In subsequent chapters changes produced in the cardiac shadow by various pathological conditions as chronic valvular diseases, congenital defects, affections of the pericardium, aortitis and aneurisms of the thoracic aorta are illustrated. The last chapter discusses the localization of war projectiles in the heart and pericardium. The points of the authors are well illustrated by diagrams.

This volume with its numerous illustrations demonstrates very clearly the importance of radiographic examination of the heart and aorta. The authors seem conservative in their claims and have apparently accomplished their purpose in compiling the work. It is fortunate that Dr. Honeij has translated it in English. It will further the employment of this valuable method of examination and should serve as a useful reference to the radiologist and the physician.

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CLINICAL STUDIES ON THE RESPIRATION

IX. THE EFFECT OF EXERCISE ON THE METABOLISM, HEART RATE, AND PULMONARY VENTILATION OF NORMAL SUBJECTS AND PATIENTS WITH HEART DISEASE *

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WITH THE ASSISTANCE OF
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BOSTON

The investigations described in this paper were undertaken with a view to obtaining further information concerning dyspnea in patients with heart disease. Attention has been directed particularly to the moderate degrees of dyspnea which are incidental to the life of most persons in whom cardiac disease is a limiting, but not an incapacitating lesion, and certain aspects of the respiration and circulation have been studied while the subjects were performing exercises which did not exceed in amount or differ in kind from what they were accustomed to in normal life. The problem has been to determine, so far as possible, the differences in reaction to exercise which account for the fact that patients with heart disease become short of breath as the result of an amount of exercise which does not affect normal persons. It seemed to be important to avoid the complicating factor of muscular fatigue by selecting a type of test exercise which did not involve muscles which the subject was unaccustomed to use, and, since patients with heart disease frequently state that they get out of breath when walking upstairs, it was considered that stair climbing was the form of exercise best adapted to the purposes in view. On account of the complex nature of the observations undertaken, it was necessary for the subject to remain as nearly as possible in one position so that a stair climbing treadmill was made use of. Two groups of subjects, of approximately the same age were studied, one group consisting of eleven normal young men, and the other of eleven young men with valvular heart disease. Unfortunately, such fundamental factors as the circulation rate and minute-volume of cardiac output cannot easily be approached by accurate experimental methods and our observations were, therefore, limited to determinations of the rate, depth, and minute-volume of the respiration, oxygen consumption, carbon dioxid production, and heart rate, before, during, and after a standard amount of exercise.

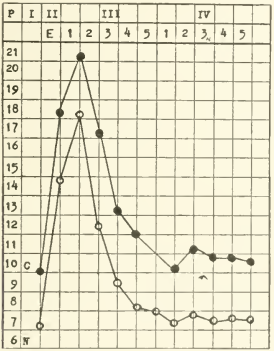
* From the Medical Clinic of the Peter Bent Brigham Hospital.

EXPERIMENTAL PROCEDURE

The experimental procedure was essentially the same in all cases. The subject came to the laboratory at about 9 a. m. after having had his usual breakfast. Electrodes connecting with the electrocardiograph, which was used for counting the heart rate, were attached to his body, and he then sat on a chair, resting, for at least one-half hour. After this a half-mask, covering the nose and mouth, was put in place, carefully tested for leaks, and the subject stepped up on the treadmill. The mask was connected with two rubber tubes of wide bore, one conducting air for inspiration from outdoors, and the other carrying expired air to large Tissot spirometers. Inspired and expired air were separated by rubber flap valves of the type used in gas masks and described by Boothby and Sandiford.[1] A pneumograph, which recorded the respiratory rate on a smoked drum, was adjusted round the chest, and the electrodes were connected to the wires leading to the electrocardiograph. The subject then stood quietly at rest for at least ten minutes more, after which the actual experiment was begun. Each experiment consisted of a series of periods in which the subject was either standing at rest or performing a given amount of exercise. The first period served as a base line for subsequent observations, and in the analysis of the results obtained the percentage variations from the standard resting conditions of this period are reported. In the first period the subject stood quietly at rest for five minutes, during which the expired air was collected, the respiration rate was determined with the pneumograph, and the heart rate was recorded by means of the electrocardiograph. From the data thus obtained the minute-volume of air breathed and the average volume per respiration could be calculated, while analyses of the expired air, with the Haldane portable apparatus, gave the data for calculation of the oxygen consumption and carbon dioxid production. Similar observations were made in each of the subsequent periods. The second period followed the first after about two minutes, during which the necessary technical adjustments were made. In this period the treadmill was started and the subject walked sixty steps upstairs in one minute. The height of each step of the treadmill was 18 cm. At the end of the second period the expired air was immediately shunted into another spirometer and observations were continued without any interval through the third period, during which the subject stood at rest for five minutes, and again through a fourth period of five minutes at rest. During the fourth period all the factors under study were usually essentially the same as they had been before the walk. During the second, third and fourth periods additional observations were made on the volume of air expired for each fifteen

1. Boothby, W. M., and Sandiford, I.: Laboratory Manual of the Technic of Basal Metabolic Rate Determinations, Philadelphia, 1920.

seconds and this proved to be of particular interest in the first minute immediately after the walk. Preliminary experiments showed that, while the amount of exercise in Period II was sufficient to produce dyspnea in the cardiac patients, it did not cause noticeable shortness of breath in the normal subjects. It was considered desirable, however, to make observations on normal persons when they were slightly short of breath and in a condition analogous to that of the cardiac patients at the end of Period II, and this was accomplished without altering the length of walk or number of steps taken, by having them repeat the walk of sixty steps upstairs in one minute while carrying a load consist-



The average ventilation (in liters) per minute of eleven normal individuals and eleven cardiac patients. The figures at the left represent liters. P, period; I standing at rest five minutes, II walking upstairs on a treadmill for one minute, period III standing at rest for five minutes, period IV a second rest period of five minutes. In periods III and IV the readings are recorded for each minute of the period. N, curve of eleven normal individuals; C, curve of eleven cardiac patients; E, point at which exercise began. In the curve of the eleven cardiac patients it was impossible to average the minute-volumes in the fifth minute of the third period, as in five instances the capacity of the spirometer did not permit the expired air to be collected during the fifth minute.

ing of a knapsack weighing 50 pounds on the back. This produced in the normals a degree of dyspnea fairly comparable to that of the cardiac patients in Period II. In the normal subjects, therefore, Period IV was followed by Period V, in which a 50 pound load was carried sixty steps upstairs in one minute, and then by Periods VI and VII, each five minutes long, in which the subjects stood quietly at rest.

In reporting results all volumes of air have been reduced to 0 C. and 760 mm. barometric pressure.

The Subjects—The eleven normal subjects were healthy medical students and doctors. None of them was in particularly good physical training at the time the observations were made, but they represent average specimens of young manhood. The eleven subjects with heart disease

TABLE 1.—VITAL CAPACITY OF NORMAL SUBJECTS AND CARDIAC PATIENTS

No.	Normal Subjects	Age	Height, Cm.	Weight, Kg.	Surface Area,* Sq. M.	Vital Capacity, C.c.	Vital Capacity,† per Cent. of Normal	Diagnosis
1	J. D. T.	31	174.2	86.3	2.01	5,000	100	
2	F. F.-S.	25	179.2	69.9	1.88	4,250	90	
3	L. L.	23	179.3	70.4	1.88	4,475	95	
4	H. B.	25	176.6	71.1	1.87	4,900	105	
5	F. W. P.	39	175.2	71.7	1.86	4,400	95	
6	F. R. S.	25	172.2	71.3	1.84	4,700	102	
7	W. E.	26	168.8	69.9	1.80	4,600	102	
8	I. C. S.	27	170.0	67.7	1.78	4,075	92	
9	J. T. L.	24	176.2	61.8	1.76	4,850	110	
10	H. R. M.	25	170.0	65.8	1.75	4,500	102	
11	J. W.	24	179.8	54.1	1.69	5,100	121	
	Cardiac Patients							
1	M. McG.	26	182.2	77.1	1.98	3,550	72	Aortic insufficiency; mitral stenosis and insufficiency; chronic bronchitis
2	F. D.	36	172.2	75.7	1.89	3,900	83	Aortic insufficiency
3	R. G.	24	180.2	68.5	1.88	4,500	96	Aortic insufficiency; mitral stenosis
4	L. I.	25	179.4	64.0	1.82	4,100	90	Aortic and mitral insufficiency
5	F. C.	17	173.4	66.7	1.79	3,600	81	Mitral insufficiency
6	M. R.	25	174.3	57.2	1.68	3,650	87	Pulmonary stenosis
7	C. S.	20	164.7	53.1	1.57	3,300	84	Aortic insufficiency; mitral stenosis and insufficiency
8	B. O.	25	154.0	58.1	1.56	3,400	87	Aortic insufficiency; mitral stenosis and insufficiency
9	A. V.	24	156.8	55.3	1.54	3,650	95	Aortic insufficiency and (?) stenosis; mitral insufficiency
10	E. W.	33	165.9	49.9	1.53	2,375	62	Aortic and mitral insufficiency; (?) mitral stenosis
11	F. K.	25	160.6	48.5	1.49	3,100	83	Aortic insufficiency; mitral stenosis and insufficiency

* DuBois, E. F., and DuBois, D.: Arch. Int. Med. **17**: 868 (July) 1915.
† West, H. F.: Arch. Int. Med. **25**: 366 (March) 1920.

all had valvular lesions but the degree of disability varied greatly from case to case. In some of them dyspnea was scarcely a more prominent symptom than it is in many normal persons, while in others it caused marked limitation of physical exertion. In conformity with previous observations [2] it was found that the degree of tendency to dyspnea was indicated with considerable accuracy by the vital capacity of the lungs,

2. Peabody, F. W., and Wentworth, J. A.: Arch. Int. Med. **20**: 443 (Oct.) 1917.

and that the subjects in whom the vital capacity was lowest became most short of breath while walking on the treadmill. With three exceptions the vital capacity of the cardiac patients was below that of all the normals when calculated according to the standards based on body surface area suggested by West.[3] All but one of the patients with heart disease were discharged soldiers and sailors who were ambulatory patients at a Public Health Service hospital, and they were in good general condition, except for their cardiac lesions. They represent very nearly the same age group as the normals, but were on the whole slightly smaller men. The average surface area[4] of the group of normal subjects was 1.83 square meters, while that of the cardiac patients was 1.70 square meters.

Oxygen Consumption.—As an index of the total metabolism of the body the oxygen consumption per square meter of body surface area was determined, and the results are shown in Table 2. In addition to the actual oxygen consumption in cubic centimeters there is also given the percentage variation from the figure in Period I, during which the subject stood at complete rest. This is taken as a base line and considered as 100. In examining the figures in Period I for the two groups it is noticeable that the oxygen consumption of the cardiac patients was slightly more than that of the normals, the average values for each of the two groups being 190 c.c. and 170 c.c., respectively, per square meter. In eight of the cardiac patients the oxygen consumption was over 185 c.c. per square meter, while it was above this figure in only two normals. This difference in the average oxygen consumption of the two groups, while standing at rest, amounts to about 12 per cent. It is quite possible that this small difference has no significance and that it depends on the fact that so limited a number of individuals has been studied, but since this is not certain it is of interest to consider the possible explanations of an increased metabolism in the cardiac patients. Previous observations[5] have shown that the basal metabolism, at complete rest and fasting, of patients with heart disease may be elevated considerably if they are severely decompensated, but that it is within normal limits in persons whose circulation is as well compensated as it was in the subjects of these investigations. Unfortunately, it was not practicable to obtain observations on the metabolism of these individuals when at complete rest and in a fasting state. It seemed possible that in some of the cardiac patients the slightly high metabolism in Period I might be due to nervousness, but in others there was absolutely no reason for considering such a factor, and it is conceivable that the

3. West, H. F.: Arch. Int. Med. **25**:306 (March) 1920.
4. DuBois, D., and DuBois, E. F.: Arch. Int. Med. **15**:868 (July) 1915.
5. Peabody, F. W.; Wentworth, J. A., and Barker, B. L.: Arch. Int. Med. **20**:468 (Oct.) 1917.

TABLE 2.—Oxygen Consumption Per Square Meter of Body Surface Area Per Minute

Normal Subjects	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation	Oxygen Consumption, C.c.	Percentage Variation
J. D. T.	166	100	420	253	290	175	175	105	504	303	303	183	180	108
F. F.S.	125	100	508	406	228	183	136	109	578	463	250	200	148	118
L. L.	171	100	474	277	294	172	187	109	568	332	294	172	185	108
H. B.	157	100	376	239	279	178	170	108	578	368	323	206	163	104
F. W. P.	145	100	445	307	239	165	147	101	585	403	277	191	147	101
F. R. S.	167	100	468	280	239	143	177	106	590	353	*	...	183	110
W. E.	202	100	519	257	301	149	182	90	583	290	347	172	173	86
I. C. S.	181	100	479	265	229	165	185	102	561	310	343	190	177	98
J. T. L.	200	100	605	303	300	150	205	102	694	347	346	173	193	97
H. R. M.	175	100	382	218	291	166	173	99	586	335	345	197	174	99
J. W.	181	100	419	232	263	146	180	100	639	353	337	186	174	96
Average	170	100	463	272	275	162	174	102	588	346	321	189	172	101
Cardiac Patients														
M. McG.	213	100	465	218	269†	126	227	107	...	...	...	...	...	...
F. D.	295	100	526	234	342‡	152	223	99	...	...	...	...	...	...
R. G.	193	100	549	284	310‡	161	206‡	107	...	...	...	...	...	...
L. T.	155	100	456	294	263	170	167	108	...	...	...	...	...	...
F. C.	172	100	492	286	242	141	162	94	...	...	...	...	...	...
M. R.	170	100	392	231	302‡	178	183	108	...	...	...	...	...	...
C. S.	200	100	497	248	247	124	167	84	...	...	...	...	...	...
B. O.	187	100	511	273	307	164	190	102	...	...	...	...	...	...
A. V.	180	100	482	255	341	180	197	104	...	...	...	...	...	...
E. W.	197	100	381	193	374§	190	241	122	...	...	...	...	...	...
F. K.	196	100	513	262	344	176	218¶	111	...	...	...	...	...	...
Average	190	100	479	252	#	...	198	104	...	...	...	...	...	...

* Gas analysis unsatisfactory in this period.
† 4 minute period.
‡ 4 minute and 30 second period.
§ 3 minute and 30 second period.
¶ 4 minute and 45 second period.
# Average could not be calculated on account of variation in length of periods.

exertion of standing produces a relatively greater increase of metabolism in patients with heart disease than it does in normal persons. It is also possible that the somewhat greater activity of the respiratory muscles, which will be discussed later, accounts for the slightly larger oxygen consumption of the patients with cardiac disease.

The actual oxygen consumption during the walk upstairs (Period II) was also greater in the group of cardiac patients than in the normals, but the average percentage increase in oxygen consumption over that in Period I was somewhat less in the case of patients with heart disease. This difference may be partly due to error inherent in using so short a period, but it was greatly accentuated by subject F. F-S., who had a very low oxygen consumption at rest, and an extraordinarily large percentage increase with exertion. The averages are somewhat misleading, for ten normals had a percentage increase of between 218 and 307, while the cardiac patients had increases between 218 and 294. The difference between the two groups is thus not great. In several instances it was not possible to obtain strictly comparable results for Period III because the minute-volumes of some of the patients with heart disease were so large that the spirometer became filled and the period was only four minutes, or, in one instance, three and one-half minutes long, but, in general, the return to normal on the part of the metabolism, at least as far as can be determined from periods of this length, seemed to proceed at about the same rate in the two groups of subjects. In Period IV the oxygen consumption had returned to approximately what it was before exercise in both groups. It is clear, therefore, that when normal subjects and cardiac patients undertake similar amounts of physical exercise, there is little or no difference in the effect of the exercise on the metabolism in the two groups.

The increase of metabolism among the normals was much greater in Period V, when they walked upstairs with a load on the back, but the return to resting condition was quite rapid and was complete in Period VII.

It is, of course, quite obvious that the periods of exercise, which lasted only one minute, were too short to give accurate information as to the actual oxygen consumption resulting from the work done, and a considerable proportion of the increased consumption fell in Period III, but the results are comparable in the two groups and they do not show any striking difference in behavior.

Carbon Dioxid Production.—In Table 3 the figures for carbon dioxid production in each period are reported. They follow closely the changes already mentioned for oxygen consumption, but it is worthy of note that the return to resting conditions after exercise was less complete in the case of the carbon dioxid production.

TABLE 3.—Carbon Dioxid Production Per Square Meter of Body Surface Area Per Minute.

Normal Subjects	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation	Carbon Dioxid Production, C.c.	Percentage Variation
J. D. T.	148	100	358	242	299	202	171	116	420	284	328	222	173	117
F. P. S.	105	100	374	356	212	202	118	112	448	427	231	220	128	122
L. L.	142	100	324	228	260	183	166	117	411	289	282	199	161	113
H. B.	134	100	270	202	232	173	149	130	449	362	306	247	156	136
F. W. P.	130	100	337	259	226	174	139	107	462	355	288	221	134	103
F. R. S.	114	100	324	284	205	180	144	126	433	380	*	...	161	141
W. E.	167	100	340	204	261	156	155	93	411	246	322	193	155	93
L. C. S.	157	100	375	239	272	173	170	108	475	303	336	214	167	106
J. T. L.	169	100	448	265	278	165	180	107	535	317	347	205	173	102
H. R. M.	151	100	261	173	256	170	151	100	428	283	360	238	159	105
J. W.	140	100	329	235	205	146	144	103	471	336	302	216	150	107
Average	141	100	338	240	245	174	153	109	449	319	310	220	156	111
Cardiac Patients														
M. McG.	182	100	373	205	355†	195	205	113	...	...	...	...	...	...
F. D.	204	100	414	203	353†	173	248	122	...	...	...	...	...	...
R. G.	189	100	471	249	332‡	176	203‡	107	...	...	...	...	...	...
L. I.	155	100	337	270	237	190	140	112	...	...	...	...	...	...
F. C.	139	100	356	256	200	144	136	98	...	...	...	...	...	...
M. R.	142	100	301	212	280§	197	162	114	...	...	...	...	...	...
C. S.	158	100	391	247	225	142	135	85	...	...	...	...	...	...
B. O.	153	100	396	259	264	172	160	105	...	...	...	...	...	...
A. V.	158	100	368	227	325	206	172	109	...	...	...	...	...	...
E. W.	172	100	369	215	379§	220	219	127	...	...	...	...	...	...
F. K.	161	100	343	213	289	204	218§	135	...	...	...	...	...	...
Average	162	100	374	231	#	...	182	112	...	...	...	...	...	...

* Gas analysis unsatisfactory in this period.
† 4 minute period.
‡ 4 minute and 30 second period.
§ 3 minute and 30 second period.
¶ 4 minute and 45 second period.
# Average could not be calculated on account of variation in length of periods.

TABLE 4.—Percentage of Oxygen Absorbed from Inspired Air and Carbon Dioxid Excreted in Expired Air

Normal Subjects	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid
J. D. T.	3.99	3.56	5.08	4.33	4.15	4.38	3.88	3.79	5.13	4.28	4.27	4.63	3.92	3.77
F. F-S.	4.09	3.44	6.16	4.53	4.52	4.20	4.14	3.60	6.07	4.70	4.55	4.20	4.28	3.69
L. L.	4.32	3.59	6.20	4.24	4.58	4.05	4.07	3.61	6.21	4.49	4.50	4.31	4.10	3.57
H. B.	3.91	3.10	4.89	3.19	4.07	3.72	3.74	3.26	4.89	3.80	4.01	3.81	3.19	3.04
F. W. P.	3.99	3.57	5.55	4.21	4.06	3.83	3.64	3.44	5.46	4.31	3.88	4.04	3.68	3.39
P. R. S.	4.24	3.90	5.00	3.47	3.69	3.16	3.96	3.23	5.06	3.72	....	....	3.12	2.75
W. F.	4.16	3.44	6.36	4.10	4.32	3.74	3.81	3.25	6.03	4.25	4.20	3.90	3.61	3.24
I. C. S.	5.03	4.56	6.17	4.83	5.28	4.81	4.74	4.35	5.88	4.97	5.28	5.17	4.74	4.47
J. T. L.	5.19	4.38	6.81	5.01	4.75	4.40	4.71	4.13	5.67	4.37	4.33	4.24	4.13	3.60
H. R. M.	4.05	3.49	5.94	4.06	4.50	3.96	3.81	3.33	6.04	4.41	4.04	4.21	3.76	3.44
J. W.	4.98	3.87	5.28	4.14	5.02	3.91	4.34	3.48	6.03	4.44	4.94	4.43	3.98	3.44
Cardiac Patients														
M. McG.	4.38	3.73	5.02	4.03	4.20‡	4.04‡	3.95	3.57	....	....	....	....	....	....
F. D.	3.67	3.34	4.73	3.72	3.48‡	3.59‡	2.77	3.05	....	....	....	....	....	....
R. G.	3.13	3.07	4.59	3.94	3.04‡	3.25‡	2.84‡	2.81‡	....	....	....	....	....	....
L. I.	3.52	2.86	4.73	3.49	3.41	3.07	3.08	2.59	....	....	....	....	....	....
F. C.	4.48	3.62	5.56	4.02	4.83	3.98	4.57	3.82	....	....	....	....	....	....
M. R.	2.89	2.41	3.88	2.98	2.88‡	2.67‡	2.58	2.28	....	....	....	....	....	....
C. S.	3.25	2.57	4.18	3.29	3.15	2.87	3.12	2.61	....	....	....	....	....	....
B. O.	4.06	3.31	4.48	3.47	3.98	3.42	3.91	3.30	....	....	....	....	....	....
A. V.	3.76	3.14	4.99	3.71	4.22	4.02	3.64	3.17	....	....	....	....	....	....
E. W.	3.38	2.46	2.75	2.66	2.56§	2.53§	2.81	2.76	....	....	....	....	....	....
F. K.	3.10	2.59	4.75	3.18	3.40	3.26	2.55¶	2.55¶	....	....	....	....	....	....

† 4 minute period. ‡ 4 minute and 30 second period. § 3 minute and 30 second period. ¶ 4 minute and 45 second period.

Table 4 gives the percentage of oxygen absorbed from the inspired air and the percentage of carbon dioxid excreted in the expired air. It will be seen that the figures for both are lower in the group of cardiac patients than in the normal subjects. The average percentage of oxygen absorbed by the normals while at rest was 4.36 and during exercise was 5.57, while the corresponding figures for the patients with heart disease were 3.60 and 4.51. These results are of special interest in connection with the observations on the minute-volume of pulmonary ventilation.

TABLE 5.—Respiratory Quotients.

Normal Subjects	Period I Rest	Period II Exercise	Period III Rest	Period IV Rest	Period V Exercise with Load	Period VI Rest	Period VII Rest
J. D. T.	0.89	0.85	1.03	0.98	0.83	1.10	0.96
F. F-S.	0.84	0.74	0.93	0.87	0.77	0.92	0.86
I. L.	0.83	0.68	0.88	0.89	0.91	0.96	0.87
H. B.	0.79	0.67	0.80	0.87	0.78	0.95	0.95
F. W. P.	0.90	0.76	0.94	0.95	0.79	1.04	0.91
F. R. S.	0.68	0.69	0.65	0.82	0.74	*	0.88
W. E.	0.83	0.66	0.87	0.85	0.71	0.93	0.90
I. C. S.	0.87	0.78	0.91	0.92	0.85	0.98	0.94
J. T. L.	0.84	0.74	0.93	0.88	0.77	1.00	0.89
H. R. M.	0.86	0.68	0.88	0.87	0.73	1.04	0.92
J. W.	0.78	0.78	0.78	0.80	0.74	0.90	0.86
Average	0.83	0.73	0.87	0.88	0.78	0.98	0.90
Cardiac Patients							
M. McG.	0.85	0.80	0.96†	0.90	....	....	....
F. D.	0.91	0.79	1.03†	1.05	....	....	....
R. G.	0.98	0.86	1.10‡	0.99‡	....	....	....
L. I.	0.81	0.74	0.90	0.84	....	....	....
F. C.	0.81	0.72	0.82	0.84	....	....	....
M. R.	0.83	0.77	0.93†	0.88	....	....	....
C. S.	0.79	0.79	0.91	0.84	....	....	....
B. O.	0.82	0.78	0.86	0.84	....	....	....
A. V.	0.84	0.74	0.95	0.87	....	....	....
E. W.	0.88	0.97	1.00§	0.91	....	....	....
F. K.	0.82	0.67	0.96	1.00¶	....	....	....
Average	0.85	0.78	#	0.90	....	....	....

* Gas analysis unsatisfactory in this period.
† Four minute period.
‡Four minute and 30 second period.
§ Three minute and 30 second period.
¶ Four minute and 45 second period.
# Average could not be calculated on account of the variation in length of periods.

Respiratory Quotients.—The respiratory quotients (Table 5) are approximately similar for the two groups of subjects in the first rest period. The figures for F. R. S. are low and probably should not be taken into consideration as there would seem to be some technical error involved. In Period II the exercise was associated with a lowering of the quotients in nine of the eleven subjects in each group. This is contrary to the results obtained by Krogh and Lindhard [6] who found a sudden rise in the respiratory quotient at the onset of hard work. Krogh and Lindhard called attention to the fact that this does not represent an altered metabolism but merely a disturbance of the balance between

6. Krogh, A., and Lindhard, J.: J. Physiol. **47**:112. 1913.

ventilation and blood flow, with a proportionally greater increase of pulmonary ventilation. The difference in findings may be due to the very mild character of the exercise performed by the subjects of this investigation. The low quotients during the exercise period indicate an inadequate excretion of carbon dioxid, and this was compensated for by the washing out of carbon dioxid after the cessation of exercise, as is shown by the general tendency to a rise in respiratory quotient in Period III. The same lowering of quotient during exercise and rise of quotient immediately after exercise was seen in the normal subjects in Periods V and VI.

Minute-Volume of Pulmonary Ventilation.—The actual volumes of pulmonary ventilation are given in Table 6, and it is seen that the figures for the first period of standing at rest (Period I) are considerably higher in the group of cardiac patients than in the group of normal subjects. On account of the fact that the cardiac patients were, in general, smaller men than the normal subjects, this difference becomes even more evident when the minute-volume is calculated per square meter of body surface area (Table 7). Nine of the patients with heart disease had a minute-volume of between 4.61 and 6.20 liters per square meter surface area, while eight of the normals had a minute-volume of between 3.63 and 4.33 liters per square meter surface area. The average minute-volume of the cardiac patients was 5.37 liters per square meter surface area, or 37 per cent. higher than the average minute-volume of the normals, which was only 3.90 liters per square meter surface area. The difference between the minute-volumes of the two groups, while standing at rest, was thus much greater than the difference in oxygen consumption which amounted to only 12 per cent. This fact, which is of considerable importance, will be discussed later.

As the result of walking upstairs (Period II) the minute-volume increased in both groups of subjects. It reached a considerably higher level in the patients with heart disease than it did in the normals, but it is striking that the percentage rise over the resting minute-volume (Period I) was approximately the same in the two groups.

In the study of the minute-volume of pulmonary ventilation the most important points are to be gathered from a careful analysis of Period III, the first rest period after the walk upstairs. Practically every subject in both groups stated that he was more conscious of his breathing, or felt more dyspneic, immediately after he stopped walking than he did during the actual exercise. In the light of this statement it is exceedingly interesting to discover that the minute-volume was almost invariably higher in the first minute of rest than it was during the exercise period. This is shown in Tables 6 and 7, in which Period IIa represents the first minute of rest, and also in the chart, in which the minute-volume is plotted for each separate minute in Periods II, III

TABLE 6.—MINUTE-VOLUME OF PULMONARY RESPIRATION

Normal Subjects	Period I Rest		Period II Exercise		Period IIa *		Period III Rest		Period IV Rest		Period V Exercise with Load		Period Va *		Period VI Rest		Period VII Rest	
	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation
J. D. T.	8.34	100	16.60	200	21.80	262	14.10	169	9.05	108	19.70	236	25.50	306	14.20	170	9.22	111
F. F-S.	5.90	100	15.80	268	18.30	310	9.70	166	6.30	107	18.30	310	19.20	326	10.50	178	6.60	112
L. L.	7.61	100	14.40	189	19.10	250	12.10	159	8.64	114	17.30	226	20.80	273	12.30	162	8.48	111
H. B.	7.50	100	14.70	196	15.50	207	11.20	149	8.57	114	22.10	295	23.50	313	15.00	200	9.57	128
F. W. P.	6.75	100	14.90	221	18.90	280	11.00	163	7.50	111	19.90	295	23.40	347	13.30	197	7.56	112
F. R. S.	7.26	100	17.30	237	20.00	276	11.90	164	8.23	113	21.40	295	28.10	387	22.20†	301	10.80	149
W. F.	8.73	100	14.90	171	20.20	232	12.60	145	8.59	98	17.40	199	24.80	284	14.90	171	8.61	99
I. C. S.	6.15	100	13.80	224	15.90	258	10.10	164	6.96	113	17.00	277	18.10	294	11.60	189	6.63	108
J. T. L.	6.78	100	15.70	232	18.70	276	11.10	164	7.67	113	21.50	307	26.20	386	14.40	212	8.23	121
H. R. M.	7.61	100	11.30	148	18.60	244	11.40	150	7.98	105	17.10	225	25.80	339	15.00	197	8.15	107
J. W.	6.13	100	13.40	218	12.70	207	8.85	144	7.02	115	17.04	292	16.60	271	11.52	188	7.38	120
Average	7.16	100	14.80	207	18.20	254	11.30	158	7.86	109	19.00	265	22.90	320	13.30‡	185	8.29	116
Cardiac Patients																		
M. McG.	9.63	100	18.33	191	26.10	271	17.42§	181	11.37	118	.....	...	.....	...	.....	...	.....	...
F. D.	11.60	100	21.10	182	23.70	204	18.60§	160	13.70	118	.....	...	.....	...	.....	...	.....	...
R. G.	11.60	100	22.50	194	23.00	198	19.20§	166	13.60¶	117	.....	...	.....	...	.....	...	.....	...
L. I.	7.98	100	17.60	220	20.80	261	14.00	176	9.84	123	.....	...	.....	...	.....	...	.....	...
F. C.	6.88	100	15.90	231	17.70	258	6.50	95	6.35	92	.....	...	.....	...	.....	...	.....	...
M. R.	9.87	100	16.07	172	22.60	229	17.60§	178	11.95	121	.....	...	.....	...	.....	...	.....	...
C. S.	9.70	100	18.70	193	19.00	205	12.30	127	8.10	84	.....	...	.....	...	.....	...	.....	...
B. O.	7.19	100	17.80	248	19.40	270	12.02	167	7.56	105	.....	...	.....	...	.....	...	.....	...
A. V.	7.75	100	14.90	192	17.70	228	12.40	160	8.35	108	.....	...	.....	...	.....	...	.....	...
E. W.	8.60	100	21.20	238	27.70	315	22.50‡‡	257	13.10	147	.....	...	.....	...	.....	...	.....	...
F. K.	9.24	100	16.10	174	19.10	215	15.00‡	163	12.85**	140	.....	...	.....	...	.....	...	.....	...
Average	9.12	100	18.30	201	21.70	238	††	...	10.60	116	.....	...	.....	...	.....	...	.....	...

* First minute of rest after exercise.
† Two minute and 45 second period.
‡ Average does not include figures for F. R. S.
§ Four minute period.
¶ Four minute and 30 second period.
‡ Three minute and 30 second period.
** Four minute and 45 second period.
†† Average could not be calculated on account of variation in length of periods.

TABLE 7.—Minute-Volume of Pulmonary Ventilation Per Square Meter of Body Surface Area.

Normal Subjects	Period I Rest		Period II Exercise		Period IIa *		Period III Rest		Period IV Rest		Period V Exercise with Load		Period Va *		Period VI Rest		Period VII Rest	
	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation	Liters	Percentage Variation
J. D. T.	4.15	100	8.26	199	11.10	268	7.00	169	4.50	109	9.82	237	12.70	306	7.09	171	4.59	111
F. F.S.	3.06	100	8.25	270	9.63	314	5.05	165	3.38	107	9.57	311	9.39	296	5.49	180	3.40	147
L. L.	4.05	100	7.64	189	10.20	253	6.41	158	4.60	114	9.15	226	11.10	274	6.53	161	4.51	111
H. B.	4.01	100	7.84	196	8.25	206	5.98	149	4.56	114	11.80	294	12.30	307	8.04	200	5.12	128
F. W. P.	3.63	100	8.62	271	10.29	284	5.89	162	4.03	111	10.70	295	12.50	344	7.15	196	4.06	112
F. R. S.	2.94	100	9.35	237	10.90	277	6.48	164	4.47	113	11.70	297	18.50	470	12.10†	307	5.87	149
W. E.	4.85	100	8.29	171	11.20	231	6.97	144	4.77	98	9.07	199	13.80	285	8.25	170	4.78	99
L. C. S.	3.45	100	7.77	225	8.93	259	5.66	164	3.91	113	9.55	277	10.50	306	6.49	188	3.73	108
J. T. L.	3.85	100	8.89	231	10.36	268	6.31	164	4.36	114	12.20	317	14.80	384	8.18	213	4.68	122
H. R. M.	4.33	100	6.43	149	10.60	245	6.46	149	4.53	105	9.70	224	14.40	333	8.54	197	4.63	107
J. W.	3.83	100	7.94	219	7.51	207	5.24	144	4.15	114	10.60	292	9.84	271	6.82	188	4.37	120
Average	3.90	100	8.06	207	9.88	253	6.13	157	4.29	110	10.40	267	12.70	326	7.26‡	186	4.53	116
Cardiac Patients																		
M. McG.	4.87	100	9.26	190	13.20	271	8.80§	181	5.74	118	.....	...	.....	...	.....	...	.....	...
F. D.	6.17	100	11.10	181	12.60	206	9.84§	161	8.04	131	.....	...	.....	...	.....	...	.....	...
R. G.	6.16	100	12.00	195	12.30	200	10.26§	166	7.24¶	118	.....	...	.....	...	.....	...	.....	...
I. I.	4.39	100	9.64	220	11.40	260	7.72	176	5.41	123	.....	...	.....	...	.....	...	.....	...
F. C.	3.84	100	8.87	231	9.87	257	5.01	131	3.55	92	.....	...	.....	...	.....	...	.....	...
M. R.	5.88	100	10.10	172	13.40	228	10.50§	179	7.11	121	.....	...	.....	...	.....	...	.....	...
C. S.	6.15	100	11.90	194	12.80	208	7.83	127	5.17	84	.....	...	.....	...	.....	...	.....	...
B. O.	4.61	100	11.40	247	12.60	273	7.71	167	4.85	105	.....	...	.....	...	.....	...	.....	...
A. V.	5.03	100	9.63	192	11.70	233	8.07	160	5.42	108	.....	...	.....	...	.....	...	.....	...
E. W.	5.82	100	13.90	239	18.10	311	15.00#	258	8.57	147	.....	...	.....	...	.....	...	.....	...
F. K.	6.20	100	10.80	174	13.50	215	10.10	163	8.62**	139	.....	...	.....	...	.....	...	.....	...
Average	5.37	100	10.78	203	12.84	238	††	...	6.34	118	.....	...	.....	...	.....	...	.....	...

* First minute of rest after exercise.
† Two minute and 15 second period.
‡ Average does not include figure for F. R. S.
§ Four minute period
¶ Four minute and 30 second period.
# Three minute and 30 second period.
** Four minute and 45 second period.
†† Average could not be calculated on account of variation in length of periods.

and IV. Determinations of minute-volume for shorter periods of time are, of course, less significant, but it is noteworthy that the pulmonary ventilation was greater for the first fifteen seconds of rest than for the last fifteen seconds of exercise in six normals and in five cardiac patients. The greatest subjective dyspnea thus corresponds closely with the highest minute-volume of pulmonary ventilation.

Immediately after the first minute of rest, in which the pulmonary ventilation reached its highest peak, there was a rapid recovery with a drop in the minute-volume from this maximum toward the level at which it was before the exercise was begun. There is a good deal of variation in the rate at which the minute-volume falls in different individuals, but in the normal subjects it generally reached to within about a liter of the original minute-volume during the fourth minute of rest. In the case of the patients with heart disease the decrease in the minute-volume after exercise was usually less rapid. This is best shown in the chart. It is impossible to determine just when the minute-volume of this group tended to return to what it was before the exercise, because in five instances the collection of air in Period III was not made in the fifth minute, but during the fourth minute the average minute-volume was two liters above the resting level. The cardiac patients thus took about one minute longer than the normals to return to approximately the same pulmonary ventilation that they had before the beginning of exercise. Even then, however, the return was less complete in the group of patients with heart disease than it was in the group of normals, for during Period IV seven of the former still had a minute-volume which was relatively higher than that of any of the normal subjects.

When walking upstairs with a pack (Period V) the normals began to experience a degree of dyspnea which was comparable to that observed in the cardiac patients in Period II. It is extremely interesting in this connection that the actual pulmonary ventilation per square meter surface area averaged almost exactly the same for the normals in Period V as for the patients with heart disease in Period II, although the increase over the ventilation at rest was proportionately much greater. In this second series of experiments the subjects again stated that dyspnea became more marked after they stopped their exercise. Period Va in Tables 6 and 7 gives the figures for the minute-volume during the first minute after the exercise. Just as in the case of the first walk (Period II), it was found that the minute-volume of air breathed was almost invariably greater in the first minute after exercise than it was during the exercise itself, and the most marked subjective dyspnea corresponded in time with the highest minute-voluume of pulmonary ventilation.

Rate of Respiration.—The observations on the rate of respiration in Table 8 show that it was distinctly higher in the patients with heart disease than in the normal subjects. This point was noticed only after the experiments on the normals had been completed, and there was no opportunity to obtain comparative observations on the rate of respiration at complete rest, but in eight cardiac patients pneumographic records were made after they had been lying on the bed absolutely quietly for at least one-half hour, and the rate was found to vary between 14 and 21 per minute. In all subjects a record of the rate of breathing was taken while they were sitting on a chair after having been at rest for at least one-half hour and before the mask was put on. The rate of respiration of the normals was between 12 and 20 per minute, and in eight subjects it was between 12 and 17, while in all the patients with heart disease it was between 17 and 26 per minute. The same difference holds with regard to the respiration rates while the subjects were standing at rest on the treadmill (Period I). In the group of normals the rate varied between 7.80 and 17.60 per minute, being below 15 in eight instances, while in the cardiac patients the rate was between 13 and 27.80 per minute, and was below 19 in only four instances. The fact that the rate of breathing was usually slower while standing in Period I than when sitting at rest resulted from wearing the face mask. During the walk upstairs (Period II) the rate of breathing increased in both groups, and the actual rate became considerably higher in the cardiac patients, but it is interesting that the average percentage increase over the average rate before exercise was almost exactly the same in the two groups. The fall in the rate of breathing, after the cessation of exercise, also appears to proceed in a similar manner in both sets of observations, and it was essentially complete in Period IV.

During the second exercise period (Period V), when the pack was carried, the rate of respiration of the normal subjects rose still further, reaching an average of 21.20 per minute, but this was followed by a rapid drop so that in Period VII the rate had returned to nearly what it was before the exercise.

Volume per Respiration.—Table 9 gives the average volume per respiration for each period in the two groups of subjects. This was obtained by dividing the total volume of air collected during the period by the rate of respiration. It is immediately apparent that the patients with heart disease breathed less deeply than the normal subjects when standing at rest (Period I). The average volume per respiration for the normals was 584 c.c. and for the cardiac patients it was 467 c.c., a difference of about 25 per cent. The variation was considerable in both groups, running from 412 to 870 c.c. among the normals, and from 320 to 683 c.c. among the patients with heart disease, but in eight of

TABLE 8.—Rate of Respiration.

Normal Subjects	Sitting at Rest	Period I Rest		Period II Exercise		Period III Rest		Period IV Rest		Period V Exercise with Load		Period VI Rest		Period VII Rest	
		Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation	Rate per Minute	Percentage Variation
J. D. T.	14.6	13.2	100	15.0	114	12.6	95	11.4	86	17.0	129	11.8	89	12.0	91
F. F-S.	15.4	14.0	100	20.0	143	16.2	116	14.0	100	22.0	157	16.4	117	14.0	100
L. L.	16.2	12.4	100	17.0	137	15.0	121	14.5	117	21.0	169	14.6	118	14.4	116
H. B.	21.8	16.0	100	25.0	156	16.0	100	14.6	91	28.0	175	20.6	129	18.4	115
F. W. P.	12.0	10.4	100	19.0	183	12.2	117	11.0	106	19.0	183	12.8	123	11.2	108
F. R. S.	16.8	17.6	100	20.0	114	22.6	128	16.4	93	30.0	170	22.6*	134	19.0	108
W. E.	20.0	17.4	100	20.0	115	19.6	113	18.6	107	18.0	103	19.2	110	18.0	103
I. C. S.	12.2	8.6	100	17.0	198	11.4	133	11.0	128	18.0	209	12.0	140	9.1	106
J. T. L.	14.2	7.8	100	11.0	141	11.6	149	9.2	118	26.0	334	16.8	215	12.6	161
H. R. M.	17.7	14.2	100	18.0	127	16.0	113	15.2	107	18.0	127	18.2	128	15.6	110
J. W.	11.8	10.0	100	15.0	150	13.0	130	12.8	128	16.0	160	13.6	136	12.6	126
Average	15.7	12.9	100	17.9	139	15.1	117	13.5	105	21.2	164	15.6‡	121	14.3	111
Cardiac Patients															
M. McG.	19.4	17.2	100	24.0	140	19.8§	115	19.6	114	....	....	....	....	....	....
F. D.	24.6	22.8	100	30.0	132	24.5§	107	21.0	92	....	....	....	....	....	....
R. G.	20.4	23.8	100	26.0	109	21.5§	90	21.2§	89	....	....	....	....	....	....
L. I.	18.6	17.0	100	27.0	159	21.6	127	20.2	119	....	....	....	....	....	....
F. C.	18.2	13.0	100	24.0	185	16.4	126	14.2	109	....	....	....	....	....	....
M. R.	24.2	22.0	100	28.0	127	28.2‡	128	27.4	125	....	....	....	....	....	....
C. S.	20.4	25.0	100	34.0	136	30.0	120	24.4	98	....	....	....	....	....	....
H. O.	24.8	20.4	100	36.0	176	28.2	138	22.6	111	....	....	....	....	....	....
A. V.	29.8	19.8	100	28.0	141	20.4	103	19.6	99	....	....	....	....	....	....
E. W.	17.2	13.0	100	23.0	177	22.2¶	178	19.0	146	....	....	....	....	....	....
F. K.	25.5	27.8	100	35.0	126	29.2	105	33.0#	119	....	....	....	....	....	....
Average	21.5	20.2	100	28.6	142	**	...	22.0	109	....	....	....	....	....	....

* Two minute and 45 second period.
† Average does not include figures for F. R. S.
‡ Four minute period.
§ Four minute and 30 second period.
¶ Three minute and 30 second period.
# Four minute and 45 second period.
** Average could not be calculated on account of variation in length of periods.

TABLE 9.—VOLUME PER RESPIRATION.

Normal Subjects	Period I Rest		Period II Exercise		Period IIa *		Period III Rest		Period IV Rest		Period V Exercise with Load		Period Va *		Period VI Rest		Period VII Rest	
	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation	Volume, C.c.	Percentage Variation
J. D. T.	630	100	1,108	176	1,830	289	1,115	177	794	126	1,157	184	2,320	368	1,202	191	768	122
E. F. S.	470	100	588	188	920	219	598	142	450	107	892	198	1,070	255	640	137	472	112
L. L.	613	100	946	178	1,170	183	807	132	596	97	820	134	1,160	189	843	138	586	96
H. B.	469	100	588	125	970	207	700	149	584	124	790	168	980	209	728	155	520	111
F. W. P.	648	100	785	121	1,250	208	963	120	682	105	1,049	162	1,670	258	1,040	160	675	104
F. R. S.	412	100	840	209	830	201	627	128	500	121	713	173	1,010	252	940†	228	568	138
W. E.	591	100	745	140	1,060	212	643	128	461	92	968	193	1,380	275	775	155	473	94
I. C. S.	716	100	813	114	1,220	170	888	124	632	88	945	132	1,010	160	946	135	729	102
J. T. L.	870	100	1,479	164	1,340	154	958	110	825	96	978	95	1,190	137	856	98	653	75
H. R. M.	536	100	638	117	1,090	203	713	133	525	98	950	177	1,290	241	825	154	522	98
J. W.	613	100	892	146	980	160	680	111	548	89	1,120	183	1,110	181	860	139	585	95
Average	584	100	807	148	1,150	197	776	132	601	103	925	158	1,310	224	879‡	151	613	105
Cardiac Patients																		
M. McG.	560	100	764	137	1,090	195	880§	157	580	104	.....	...	.....	...	.....	...	.....	...
F. D.	510	100	726	137	850	167	760§	149	652	128	.....	...	.....	...	.....	...	.....	...
R. G.	488	100	865	177	1,060	215	803§	183	641§	131	.....	...	.....	...	.....	...	.....	...
L. I.	470	100	632	139	990	211	648	138	487	104	.....	...	.....	...	.....	...	.....	...
F. C.	529	100	663	125	740	140	397	75	447	85	.....	...	.....	...	.....	...	.....	...
M. R.	447	100	605	135	840	188	635§	142	436	98	.....	...	.....	...	.....	...	.....	...
C. S.	387	100	550	142	540	140	410	106	332	86	.....	...	.....	...	.....	...	.....	...
B. O.	352	100	496	141	570	162	427	121	334	95	.....	...	.....	...	.....	...	.....	...
A. V.	391	100	534	137	770	197	598	153	425	109	.....	...	.....	...	.....	...	.....	...
E. W.	683	100	924	135	1,150	168	987‡	144	680	100	.....	...	.....	...	.....	...	.....	...
F. K.	339	100	490	144	660	206	515	161	390**	122	.....	...	.....	...	.....	...	.....	...
Average	467	100	656	141	840	180	††	...	491	105	.....	...	.....	...	.....	...	.....	...

* First minute of rest after exercise.
† Two minute and 45 second period.
‡ Average does not include figures for F. R. S.
§ Four minute period.
¶ Four minute and 30 second period.
‡ Three minute and 30 second period.
** Four minute and 45 second period.
†† Average could not be calculated on account of variation in length of periods.

the normal subjects the volume per respiration was between 501 and 870 c.c., while in nine of the cardiac patients it was between 320 and 529 c.c. The difference in volume per respiration between the two groups depends, in part, on the fact that the normals were the larger men, but this does not completely explain it, for, when the volume per respiration was calculated with relation to the size of the subject, it was found that the average for the normal group was 317 c.c. per square meter of body surface area, and for the cardiac patients 274 c.c. per square meter. In eight of the normals the volume per respiration was between 278 and 483 c.c. per square meter of body surface area, and in ten of the cardiac patients it was between 215 and 283 c.c. per square meter.

In the period of exercise (Period II) the depth of respiration became greater in both groups of subjects. The actual volumes were considerably larger among the normals than among the cardiac patients, but, as was the case with the minute-volume and rate of respiration, the percentage increase of the volume per respiration over that before exercise was approximately the same in the two series of experiments. Immediately after the cessation of exercise, when the pulmonary ventilation was greatest (Period IIa), the depth of breathing increased in all the subjects, but the increase was proportionally more in the normal subjects than in the patients with heart disease. The actual tendency to more shallow breathing on the part of the cardiac patients was shown by the fact that at this period the volume per respiration was between 540 and 850 c.c. in seven of the eleven subjects, while in ten of the eleven normals it was more than 900 c.c

During the rest period after exercise (Period III), there was a rapid fall in the volume per respiration which proceeded at about the same rate in the two groups, and in the second rest period (Period IV) the depth of respiration in both groups was very nearly the same as it was before the exercise began.

In Period V, in which the normal subjects walked with the load, the volume per respiration was almost constantly a little greater than in the first exercise period, and it increased considerably in the first minute of rest after exercise (Period Va), but decreased again rapidly during the rest after exercise and was practically normal during Period VII.

An analysis of the factors of the pulmonary ventilation which have been studied shows that there is a fairly definite relationship between the rate of respiration and the minute-volume of respiration, in that there is a general tendency, to which there are individual exceptions, for the higher minute-volume to be associated with the more rapid rates of breathing. In a similar manner, the higher minute-volumes are usually accompanied by more shallow respirations. This general association between high minute-volume and rapid, shallow respiration is

probably explained by the fact that with shallow breathing the "dead space" of the upper respiratory tract becomes a more important factor since a relatively larger portion of each inspiration remains in it and takes no part in gaseous exchange. In order to maintain the necessary volume of alveolar ventilation it is, therefore, essential that the rate, and consequently the total minute-volume of respiration, shall be increased. There was no definite relationship between the volume per respiration and the vital capacity of the lungs in the patients with heart disease studied in these experiments. This is not at all surprising since the vital capacities were on the whole only slightly less than normal and the exercise was not severe enough to require deeper respiration than could easily be produced.

Heart Rate.—In an investigation of dyspnea in heart disease it would, of course, have been highly desirable to obtain information regarding the output of the heart, but owing to the lack of any suitable method it was necessary to limit the observations to determinations of the heart rate. In how far the heart rate and the minute-volume of cardiac output run parallel in such cases as are under consideration is a problem which cannot be settled definitely on the basis of our present knowledge, but the relation between the two is probably close enough to warrant a careful study of the cardiac rate. Since it is almost impossible to count the heart rate accurately by ordinary methods when subjects are walking on the treadmill, recourse was had to the electrocardiograph, which has the great advantage of enabling one to obtain continuous graphic records. By the use of two electrodes applied firmly to the sides of the body just below the axillae and a third electrode, which was grounded, placed just above the pubis, it was possible to obtain satisfactory records in almost every instance. Short electrocardiographic records were taken after the subject had been sitting quietly for one-half hour and again when he was standing on the treadmill (Period I). Twenty seconds before the exercise was begun a continuous electrocardiographic record was started which ran through the exercise period (Period II) and throughout the first minute after exercise. Frequent counts of the heart rate were made after this by watching the string of the electrocardiograph, and these counts were averaged to get the rate in each of the following minutes of the two rest periods (Periods III and IV). The same method was followed in Periods V, VI and VII. The results are shown in Table 10.

The heart rate was, in general, somewhat more rapid in the patients with heart disease than in the normal subjects. While sitting at rest the rates of the cardiac patients were between 86 and 102, while the rates of the normals were between 69 and 95, and in ten out of eleven subjects they were between 69 and 88 per minute. The same difference holds true for the heart rate while standing at rest on the treadmill

TABLE 10.—Heart Rate

Normal Subjects	Sitting	Period I *	Preliminary	Period II †				Period III ‡								Period IV *	Preliminary	Period V †				Period VI ‡								Period VII *
				15 sec.	30 sec.	45 sec.	60 sec.	15 sec.	30 sec.	45 sec.	60 sec.	2 min.	3 min.	4 min.	5 min.			15 sec.	30 sec.	45 sec.	60 sec.	15 sec.	30 sec.	45 sec.	60 sec.	2 min.	3 min.	4 min.	5 min.	
J. D. T.	73	76	76	88	98	102	110	98	95	78	80	71	72	99	69	74	76	96	108	108	116	114	109	90	86	80	69	67	69	73
F. F-S.	69	74	70	92	104	113	120	115	96	75	60	61	67	72	75	78	79	104	116	118	126	124	105	81	76	70	69	72	69	76
L. L.	88	88	88	104	112	112	116	108	103	97	80	88	78	90	82	85	84	108	116	120	124	120	104	104	84	88	78	78	72	81
H. B.	86	90	84	100	112	114	122	112	101	92	88	79	78	90	86	95	90	110	124	133	144	138	126	112	96	97	95	86	90	91
F. W. P.	76	87	86	96	105	110	110	111	108	93	90	86	90	86	95	92	98	102	115	127	126	123	114	104	99	89	86	95	90	92
F. R. S.	72	78	84	100	104	104	105	...	85	68	64	65	72	72	72	74	...	100	116	120	138	138	120	104	92?	75	66	60	64	77
E. W.	83	88	97	104	109	111	114	112	102	92	82	77	86?	84	90	87	91	102	116	120	128	124	116	103	91	83	78	80	90?	84
I. C. S.	77	81	...	...	...	...	...	...	...	...	...	...	67	...	...	80	...	...	...	...	...	...	...	...	...	...	78	82	86	82
J. T. L.	86	92	98	112	121	128	132	129	106	100	88	97	100	95	100	98	110	116	126	128	135	...	...	...	...	...	106	100	95	95
H. R. M.	80	84	...	99	110	115	116	116	112	97	88	79	77	78	82	85	91	108	120	124	132	139	136	123	108	94	78	72	78	82
J. W.	95	113	121	134	140	138	138	132	124	118	113	110	113	113	103	104	124	138	147	144	146	144	135	125	116	115	113	113	113	114
Cardiac Patients																														
M. McG.	87	...	98	112	123	128	133	136	128	120	112	84	82	90	98	101	...	...	...	...	...	...	...	...	...	...	...	...	...	...
F. D.	86	86	106	123	122	118	118	116	101	97	94	92	95	100	95	94	...	...	...	...	...	...	...	...	...	...	...	...	...	...
R. G.	97	112	102	115	125	130	133	140	136	125	110	106	111	113	113	110	...	...	...	...	...	...	...	...	...	...	...	...	...	...
L. I.	62	76	80	89	92	97	108	108	101	95	86	77	78	78	81	83	...	...	...	...	...	...	...	...	...	...	...	...	...	...
F. C.	82	96	...	112	126	128?	132	136	116	104	90	82	82	86	91	97	...	...	...	...	...	...	...	...	...	...	...	...	...	...
M. R.	90	90	...	100	109	115	120	119	108	104	94	88	86	82	90	93	...	...	...	...	...	...	...	...	...	...	...	...	...	...
C. S.	96	97	100	121	129	136	136	126	120	104	99	96	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
B. O.	68	82	83	104	114	119	120	106	88	80	75	70	64	72	72	71	...	...	...	...	...	...	...	...	...	...	...	...	...	...
A. V.	92	93	92	116	132	139	136	142	132	122	130	112	105	98	97	97	...	...	...	...	...	...	...	...	...	...	...	...	...	...
E. W.	99	105	...	108	124	136	144	148	148	148	148	146	134	139	127	119	...	...	...	...	...	...	...	...	...	...	...	...	...	...
F. K.	102	118	124	138	150	150	150	154	148	145	136	130	134	134	132	129	...	...	...	...	...	...	...	...	...	...	...	...	...	...

* Average rate for 5 minute period.
† Heart rates are given for each 15 seconds during exercise period of 1 minute.
‡ Heart rates are given for each 15 seconds for first minute, and then for each minute during remainder of period.

(Period I). Eight out of ten of the cardiac patients had rates between 86 and 118, and eight out of eleven normals had rates between 74 and 88 per minute. The average heart rate of the cardiac patients while standing at rest was 95 and that of the normal subjects was 86 per minute. The difference is thus about 11 per cent.

The column of figures under the heading "preliminary" in Table 10 gives the heart rate during the twenty seconds preceding the exercise period. The subject knew that he was about to start to walk and the changes in heart rate represent what is probably largely a nervous reaction. Among the normals there was an increase in rate of from five to nine beats per minute in four instances, a decrease of from one to three beats in three, and no change in two instances. In the group of cardiac patients seven showed a rise of from one to twenty beats, with an average increase of five, and three showed a fall of from one to ten beats, the average being four per minute. There is thus no constancy in the behavior of the subjects in this preliminary period and no distinct difference between the two groups.

At the onset of the exercise (Period II) there was an immediate rise in heart rate in both groups of subjects. In the normals the rate during the first fifteen seconds of exercise averaged 16 beats per minute higher than the rate while standing at rest, with variations of from nine to twenty-two among ten individuals. In the cardiac group the corresponding average increase was 17 beats, with variations of from three to thirty-seven in ten cases. During the last fifteen seconds of exercise, when the heart rate was usually greatest, the average increase of the normals was thirty-one, with extreme variations between twenty-three and forty-six, while the average increase in the group of cardiac patients was thirty-four, with extreme variations between twenty-one and forty-three per minute. The mean increase in heart rate was a little greater in the cardiac group than in the normals, as in seven out of ten cases of the former there was an increase of between thirty-two and forty-three, while in seven out of ten of the latter it was between twenty-one and thirty-two per minute. The differences are not striking, however, and the high heart rates reached by the patients with heart disease seem to depend largely on the fact that they started with a higher resting pulse rate.

Immediately after the cessation of exercise there was almost invariably a sudden drop in pulse rate in the normal subjects. This was such that even in the first fifteen seconds of the rest period (Period III) there was a fall of from two to twelve beats per minute from the rate at the end of exercise, with an average decrease of seven beats per minute in seven out of nine of the normal subjects. In one instance there was an increase of one beat per minute and in one instance there was no change in rate. The drop in pulse rate did not begin

so promptly in the cardiac patients, for in six out of eleven cases it rose slightly (between three and seven beats), in one it remained unchanged, and in only four was there a fall of between one and fourteen beats per minute in the first fifteen seconds of rest. The decrease in heart rate continued to be rapid in the normals so that between thirty and forty-five seconds after the exercise was stopped only four of the ten subjects had a pulse rate more than five beats per minute higher than it was before exercise was begun, and between forty-five and sixty seconds after cessation of exercise none had a heart rate more than five beats per minute above the rate standing at rest, and in six instances it was below this rate. This tendency to bradycardia continued so that during the second minute of rest the pulse was lower than it was before exercise in eight subjects. In the patients with heart disease the fall in heart rate went on more slowly. Between fifteen and thirty seconds after exercise was stopped the heart rate remained above what it was during exercise in two cases. Between thirty and forty-five seconds after exercise the heart rate was more than five beats per minute above that before exercise in all but one instance, and between forty-five and sixty seconds after exercise five of the ten cases still had a rate of more than five per minute above the rate while standing before exercise. Three out of nine patients with cardiac disease continued to have a heart rate considerably above that preceding exercise even during the second rest period (Period IV).

An analysis of the heart rate in these two groups of subjects does not allow of any satisfactory quantitative relation being established, but it is quite evident that the fall in heart rate in the normal subjects usually began immediately after exercise stopped and was constantly such that within one minute it had reached the level that it was before the exercise began, while in the group of patients with heart disease there was often a slight rise in rate after exercise stopped, followed by a slower fall to the level at which it was before exercise. During the rest period there was a tendency, in both groups of subjects, for the heart rate to pass through a phase in which it was even more slow than it was before the exercise.

In the period in which the normal subjects walked upstairs carrying a load on their backs there was again a rapid rise in pulse rate varying from ten to thirty-four beats per minute, with an average rise of twenty-one above the heart rate at rest in the first fifteen seconds of exercise. In the fourth fifteen seconds of exercise the increase of heart rate was from thirty-four to fifty-four, with an average rise of forty-two beats per minute. When the exercise was stopped there was an immediate slight fall in rate, averaging three beats per minute in the first fifteen seconds of rest in seven subjects, a rise of seven beats in one, and in one subject no change of rate. Between thirty and

forty-five seconds after the cessation of exercise all but one of the subjects continued to have a rate of more than five beats above the resting values, and between forty-five and sixty seconds after exercise the rate was more than five beats per minute above the rate before exercise in all but four subjects. In the second minute of rest the rate had come down at least to what it was before exercise in six out of nine instances, and in the third minute of rest this was the case in nine out of eleven subjects. There was a general tendency here also for the heart to assume temporarily a slower rate than before exercise. In general, therefore, this more severe exertion was followed by a rather gradual fall in heart rate in the normal subjects which resembled that observed in the patients with cardiac disease after moderate exercise.

DISCUSSION

In the previous sections a detailed analysis has been given of the changes produced by slight amounts of exercise in the metabolism, pulmonary ventilation, and heart rate in a group of normal young men and in a group of patients of approximately the same age with valvular heart disease. All of the latter were ambulatory patients, but the effect of the cardiac lesion varied in different cases so that while some of them suffered from dyspnea on moderate exertion, others were scarcely at all limited in their physical activities. In general, those subjects with the greatest tendency to dyspnea were those in whom the vital capacity of the lungs was lowest. Certain fundamental differences between the two groups were observed while they were standing at rest before the exercise began. In the patients with heart disease, the oxygen consumption, the heart rate, and the minute-volume of pulmonary ventilation were greater than in the normals, and the respiration was more rapid and more shallow than in the normal subjects. The metabolism of the group of cardiac patients, as measured by the oxygen consumption, averaged 12 per cent. higher than that of the group of normals, and, in the light of the fact that basal metabolism and heart rate have frequently been found to bear a close relation to one another, it is interesting to find that the average heart rate for the group of cardiac patients was about 11 per cent. above that of the group of normals. It seems probable that the more rapid heart action depended largely on the higher rate of metabolism. The minute-volume of pulmonary ventilation, on the other hand, averaged 37 per cent. greater in the group of cardiac patients than in the normals—an increase which is much too large to be accounted for entirely by the difference in metabolism. This high minute-volume of the respiration was associated with breathing which was more rapid and more shallow, and in which the percentage of oxygen taken out of the inspired air was less than in the case of the normal subjects. The higher minute-volume

breathed by the cardiac patients was probably the result of shallow breathing, with a consequent increase of the effect of the "dead space" of the upper respiratory tract. Under such circumstances the ventilation of the alveoli which is essential for proper gaseous exchange can only be obtained if the total amount of air breathed is increased, and this must be accomplished by raising the rate of respiration. Another possible explanation, however, deserves attention. It has been shown by Barr and Peters [7] that not only the total pulmonary ventilation, but also the effective minute-volume, is increased above normal in patients with cardiac decompensation. According to their observations this is due to the low percentage of carbon dioxid in the alveolar air of patients with cardiac decompensation and the consequent necessity of an increased effective ventilation in order to bring about the requisite elimination of carbon dioxid. Further studies on the blood by Peters and Barr [8] indicate that this low alveolar carbon dioxid is "largely brought about by an impairment of the efficiency of the pulmonary mechanism for the exchange of gases between the blood and the outside air" which "necessitates the maintenance of a greater difference in carbon dioxid pressure between the blood in the pulmonary circulation and the alveolar air to effect the normal carbon dioxid output." The cardiac patients who were the subjects of the present investigations, however, were all ambulatory, and one can hardly assume that they had a low alveolar carbon dioxid tension since Barr and Peters found this to be characteristic only of patients who were actually decompensated.

According to the calculations of Barr and Peters, the effective ventilation of a group of decompensated patients studied by Peabody, Wentworth and Barker [5] was about 30 per cent. greater than that of a similar group of compensated patients. Calculated on the same basis, with the assumption of a "dead space" for the subjects of 130 c.c. and an instrumental "dead space" of 50 c.c. additional, it is found that the average effective alveolar ventilation of the present group of normal subjects, while standing at rest (Period I), was 5,210 c.c., while that of the patients with heart disease, under the same circumstances, was 5,800 c.c. The difference, which is scarcely more than 10 per cent., can well be accounted for by the fact that the oxygen consumption of the group of cardiac patients was about 12 per cent. greater than that of the normals. Beyond this, therefore, the evidence indicates that in the two groups the effective, or alveolar ventilation, is of essentially the same magnitude and thus the findings of Barr and Peters do not account for the high minute-volumes observed in the compensated cases studied in this investigation.

7. Barr, D. P., and Peters, J. P., Jr.: Am. J. Physiol. **54**:345, 1920.
8. Peters, J. P., Jr., and Barr, D. P.: J. Biol. Chem. **45**:537, 1921.

The fact that cardiac patients have a greater total pulmonary ventilation while obtaining practically the same effective ventilation as normal subjects has an important bearing on the production of dyspnea, because it has been found that the sensation of dyspnea is closely associated with the breathing of a high minute-volume of air, and the explanation of this phenomenon should be sought. The question arises as to whether an essentially mechanical cause may underlie the tendency to a rapid and shallow respiration observed in patients with heart disease. In the group of patients under consideration the vital capacity was so little below normal that it is rather difficult to conceive of there being any restriction to the depth of breathing, especially while they were standing quietly at rest and using only a small portion of their vital capacity at each respiration. The possibility of some limitation to the depth of breathing is, nevertheless, worthy of consideration. Drinker, Peabody and Blumgart[9] have shown experimentally that engorgement of the pulmonary vessels may interfere with the entrance of air into the lungs, and their results indicate that the decrease in the vital capacity of the lungs in early cases of heart disease, in which there is no pulmonary edema or effusion into the pleural cavities, is due to congestion of the pulmonary circulation. Cardiac lesions potentially capable of causing engorgement of the pulmonary vessels were present in all the patients in the present study and in all but three the vital capacity was below the usual normal limits. The decrease was not great in any of the cases but it does not seem unreasonable to suppose that whereas the violent muscular effort exerted in measuring the vital capacity of the lungs would result in an essentially normal volume being taken into them, nevertheless, it might be easier for the same subject to take shallow respirations. If such were the case, they would instinctively breathe less deeply, even when they were at rest, than normal persons. Quite possibly this is a matter which concerns the Herring-Breuer reflex and there is much evidence to indicate the extreme sensitiveness of this mechanism. Even if such a conception is accepted it is not surprising to fail to find complete harmony in individual cases between the volume of the tidal air and the decrease of the vital capacity of the lungs. E. J. W., for instance, whose vital capacity was 62 per cent. of normal, breathed slowly and deeply while at rest and even during exercise. This may have been due to more or less conscious effort. Individual exceptions will always be found in the study of any mechanism which, like the respiration, is under the control of so many factors, chemical and nervous, and at present one can only suggest that the general tendency to shallow breathing seen in patients with heart disease is due to engorgement of the pulmonary circulation.

9. Drinker, C. K.; Peabody, F. W., and Blumgart, H.: J. Exper. M. (in press).

During the period of exercise, which consisted in walking sixty steps upstairs in one minute, there was an increase in oxygen consumption, heart rate, minute-volume, and rate and depth of respiration in the two groups of subjects, and the effect produced was essentially the same in both. A given amount of exercise apparently causes a rise in metabolism, heart rate and pulmonary ventilation in patients with cardiac disease that is proportionally the same as that observed in normal subjects. There was no difference in the type of reaction to exercise between the two groups.

The patients with heart disease became more short of breath as the result of the exercise than the normal subjects did, but in both groups the dyspnea was almost constantly described as being greater immediately after the exercise stopped than it was during the actual exercise itself. For this reason the first minute of rest after exercise was studied with particular care. It was found that the minute-volume of the respiration rose so that it was considerably higher during the first minute of rest than during the minute of actual exercise in both groups of subjects. The highest minute-volume of pulmonary ventilation was thus coincident with the greatest subjective dyspnea. The actual volumes breathed were greater in the case of the cardiac patients than in the case of the normals. The former, therefore, approached nearer to their maximum pulmonary ventilation and encroached farther on their pulmonary reserve.

Why is the sensation of dyspnea more noticeable after exercise than during exercise? It is reasonable to seek the answer to this question in the explanation of the high pulmonary ventilation after exercise, for the degree of dyspnea varies with the intensity of the stimulus to respiration, and the response of the respiratory center is indicated by the extent of the pulmonary ventilation. One of the most important stimuli to the respiratory center is carbon dioxid, and the respiratory quotients, which were generally low during exercise and high during the period following exercise, suggest that there was a lag in its excretion. This would result in a prolongation of its stimulation of the respiratory center, and cause a high pulmonary ventilation even after the exercise was stopped. The fact that the minute-volume of respiration was sometimes actually greater immediately after exercise than during exercise may depend in part on mechanical interference with the respiratory movements at a time when other bodily movements are being actively carried on.

Following the rise in the minute-volume of the respiration, which occurred immediately after exercise, there was a gradual decrease in minute-volume in both groups of subjects, but the return to the level which existed before exercise was distinctly slower in the patients with

heart disease than in the normal subjects. Hunt and Dufton [10] have recently called attention to the same phenomenon. It is undoubtedly due to an abnormal delay in the excretion of carbon dioxid or other stimuli of the respiratory center. The fact that the minute-volume increased during and after exercise in the same proportion in the cardiac patients as in the normals indicates that this lag is not due to the pulmonary ventilation being less efficient in the patients with heart disease. Further evidence of this is gained if the effective alveolar ventilation is calculated for the exercise period. Assuming again a total "dead space" of 180 c.c. the average effective ventilation of the normals was 11.6 liters and of the cardiac patients 13.2 liters per minute. The difference amounts to approximately 13 per cent. and is just about the same as the difference found during the rest period before exercise. There is, thus, no reason for considering that the prolonged increase of pulmonary ventilation after exercise in the patients with heart disease studied in this investigation was the result of inefficiency of the lungs in removing carbon dioxid from the system. The cause must be sought elsewhere and it is natural to consider the circulation.

The evidence to be derived from these investigations is incomplete because there were no direct determinations of the minute-volume of the circulation before and during exercise, but the observations on the heart rate bear on the question and are suggestive. In the group of normal subjects the heart rate dropped suddenly and rapidly immediately after the cessation of exercise, reaching the level at which it was before exercise in less than one minute. In contrast to this the decrease in heart rate after exercise in the patients with heart disease began later, was slower, and was sometimes preceded by a slight rise in rate just after the cessation of exercise. Martin and Gruber [11] believe that the sudden rise of heart rate at the onset of exercise is due to associated innervation and the passage of impulses from the cortex which inhibit vagus activity. The sudden fall in heart rate after exercise might be explained by the cessation of such depressing impulses but it is difficult to understand, on this basis alone, why the heart often remains rapid in the patients with cardiac disease. It may, perhaps, be accounted for by assuming the existence of some metabolic stimulus to cardiac acceleration which had failed to be eliminated with normal rapidity in these patients with impaired hearts. The rapid heart action would, then, represent an attempt to raise the minute-volume of the circulation, and this abnormal acceleration would constitute an indication of the inefficiency of the heart to meet the demands put upon it by the strain of exercise. It is, of course, in this sense that the same

10. Hunt, G. H., and Dufton, D.: Quart. J. Med. **13**:165, 1919.
11. Martin, E. G., and Gruber, C. M.: Am. J. Physiol. **32**:315, 1913.

phenomenon is commonly used as a clinical test. With an inadequate circulation the slow elimination of carbon dioxid is easily explained and its retention would result in a stimulation of the respiratory center and account for the prolonged increase of pulmonary ventilation.

According to the conceptions which have been outlined, therefore, the fact that the patients with heart disease had a greater subjective sensation of dyspnea after slight amounts of exercise than normal persons depends on two factors. They had a tendency to breathe less deeply than normal individuals, with the result that the total pulmonary ventilation was greater in order to obtain the same effective alveolar ventilation, and this large pulmonary ventilation was maintained for a longer period of time because the circulation became inadequate during the strain imposed by exercise and the elimination of carbon dioxid was delayed. In cases of heart disease which are more severe than those reported on here, and in whom the vital capacity of the lungs is markedly decreased, the mechanical interference with pulmonary ventilation, owing to inability to breathe deeply, plays a considerably greater rôle in the production of dyspnea.

The normal subjects did not become definitely short of breath as a result of walking upstairs and they were put through a second test, in which they took the same number of steps carrying a load on their backs in order that the development of dyspnea in them comparable in degree to that which occurred in the cardiac patients, might be studied. Greater changes were observed in the metabolism, heart rate and pulmonary ventilation, but the general type of change was the same as was present in the patients with heart disease who undertook less exercise. Even the slower fall in heart rate and minute-volume of respiration after cessation of exercise was seen. The most striking difference noted was that the tendency of the normals to breathe more deeply gave them more effective ventilation of the alveoli of the lungs and thus enabled them to meet a greater demand for oxygen with a lower total pulmonary ventilation. Thus, when walking upstairs and carrying a pack, the normal subjects had a considerably higher oxygen consumption than either they or the cardiac patients had when walking without the pack, but the average minute-volume of pulmonary ventilation was almost exactly the same for the normals when walking with the pack as for the cardiac patients when walking without the pack.

CONCLUSIONS

In a group of eleven ambulatory patients with heart disease it was found that the oxygen consumption and heart rate were slightly greater than in a similar group of normal subjects while standing at rest. Under the same conditions the minute-volume of the respiration was much greater in the cardiac patients and the breathing was more rapid and more shallow.

The slight amount of exercise involved in walking up sixty steps produced the same relative changes in oxygen consumption, pulmonary ventilation and heart rate in the two groups, but it caused more subjective dyspnea in the patients with heart disease. Exercise which was severe enough to cause a corresponding amount of dyspnea in normal subjects caused the same type of changes in oxygen consumption, pulmonary ventilation, and heart rate, but they were greater in degree. The response to exercise of patients with heart disease is qualitatively the same as that in normals, and their greater liability to dyspnea depends on a quantitative limitation.

Shortness of breath was most noticeable immediately after exercise was stopped, and at this time the pulmonary ventilation was largest. The return to normal of the minute-volume of the respiration and of the heart rate was delayed in the cardiac patients.

It is suggested that the two factors which account for the greater dyspnea in the cardiac patients are the inadequate circulation, which results in a delayed elimination of carbon dioxid, and the tendency to shallow breathing, which necessitates a relatively large pulmonary ventilation.

This investigation was begun in association with Dr. Howard F. West and Miss Edna H. Tompkins, and a large amount of preliminary work was done while they were in the laboratory. We regret that they were forced to leave Boston before the present series of experiments was begun, and wish to express our great appreciation of the assistance which they contributed.

STUDIES IN DIABETES INSIPIDUS, WATER BALANCE, AND WATER INTOXICATION

STUDY I

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Two years ago we developed a special interest in diabetes insipidus,[1] and as a result have been carrying out investigations on patients suffering from this disease. During the course of clinical studies certain observations were made which led to experiments in animals relative to water balance and to water intoxication.

In this study we shall report (1) the results of our clinical studies in the fifteen cases of diabetes insipidus observed during the last two years in the Mayo Clinic and in the University Hospital, Minneapolis; (2) the effects on urinary secretion of the subcutaneous injections of the extract of the posterior lobe of the pituitary gland in normal dogs and in dogs which have undergone resection of the renal nerves; and (3) the production of water intoxication by the administration of water by mouth subsequent to the subcutaneous administration of pituitary extract.

STUDIES IN DIABETES INSIPIDUS[2]

Etiology.—We have made an attempt to determine the etiology of the diabetes insipidus in our cases. One patient had brain tumor, not definitely localized but known to be supratentorial; another had a hypophyseal tumor, and four had syphilis; in nine cases no causative factor could be determined. The incidence of syphilis in our series is high. Its etiologic importance has been emphasized by Fournier,[3] Futcher,[4] and Oppenheim.[5] Whether or not syphilis was responsible for the diabetes insipidus in our cases could not be determined, but vigorous treatment for syphilis failed to exercise any significant effect on the course of the diabetes insipidus.

1. Rowntree, L. G.: Diabetes Insipidus. In: Oxford Medicine, London, Oxford Univ. Press **4**:179, 1921.

2. The details of the clinical studies will appear in a separate publication by Dr. E. E. Larson.

3. Fournier: Quoted by Futcher.

4. Futcher, T. B.: Diabetes Insipidus. In: Osler, W., and McCrae, T.: Modern Medicine, Its Theory and Practice, Philadelphia, Lea & Febiger, 1914 **2**:721.

5. Oppenheim, H.: Die syphilitischen Erkrankungen des Gehirns. Specielle Pathologie und Therapie, Vienna, Nothnagel **9**:196, 1896.

The Nature of the Disturbance of Water Balance.—The cardinal symptoms of diabetes insipidus are related to disturbance of water metabolism; water is ingested and excreted in amounts far in excess of normal. In Trousseau's[6] case, for example, the most extreme on record, the fluid intake amounted to 40 liters and the urinary output to 43 liters a day. Thirst, the most annoying symptom, occasions extreme discomfort at times, while polyuria and polydypsia are the source of great inconvenience. Constipation and absence of sweating minimize the loss of fluid from the bowels and skin. The exact amount of fluid lost by way of the lungs and skin has not been determined accurately in diabetes insipidus so far as we know. Such studies are most desirable, but they necessitate the employment of special apparatus. Loss of fluid by way of the lungs plays a relatively smaller part than in the normal person. Studies of fluid balance in our cases show a striking correlation between the fluid intake and the urinary output. The literature abounds with similar results; but some writers have recorded urinary excretion somewhat in excess of the fluid ingested.

The fundamental question of whether the thirst or the polyuria is primary, we find difficult to answer. In this connection we have considered factors as follows: (1) the sequence of onset of symptoms, that is, whether thirst or polyuria constitutes the initial symptom; (2) the influences of various procedures in controlling thirst and urinary output; and (3) the presence or absence of organic or functional changes in the urinary tract.

Sequence of Symptoms.—By careful questioning with regard to the onset of the disease, it was possible, in three of our cases, to elicit a definite history of sudden onset of thirst, and to establish that in two thirst was primary, that is, it preceded the polyuria. In the first case the circumstances surrounding the onset of the disease were such as to make the evidence almost conclusive. The patient, a farmer's wife, was left alone in her home throughout the entire evening. She became extremely nervous and was frantic with fright. She lay in bed most of this time too frightened to move. During this period she developed a terrific thirst. She suffered no discomfort from bladder distention, nor did she void. She states that on the return of the family she rushed to the spigot and drank copiously of water, taking about two quarts. She insists that she did not void at this time, for in order to do so she would have been compelled to pass through several dark vacant rooms, which in her nervous state she would not have attempted. Polyuria developed on the following morning. The second patient, an intelligent man, insists that thirst was the primary symptom, and that it developed during the night. He got up and drank copiously of water,

6. Trousseau, A.: Lectures on Clinical Medicine, London, New Sydenham Soc. **3**:528, 1870.

voided but little, and did not suffer from any discomfort from bladder distention. In the third case both thirst and polyuria came on suddenly, but the patient was unable to recall the order of their appearance. In the remaining twelve cases the onset of the disease was insidious and consequently no conclusions could be reached concerning the priority of the symptoms.[7]

The Influence of Various Procedures in the Control of Thirst and Urinary Output.—Cannon [8] explains normal thirst on the basis of a local sensation resulting from local dryness of the buccal mucous membrane due to decreased secretion from the salivary glands, which in turn is dependent on the diminished supply of fluid furnished these glands by the body because of its depletion in water. Cannon further states that the osmotic pressure of the blood remains unchanged despite deprivation of fluids in the tissues. Dehydration of all tissues, including salivary glands, leads to diminished secretion of water by these glands. Normally the salivary glands furnish the index to the body need for water.

Thirst and a dry mouth were complained of by all our patients. Two volunteered the information that they experienced a peculiar sensation "as though the mouth were full of cotton." One demonstrated that "tenacious strings of saliva stretched from the roof of the mouth to the tongue, when the mouth was opened wide." There is little doubt that the viscidity of the saliva is increased.

We attempted to determine the rôle of the local sensation in the mouth with regard to water intake and urinary output in diabetes insipidus. We believe that specific local nervous influences have been excluded as a cause of the thirst since cocainization of the mucous membrane of the mouth and of the nasopharynx to the point of anesthesia failed to control either the polydypsia or the polyuria. In fact, in one case cocainization was pushed to the point of mild constitutional toxicity with no effect on the diabetes insipidus. In other cases pilocarpin was injected to procure salivary secretion, but without results. In four of these cases there was no evidence of decreased urinary output nor of diminution of thirst. As a result of these studies it appears that the thirst in diabetes insipidus is more than the mere expression of dryness of the oral mucous membrane.

The Presence or Absence of Organic and Functional Disturbances in the Urinary Tract.—Careful studies of renal function in diabetes

7. Since this paper was written Bailey and Bremer have reported their studies in experimentally induced diabetes insipidus before the Society of Endocrinology, Boston, June, 1921. They have demonstrated conclusively that thirst and polydipsia may precede polyuria.

8. Cannon, W. B.: The Physiological Basis of Thirst, Proc. Roy. Soc. London, s. B. **90**:283, 1918.

insipidus failed to incriminate any part of the urinary tract as an etiologic factor, and revealed no deviations from normal function, except in relation to water excretion and perhaps to salt excretion.

In all our cases the urinary output was markedly increased, from 3 to 14 liters a day. The specific gravity was markedly decreased, ranging, as a rule, between 1.001 and 1.004. Albumin appeared intermittently in small amounts in three cases, while demonstrable glycosuria was persistently absent. The excretion of phenolsulphonephthalein and the values for blood urea, creatinin, and uric acid were uniformly normal. Cystoscopic examination in two cases showed normal bladders. Ureteral catheterization revealed the fact that the increased secretion of urine was bilateral, and approximately proportional for both kidneys, and that the appearance time for phenolsulphonephthalein was normal from each side. Administration of pituitary extract with the ureteral catheters in place, reaching to the pelvis of the kidney, resulted in control of the polyuria and in a change in the concentration and color of the urine, within eight minutes in one case, and within ten minutes in another. These results conclusively exclude constriction of the ureter as a factor in the control exercised by pituitary extract on the polyuria and gross organic changes in the kidney and urinary tract. Hoppe-Seyler[9] presents the situation aptly when he says of renal function in diabetes insipidus, "it fails only by a little pituitrin of being normal."

The Results of Treatment.—The discovery by Schäfer[10] and his colleagues of the influence of the extract of the posterior lobe of the pituitary on the urinary output has created a new and growing interest in the subject of diabetes insipidus. Unfortunately, Schäfer's observations were made on anesthetized animals and led to the belief that the active substance of the posterior lobe possesses diuretic properties. Physiologists and clinicians were alike deceived with the result that diabetes insipidus was looked on by many as the result of overactivity of the posterior lobe. However, in 1913, von der Velden,[11] in Germany, and Farini and Ceccaroni,[12] in Italy, working independently, administered extract of the posterior lobe to patients suffering from diabetes insipidus and obtained an effect almost specific; thirst, polydypsia, and polyuria were all promptly and effectively controlled, at least for a temporary period.

9. Hoppe-Seyler, G.: Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextrakt, München. med. Wchnschr. **62**:1633, 1915.

10. Schäfer, E. A., and Herring, P. T.: The action of Pituitary Extracts on the Kidney, Proc. Roy. Soc. London, s. B. **77**:571, 1905.

11. Von der Velden, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berl. klin. Wchnschr. **1**:2083, 1913.

12. Farini, A., and Ceccaroni, B.: Influenza degli estratti ipofisari sull' eliminazione dell' acido ippurico, Gazz. d. osp. **34**:879, 1913.

DATA CONCERNING THE FIFTEEN CASES IN THE SERIES

The Effect of Pituitary Extract.—The effect of pituitary extract was studied in all our cases. Marked temporary results were obtained in all. The effects were immediate, and lasted for periods ranging from a few hours to four or five days (Figs. 1, 2 and 3). In mild cases the water balance was reduced to its normal level, while in more severe cases the level was reduced strikingly. Pituitary extract in gum acacia exercised as good an effect and resulted in a somewhat more prolonged control, although the local reaction was somewhat more severe. Effects of short duration sometimes follow the administration of pituitary extract by rectum.

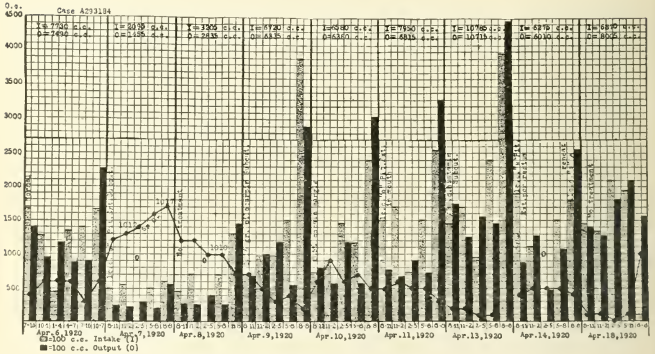

Fig. 1 (Case A 293,184).—Fluid intake, urine volume and specific gravity in the three-hour periods while the patient was receiving varying treatment.

With the decrease in the amount of urine the specific gravity rose to 1.010 or 1.025, and the color increased proportionately. With the readjustment of urine secretion the saliva flowed more freely; the skin became moist, and actual perspiration occurred in a large number of the cases. With the diminished desire for water the taste for it was frequently perverted, the patients referring to water at these times as being "stale" or "flat." A sensation of satiety and a feeling of fulness resulted from the intake of small quantities of water, for example, half a glass. This is in striking contrast to their usual experience. Prior to the administration of pituitary extract, a quart of water often failed to relieve the consuming thirst.

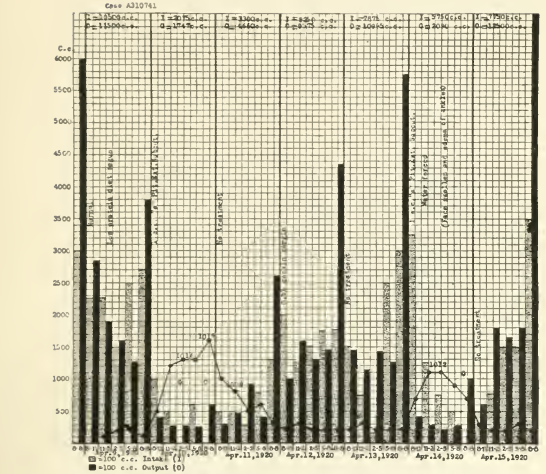

Fig. 2 (Case A 310,741).—Fluid intake, urine volume and specific gravity in three-hour periods during marked antidiuretic effect of pituitary extract and water intoxication.

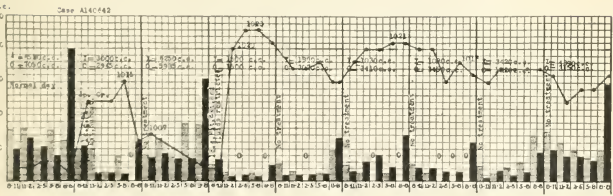

Fig. 3 (Case 140,642).—Prolonged antidiuretic effect of pituitary extract when patient exercised voluntary restriction on his thirst.

The volume of saliva secreted after the administration of pituitary extract increased definitely. This is illustrated in Figure 4 which contrasts the action of pituitary extract on the volume of urine and saliva of normal persons and of a patient with diabetes insipidus.

Effects of Histamin.—Histamin was administered subcutaneously in three cases. Constitutionally and locally its effect differed entirely from that of pituitary extract. In no instance was either the thirst or

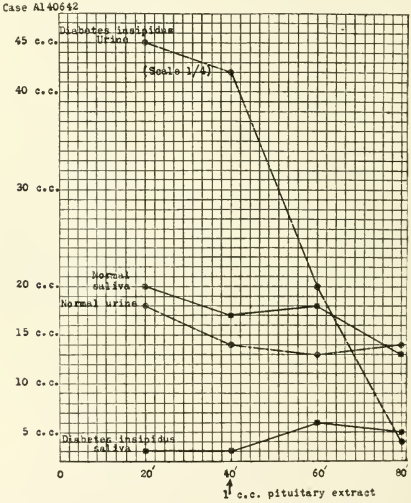

Fig. 4 (Case A 140,642).—Effect of pituitary extract on salivary and urinary secretion.

the polyuria decreased, except on one occasion when slight control was noted for three hours. The usual type of result may be seen in Figure 1.

Results of Spinal Puncture.—A spinal puncture with the withdrawal of from 5 to 10 c.c. cerebrospinal fluid was performed in six cases, without demonstrable effect on any of the cardinal symptoms. Because of the favorable reports in the literature we believed that the

amount of fluid withdrawn might be of significance. Consequently spinal drainage was done in three other cases, but in not a single instance was a favorable effect obtained.

Results of Treatment for Syphilis.—In the four cases with evidence of syphilis, treatment was carried out, but it has proved unavailing to date. Spinal puncture in three of these cases also failed to give relief.

The Effect of Restriction of Fluids.—Voluntary restriction of fluids was attempted in several of our cases, but it met with minor success in two only. One patient, a woman, succeeded in decreasing the intake from 5 to 6 liters a day to 1.5 liters, through her determined effort to refrain from water. Her case was unusual, however, the diabetes in all probability being hysterical in nature. In the second case early syphilis of the central nervous system complicated the diabetes insipidus. By the aid of 1 c.c. pituitary extract restriction to approximately normal amounts was obtained for a period of five days (Fig. 3). Without pituitary extract attempts at restriction accomplished but little, while pituitary extract alone failed to exercise control for periods longer than two days.

Before prescribing restriction of fluids the intense distress accompanying water fasting should be duly considered. One of our patients who had undergone a "restriction cure" at the hands of her local physician, had tears streaming down her face as she told us her story. In true diabetes insipidus little or nothing can be accomplished through restriction of the fluid intake, and the suffering inflicted is out of all proportion to the slight benefit obtained.

Metabolism.[13]—In a consideration of metabolism in diabetes insipidus the changes induced in normal persons by copious water drinking must be kept in mind, as has been pointed out by several authors. Rosenbloom and Price [14] give an excellent review of the literature on the metabolism in this disease. Gibson and Martin [15] have recently published results of metabolic studies before and after administration of pituitary extract.

Metabolism studies have been carried out in two cases of diabetes insipidus (Cases 140,642 and 330,908), the study in one being repeated during the patient's second visit to the clinic. Studies of blood chemistry were made in two other cases (Cases 317,545 and 323,015) before and after the administration of pituitary extract. The results in one case (Case N 330,908) are shown in Tables 1, 2 and 3. The water intake

13. The details of these metabolic studies will appear in a separate publication by Dr. J. F. Weir.

14. Rosenbloom, J., and Price, H. T.: A Metabolism Study of a Case of Diabetes Insipidus, Am. J. Dis. Child. **12**:53, 1916.

15. Gibson, R. B., and Martin, F. T.: The Administration of Pituitary Extract and Histamin in a Case of Diabetes Insipidus, Arch. Int. Med. **27**: 351, (March) 1921.

TABLE 1.—URINE ON METABOLIC EXPERIMENT (A 330908)

Day	Volume, C.c.	Specific Average Gravity	N/10 Acid, C.c.	Chlorin, Gm.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinin Nitrogen, Gm.	Uric Acid, Nitrogen, Gm.	Urea Nitrogen, Per Cent. Total	Ammonia Nitrogen, Per Cent. Total	Creatinin Nitrogen, Per Cent. Total	Uric Acid, Per Cent. Total
Before treatment													
1	4,525	1.007	398	3.45	8.26	6.56	0.316	0.316	0.092	79.4	3.8	3.8	1.1
2	4,980	1.009	343	4.30	8.02	....	0.266	0.311	0.048	....	3.3	6.4	0.6
During treatment													
3	915	1.025	268	2.59	8.134	5.497	0.466*	0.493	0.071	67.5	5.7	6.1	0.9
4	1,200	1.024	356	3.40	8.20	7.092	0.209	0.587	0.120	86.5	2.5	6.5	1.5
After treatment													
5	4,445	1.018	318	7.19	9.27	7.998	0.369	0.501	0.116	86.4	3.3	5.4	1.2
6	5,960	1.006	419	5.721	8.02	6.385	0.368	0.475	0.117	79.6	3.81	5.9	1.5

* Urine voided, alkaline at one period on this day.

TABLE 2.—BALANCE OF WATER, NITROGEN AND CHLORIN (A 330908)

	Intake			Urine Output			Balance			
Day	Water, C.c.	Nitrogen, Gm.	Chlorin, Gm.	Water C.c.	Nitrogen, Gm.	Chlorin, Gm.	Water C.c.	Nitrogen, Gm.	Chlorin, Gm.	Weight, Pounds
1	5,189	8.42	5.94	4,525	8.26	3.45	+ 664	+0.16	+2.49	162.5
2	5,740	8.22	6.58	4,980	7.96	4.30	+ 760	+0.26	+2.08	162.5
3	3,193	7.78	5.44	915	8.14	2.59	+2,278	—0.36	+2.85	163.0
4	2,380	7.92	6.27	1,200	8.20	3.40	+1,180	—0.28	+2.87	164.7
5	4,732	8.61	5.62	4,445	9.27	7.19	+ 287	—0.66	+1.57	164.2
6	6,382	7.57	5.80	5,960	8.02	5.72	+4,422	—0.45	+0 08	162.0

TABLE 3.—BLOOD ON METABOLIC EXPERIMENT (A 330908)

			Plasma Mg. per 100 C.c.		Whole Blood Mg. per 100 C.c.					
Day	Hematocrit, Per Cent. Plasma	Degrees △	Total Nitrogen	Sodium Chlorid	Total Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Creatinin	Sugar	Remarks
Before treatment										
1	67	0.515	1,171	648	29.8	14.9	2.68	1.90	128	Normal
2	68	0.530	1,142	653	26.5	14.9	....	...	108	Normal
During Treatment										
3	69	0.542	1,082	640	26.6	16.2	....	....	144	Pituitary extract
4	72	0.531	1,060	623	24.8	14.8	....	....	108	Pituitary extract
After treatment										
5	71	0.522	1,089	633	28.1	14.8	....	....	108	After period
6	69	0.546	1,129	648	27 0	13.3	....	....	112	After period

showed a marked fall in the three hourly and daily quantities after the administration of pituitary extract. The variations in the volume and specific gravity of the urine were marked and obvious. The positive water balance in the control period was small, harmonizing with the clinical observation of dry skin and mouth. There is marked retention of water after the first dose of pituitary extract, corresponding with the decreased urinary output. The patients generally report an increased excretion of urine in the period after treatment. In this case, however, the water intake kept pace with the increased excretion, but this fact, together with the increase in weight during treatment and the return to normal in the after period, indicates retention of water in the blood or tissues. The excretion of nitrogen varied but slightly

TABLE 4.—Effect of Pituitary Extract in Normal Person and in Patient with Diabetes Insipidus Contrasted in Blood Picture

			Plasma Mg. per 100 C.c.		Whole Blood Mg. per 100 C.c.					
Day	Hematocrit. Per Cent. Plasma	Degrees Δ	Total Nitrogen	Sodium Chlorid	Total Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Creatinin	Sugar	Remarks
					Normal					
1	65	0.523	880	600	42	....	. . .	....	...	Control
2	58	0.534	1,008	605	43	16	..	. . .	146	Control
3	60	0.533	977	610	40	15	....	. .	152	Pituitary extract
4	61	0.534	942	618	37	13	...	. .	149	Pituitary extract
					Diabetes insipidus (A317543)					
1	61	0.522	1,058	629	....	5.0	2.4	1.3	...	Control
2	65	0.549	1,163	640	. . .	5.8	2.4	1.3	...	Control
3	67	0.511	940	607	....	6.6	2.4	1.2	...	Pituitary extract
4	67	0.513	970	597	. . .	6.1	2.3	1.3	...	Pituitary extract

throughout the experiment and the nitrogen balance showed no appreciable change. The chlorin excretion was decreased under treatment and chlorin retention was evident.

In the second case (Case 140,642), similar changes in the urine were noted, and more marked change in the water balance; there was a large negative balance as the effects of the drug wore off. There was a definite decrease in the excretion of nitrogen and an increased positive balance in the period of treatment. Chlorin also showed rather marked retention.

In the analysis of the blood in diabetes insipidus before and after administration of pituitary extract certain definite changes appeared. Typical results in one case (Case 317,545) are contrasted with those of a normal person (Table 4). The relative plasma volume is increased, and the molecular concentration, the total nitrogen, and the sodium chlorid of the blood are somewhat decreased, findings which might indicate a dilution of the blood. However, in the findings in the

experiments on metabolism there is evidence of a slight retention of nitrogen and chlorin, which does not appear in studies on the blood. Evidently water retention is the most prominent feature following administration of pituitray extract, and in all probability the effects on nitrogen and chlorin are secondary to water retention.

In all our experiments on metabolism and in all our cases of diabetes insipidus in which pituitary extract has been administered, there has been no diarrhea,[16] and an analysis of the feces in one case showed a normal quantity of water. There is no evidence that pituitary extract prevents the absorption of water from the gastro-intestinal tract of man, as has been claimed for it for rabbits by Rees.[17] Only small quantities of water have been found in the intestines and feces of our animals at necropsy.

Blood Volume.—Blood volume determinations by the vital red method were carried out in four of our patients, and in three of them before and after the administration of pituitary extract, that is, in the periods of high and low urinary excretion. The results obtained in the two earlier cases led us to believe that the blood volume, particularly the plasma volume, was increased in diabetes insipidus following the administration of pituitary extract, that the pituitary extract had specifically raised the renal threshold for water, and that the kidney failed to excrete water even in the presence of hydremic plethora in the blood. However, in one case no increase was found in either total blood volume or plasma volume, despite the completeness of control exercised by the pituitary extract on the polyuria. Prior to the administration of the drug the plasma and total blood volume were 3,460 and 4,805 c.c., respectively, and after the drug, 3,495 and 4,855 c.c., respectively. From these results it is evident that pituitary extract can cantrol the polyuria of diabetes insipidus and prevent polyuria following excessive ingestion of water without the development of any significant increase in blood or plasma volume. These findings are in keeping with the experimental results which we obtained in animals.

THE EFFECTS OF PITUITARY EXTRACT ON THE WATER BALANCE

Behavior and Rôle of Water in Metabolism.—In order better to understand the effect of the pituitary extract on the water balance, it is desirable to know more concerning the nature of water exchange in the body, the mechanism involved in its regulation, and the part played by the pituitary gland under normal and abnormal conditions. Water plays a fundamental part in metabolism, and is essential to the life

16. Diarrhea was present in animals suffering from water intoxication, but the amount lost by way of the bowels was relatively very small.

17. Rees, M. H.: The Influence of Pituitary Extracts on the Absorption of Water from the Small Intestine, Am. J. Physiol. **53**:43, 1920.

and function of every living cell. It is transported to and from the cells by the blood, provision for its exchange being made locally by the presence of lymph spaces and lymph channels. It constitutes 80 per cent. of the blood. Oxygen and food are also transported to the cells by the blood. Nature has arranged to supply the blood with water, oxygen, and food, according to the constancy of the need of the cells for each and in accordance with the complexity or simplicity of the mechanism involved in their metabolism. Water holds a position intermediate between oxygen and food, the continuation of its supply being less vital than that of oxygen and more than that of food. In

TABLE 5.—SUPPLY AND OUTPUT OF WATER

	Amount			Author	Remarks
Supply					
Water from drink and food	Average	Maximum	Minimum	Forster.....	Data collected in Munich; fluid includes 1 to 2 liters beer
	2,260	3,560	2,300		
	2,260	2,440	880	Atwater and Benedict	Over a period of 49 days with subject in repose
	3,760	4,550	2,225		Over a period of 66 days with subject doing moderate work
Water from oxidation of Food	. .	480	240		On mixed diet of approximately 4,000 to 2,000 calories, respectively
	. . .	. . .	. . .		
Output					
Urine.... ..	1,500	3,000	800	Emerson....	So many factors effect the urinary output that only a general average is given here*
	2,000	.....	. . .		
Skin.....	550	. . .	...	von Noorden	These are average figures for patient indoors on a medium diet of 1,800 to 2,000 calories. Total fluid lost by evaporation may reach 1,600 c.c. on diet of 3,500 calories and 3,250 c.c. on diet of 5,000 calories with patient doing moderate or heavy work. As much as 7.5 liters may be lost during excessive work
Lungs	400	. . .	.....		
Feces†.... ..	60	300	60		On vegetarian diet with large stools the water content may reach 300 c.c. In diarrhea greater losses may occur
	to	.....	.....		
	300	. . .	.....		

* In five cases followed by us during summer months, the output varied from 750 to 1,200 c.c. The figures for maximum and minimum simply indicate ordinary physiologic limits.
† Obviously this refers to normal loss in the stools.

health blood varies in volume and consistency within narrow limits only, possibly in order that the supply of these essentials to the cells may be kept almost constant. Fluctuations in physiologic needs, depending on variations in function are met largely by changes in the rate and volume of the blood flow to various organs.[18]

The source of the water of the body is found in the fluids taken by mouth in the form of food and drink and in the water which results from oxygenation of food within the organism. Water is excreted by the skin, lungs, kidneys, and bowels. The intake and output vary tremendously with the life, habitat, and habits of the individual. The

18. The intermediary water metabolism and the effects exercised by water ingestion are purposely omitted from discussion.

relative amount excreted through the various channels also varies extremely, reciprocal relationships playing a striking part at times, particularly with regard to sweat and urine. Although the variations are extreme, some idea concerning the normal relations in water balance, that is, in the intake of fluids and in the output of water by the various channels under differing conditions of diet and activity are presented in Table 5.

Effect of Extract of Posterior Lobe of the Pituitary Gland on the Urinary Excretion in Normal Men and Animals.—In order to ascertain the effects of pituitary extract on the urinary excretion of normal persons, five men were placed under careful observation. Urine was collected in three-hourly periods throughout the day, and as a single

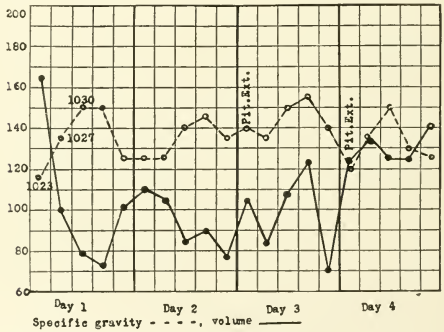

Fig. 5.—Average three-hour volume and specific gravity of the urine of five normal men before and after pituitary extract.

specimen at night. Diet and climatic conditions remained fairly constant during the period of observation, August, 1920. A two-day period of control preceded the administration of the drug, which was given at 8 a. m. on each day of the experiment. A composite curve in the urinary output and the specific gravity is shown in Figure 5. From these studies it is evident that the subcutaneous injection of 1 c.c. pituitary extract produced no appreciable effect on the urinary excretion, on the daily or three-hourly amounts, or on the specific gravity.

Other experiments were carried out on dogs; the water was given with pituitary extract and in some instances repeated at varying periods after the administration of the drug, in order to determine if diuresis

could be induced. Characteristic curves are reproduced in Figure 6. It is evident that diuresis can be readily induced by forcing the water intake after a single dose of 1 c.c. pituitary extract.

In Figure 7(a) is shown a composite curve of the results of a series of experiments in dogs, in which the urine was collected in half-hourly periods during the course of three hours. Each animal was studied under three conditions: (1) normal conditions, (2) after administration of water by mouth in amounts corresponding to 50 c.c. per kilo-

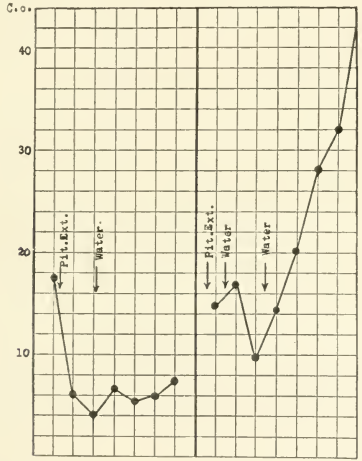

Fig. 6.—The antidiuretic effect of 1 c.c. pituitary extract in dogs can be overcome by repeated administration of water.

gram of body weight, and (3) after the simultaneous administration of pituitary extract, subcutaneously, and water by mouth in the amounts already indicated. These experiments demonstrate that the subcutaneous administration of pituitary extract definitely checks the production of water diuresis, although if the water is administered, urinary excretion is on a somewhat higher level than normal.

The next step was an attempt to localize the site and mode of action of the pituitary extract, that is, to ascertain the relation of pituitary

extract to the nervous control of renal function. The dogs of the first series were operated on and the splanchnic nerves to both kidneys sectioned.[19] A second series of experiments identical with those described was carried out (Fig. 7 [b]). A comparison of the total

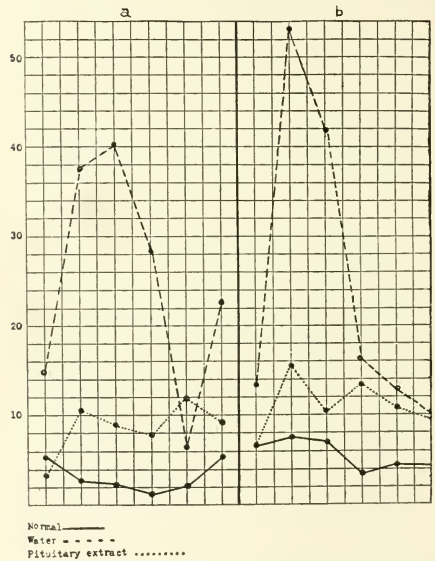

Fig. 7.—Average half-hour rate of secretion of urine in dogs under normal conditions, after water, and after water and pituitary extract (a) before section of the renal nerves (six dogs), and (b) after section of the renal nerves (four dogs).

results under these two conditions is shown in Figures 7 and 8. From these two series of experiments it is possible to deduce that (1) kidneys with nerves sectioned respond normally with a diuretic curve to

19. We wish to thank Dr. F. C. Mann and his associates for their kindness in performing the operative work on the animals used in these experiments.

water [20]; (2) this curve is largely abolished by pituitary extract, as in normal kidneys (the diuretic response after pituitary extract administration is on a slightly higher plane than under normal conditions), and (3) practically no change in the curve of the average half-hourly output under the three conditions of the experiment result from section of the renal nerves. It is evident, therefore, that the influence of pituitary extract in the prevention of diuresis is independent of the nerve supply of the kidney.

The Mechanism Involved in the Control of Diuresis by Pituitary Extract.—It is obvious from our clinical studies in diabetes insipidus and our experimental observations on the effect of pituitary extract in

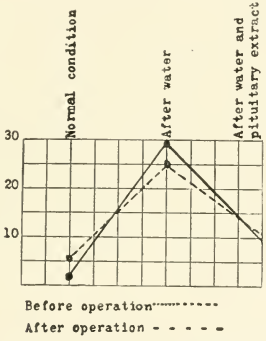

Fig. 8.—Curves showing average of secretion of urine in a series of dogs under normal conditions, after water, and after water and pituitary extract, before and after section of renal nerves.

the prevention of polyuria and our investigations of water intoxication that pituitary extract prevents polyuria. The mechanism of its action is difficult to explain.

Earlier in our work we were inclined to believe that pituitary extract raised the renal threshold for water and that a hydremic plethora resulted. However, in one case of diabetes insipidus and in several animal experiments, blood volume determinations failed to

20. Our results with the denervated kidney correspond to those already described by Marshall and Kolls.

Marshall, E. K., Jr., and Kolls, A. C.: Studies on the Nervous Control of the Kidney in Relation to Diuresis and Urinary Secretion, Am. J. Physiol. **49**:302, 1919.

indicate any increase of total blood or plasma volume. As a result of our failure to demonstrate hydremic plethora and increased renal threshold for water we are considering other possibilities.

In view of the results of our studies of blood chemistry and blood volume we are at present attempting to determine if it is possible that pituitary extract disturbs the relative ease with which the water of the blood leaves the blood stream to pass through the kidney to form urine, or to the tissues as body fluid. At present we are forced to admit our inability to explain the antidiuretic effect of pituitary extract. We are investigating the possibility of an abnormal escape of fluid from the circulating blood into the tissues.

INTOXICATION FOLLOWING THE ADMINISTRATION OF WATER BY MOUTH SUBSEQUENT TO GIVING EXTRACT OF THE POSTERIOR LOBE OF THE PITUITARY SUBCUTANEOUSLY

One of our patients at our solicitation continued, after the administration of pituitary extract, to take water in amounts to which he had become accusomed[21] and during a period of eight hours he ingested 5.25 liters, and excreted 800 c.c. of urine. In the course of three or four hours he became very ill, was nauseated and developed severe headache, and was forced to go to bed. Physical examination revealed only puffiness of the lower eyelids and slight edema of the ankles. Repetition of this experiment on the same and on another patient gave similar results, that is, nausea, vomiting, and headache, which forced the patient to go to bed. In one instance definite ataxia appeared.

On account of the severity of the reaction no further experiments were tried on patients, but similar studies were carried out on dogs. Water in large quantities was given by mouth subsequent to the administration of pituitary extract. This resulted in marked tremor, salivation, and at times vomiting. The symptoms were independent of the temperature of the water and were elicited with warm water as rapidly as with cold. On forcing the experiment convulsions and coma developed, and in one instance death supervened. As a result of these observations we undertook an investigation to determine the responsible factors, and studied separately the toxicity of water and of pituitary extract, and later the toxicity of water following the administration of pituitary extract.

Toxicity of Water.—In the classical experiments of Cohnheim and Lichtheim[22] in which they demonstrated the absence of anasarca,

21. The edema and toxicity resulting in this case were reported by one of us before the Society of Clinical Investigations, Atlantic City, 1920.

22. Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Oedem, Arch. f. path. Anat. u. Physiol. **69**:106, 1877.

especially of edema of subcutaneous tissues when animals were given physiologic salt solution intravenously in large amounts (up to 90 per cent. of body weight) cramps were reported in a few instances. In an elaboration of this work by Magnus and Schäfer [23] no mention is made of these toxic manifestations.

Miller and Williams [24] recently published their results following the administration of large quantities of water to patients with chronic nephritis. They observed headache, dizziness, restlessness, chills, fulness of the abdomen, vomiting, dyspnea, and cramps in the legs, which were associated with marked increase in weight and definite elevation of blood pressure. In our experiments large amounts of water were given to dogs without the development of untoward signs or symptoms. One animal retained 2,500 c.c. during the course of seven hours and passed 1,500 c.c. urine without manifesting symptoms of intoxication. In another the administration of 3,500 c.c. resulted in salivation, vomiting, asthenia, and ataxia.

One of our colleagues, Dr. Amberg, has kindly furnished us with the following note, which is of interest in this connection. For the purpose of studying the influence of water ingestion on the elasticity of the skin as determined by the elastometer of Schade, two normal adults drank from 2 to 3 liters of water (not cold) within about fifteen or twenty minutes. For some time following the ingestion of the water no elastometric determinations could be made, on account of muscular twitchings. In the light of the experiments here reported it appears not impossible that this was the result of a slight water intoxication. There were no particularly uncomfortable subjective sensations.

Toxicity of Pituitary Extract.—Schäfer and Vincent [25] state that subcutaneous injections of pituitary extract to small mammals results in paralytic symptoms similar to those observed after suprarenal extracts. Cushny [26] states that large quantities can be injected without producing symptoms other than somnolence and muscular weakness.

23. Magnus, R.: Ueber die Enstehung der Hautödeme bei experimenteller hydrämischer Plethora, Arch. f. exper. Path. u. Pharmakol. **42**:250, 1899. Magnus, R., and Schäfer, E. A.: The Action of Pituitary Extracts on the Kidney, J. Physiol. **27**: Proc., ix, 1901.

24. Miller, J. L., and Williams, J. L.: The Effect on Blood-Pressure and the Nonprotein Nitrogen in the Blood of Excessive Fluid Intake, Am. J. M. Sc. **161**:327, 1921.

25. Schäfer, E. A., and Vincent, S.: The Physiological Effects of Extracts of the Pituitary Body, J. Physiol. **25**:87, 1899.

26. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1910, p. 340.

According to Sollmann,[27] ataxia and motor symptoms, changes in carbohydrate metabolism, and emaciation develop after the excessive and long continued use of pituitary extract.

In order to determine the etiologic relationship of the extract of the posterior lobe of the pituitary to the symptoms observed in our studies some experiments were carried out; illustrative results appear in the following protocols:

PROTOCOLS OF EXPERIMENTS

Protocol 1.—Dog 1, weight 9.8 kg. Pituitrin (Parke, Davis & Co.) subcutaneously.

Feb. 11, 1921.—Pulse 100, regular.

10:00 a. m.: 1 c.c. pituitary extract.
10:30 a. m.: 1 c.c. pituitary extract.
11:00 a. m.: 1 c.c. pituitary extract; diarrhea.
12:00 m.: 1 c.c. pituitary extract; diarrhea.
1:00 p. m.: 1 c.c. pituitary extract.
1:30 p. m.: 1 c.c. pituitary extract.
1:45 p. m.: Pulse 48, sinus arrhythmia, extrasystoles; bright and interested in other animals; no salivation; respiration 30.
2:25 p. m.: 1 c.c. pituitary extract.
3:15 p. m.: 1 c.c. pituitary extract. Pulse, 60; respiration, 40; appeared sick; lost "pep"; no interest in other animals; sleepy; no diarrhea or bladder frequency; no ataxia.
5:00 p. m.: 1 c.c. pituitary extract.
5:30 p. m.: 1 c.c. pituitary extract.
5:45 p. m. Animal more sleepy; no ataxia.

February 12: 10:00 a. m., pulse, 140, regular; animal active; appears normal. Intake from 6:00 p. m. to 10:00 a. m. 65 c.c.; output, 300 c.c.

Protocol 2.—Dog 2, weight, 5.4 kg. Pituitary extract (Lilly Company) intravenously.

Feb. 16, 1921: Animal active; pulse, 80, regular.
2:25 p. m.: 3 c.c. pituitary extract; two minutes later inactive.
3:00 p. m.: "Sick"; at times seems unable to use hind limbs; lies flat on side.
3:05 p. m.: Heart rate, 44; sinus arrhythmia; restless.
3:07 p. m.: Defecation.
3:13 p. m.: 3 c.c. pituitary extract; lacks "pep"; diarrhea; pulse, 60; sinus arrhythmia.
3:29 p. m.: 3 c.c. pituitary extract; no resistance; slight tremor; appears weak.
3:31 p. m.: Vomited 15 c.c. yellow fluid, frothy.
3:40 p. m.: Pulse 62; reflexes active; vomiting again.
3:45 p. m.: 3 c.c. pituitary extract; several attacks of vomiting and bowel movements.
4:00 p. m.: 3 c.c. pituitary extract; feces and vomitus bile stained; mucus present.
4:15 p. m.: 3 c.c. pituitary extract; inactive; does not resist; pulse, 80.
4:40 p. m.: Greater activity.
February 17, 10:00 a. m.: Normal activity.

27. Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1917, p. 344.

Toxicity of Water After the Administration of Pituitary Extract.[28]—Subsequently animals were given pituitary extract subcutaneously and large amounts of water through a stomach tube. Blood volume determinations and studies of the blood chemistry were made before the administration of pituitary extract, and again after the onset of the symptoms. The summary of the results is given in Table 6.

Early Manifestations of Toxicity.—The first symptoms noted may possibly be due to pituitary extract alone, namely asthenia, restlessness, frequent attempts at urination, diarrhea, and vomiting. Other symp-

TABLE 6.—Blood Volume in Water Intoxication

Dog	Weight, Kg.	Pituitary Extract, C.c.	Intake, C.c.	Output, C.c.	Hematocrit, Per Cent. Plasma	Total Plasma Volume, C.c.	Total Blood Volume, C.c.	Plasma per Kg.	Blood per Kg.	Total Nitrogen, Gm. per 100 C.c.	Sodium Chlorid, Mg. per 100 C.c.	Symptoms
E116	10.4	7 (4+3)	6,400 (4,000+ 2,400)	2,800 (1,500+ 1,300)	49 51	613 601	1,251 1,178	59 58	120 113	0.763 0.743	480 430	Drowsiness, salivation, restlessness. Frequent attempts at urination, vomiting, ataxia, convulsions, coma
E291	7.4	3	1,500	500	46 46	370 389	794 840	50 53	107 114	....	... ...	Drowsiness, salivation, tremor, ataxia, vomiting, convulsions, coma, involuntary evacuations of bowels and bladder
E290	9.0	5	5,000	2,000	53 57	618 526	1,157 923	69 58	128 102	0.490 0.595	460 390	Preoperative: Marked frequent attempts at urination; diarrhea, drowsiness, restlessness, ataxia, tremor, twitchings, salivation, convulsions, coma
E290	8.5	3	3,150	2,325	55 57	570 650	1,036 1,140	67 76	122 134	....	... ...	Postoperative Same symptoms

toms, tremor and salivation, next appear, possibly due to water alone. These develop usually after approximately 300 c.c. of water has been given per kilogram of body weight as a minimum. This stage continues for a variable period when another set of symptoms develops. The animal becomes very drowsy, and later shows muscular twitchings and ataxia on standing or walking. This may be designated as the preconvulsive stage. In spite of mental dullness the animal evidences hypersensitiveness to external stimuli, such as result from picking up the stomach tube or passing it. Such procedures may precipitate the convulsive stage.

28. Water introduced intravenously as physiologic solution of sodium chlorid results in an entirely different set of phenomena, the dogs dying with edema of the lungs.

Later Manifestations of Toxicity; Convulsions, and Coma.—Convulsions were characteristically epileptiform in type; first a tonic stage, followed immediately by a clonic stage. During the tonic phase the head retracted, the jaws set, respiration ceased, and the animal became cyanosed. Then sudden and violent clonic spasms developed, accompanied by frothing at the mouth and involuntary bowel and bladder evacuations. During the convulsive stage the pupils were markedly dilated, contraction occurring immediately after the cessation of the clonic spasms. During or following the convulsive stage the dog usually showed running, swimming, or snapping movements and at times barked and growled, as though participating in a fight. Coma or somnolence persisted for a longer or shorter period, but the animal usually recovered fully during the course of the next few hours. Passage of the stomach tube and the administration of more water brought on further convulsions, which, if continued, ended in death. Vomiting and salivation occurred usually after the administration of from 200 to 300 c.c. water per kilogram of body weight. Occasionally an animal failed to manifest salivation. Some animals made frequent attempts to urinate while others apparently exhibited no evidence of bladder irritability.

Several animals in which double renal nerve section had been performed were given pituitary extract and water. The same toxic symptoms developed but no increase or decrease in the facility with which they could be produced was noted. This further indicates that the antidiuretic action of pituitary extract is independent of the nerve supply of the kidney. A protocol of one of these experiments is presented below:

PROTOCOL 3.—Dog E 249, weight, 11.4 kg.[29] Water by mouth subsequent to pituitary extract subcutaneously.

Feb. 7, 1921.—11:50 a. m.: 1 c.c. pituitary extract and 500 c.c. water.
1:45 p. m.: 1 c.c. pituitary extract and 500 c.c. water.
2:45 p. m.: 1 c.c. pituitary extract and 500 c.c. water; some frequency of micturition.
3:15 p. m.: Has vomited 1,000 c.c.
3:25 p. m.: Animal found in cage, unconscious, frothing at mouth, head retracted; jerking of jaw and leg muscles. On being taken from cage, was unable to walk, lay on side and went through running movements, jaws still snapping. Prostration marked, movements easily restricted; semiconscious.
3:40 p. m.: Involuntary bowel evacuation, liquid. Running movements stopped; attempts to walk unsuccessful.
3:45 p. m.: Conscious, but lies quiet; unable to attract animal's attention; few attempts at walking movements; respiration, 70; muscles rather flaccid.

29. Other experiments are in progress which involve more careful consideration of the weight of the animal. To date increases in weight greater than 1 kg. have not been encountered.

3:57 p. m.: Pulse, 100; pupils small; twitching muscles; feet lie as if asleep; eyes open; listless; few attempts to get up; respiration, 32.
3:59 p. m.: Gets up, walks in circular course, lies down.
4:02 p. m.: Diarrhea, hardly able to stand up, does not respond to call, is not frightened.
4:06 p. m.: Various attempts to rise.
4:08 p. m.: Walks, seems blind, bumps into objects.
4:15 p. m.: Walks again, bumps into objects; weight, 11.6 kg.
4:18 p. m.: Walks until exhausted; defecation.
4:25 p. m.: Improving; vision returning; attention can be attracted slightly.
4:27 p. m.: Pulse 108, deep respiration; frequent urinations, little or no urine.
4:45 p. m.: 500 c.c. water; very restless, running.
4:48 p. m.: Defecation.
4:50 p. m.: Running less rapidly, slightly ataxic, salivated.
4:52 p. m.: Running less rapidly, walks some, more ataxia, lists to left.
4:55 p. m.: Complete ataxia, unable to stand.
4:56 p. m.: Convulsion, head retracted; tonic and clonic phases, running movements; vomited; salivated.
5:03 p. m.: Convulsion.
5:04 p. m.: Convulsion.
5:12 p. m.: Convulsive movements.
5:20 p. m.: Has been in continuous convulsions, unconscious, continuous snapping movements of jaws, pupils widely dilated.
5:30 p. m.: Same condition, more convulsions, pupils contracted after convulsion, dilated during convulsion.
5:45 p. m.: Died in convulsion.

Necropsy revealed early onset of rigor mortis, normal chest and lungs, and slight congestion of the liver and kidneys. The stomach contained about 65 c.c. fluid and the intestine about 25 c.c. No free fluid was found in the pleural or peritoneal cavities, and there was no evidence of edema of the subcutaneous tissues of the neck or of the extremities. The brain, on removal, appeared to be normal in every respect.

Thus we have definite evidence of toxic symptoms produced by water, when the water-secreting function of the kidney is diminished through the subcutaneous administration of 3 c.c. pituitary extract.

While the experiments were in progress an attempt was made to determine the mechanism of production of the convulsions. Kymographic records were procured in some of these experiments. A typical tracing is presented (Fig. 9). Hydremic plethora as a cause was first considered, but no increase in the total blood or plasma volume by the vital red method, nor any constant increase in relative plasma volume by the hematocrit could be demonstrated (Table 6).

The total nitrogen and the sodium chlorid content of the plasma showed usually a slight decrease after the onset of symptoms. The urine volume during the following twelve hours was always increased, usually to about 500 c.c., indicating a rather rapid excretion of the retained fluids. Clinical evidence of edema was absent in all the animals studied.

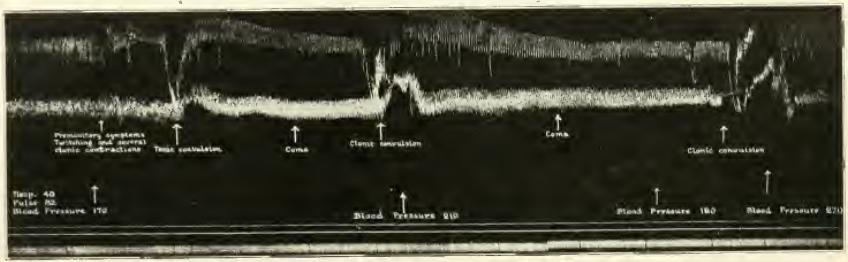

Fig. 9.—Water intoxication. Respiration, pulse and blood pressure during convulsions in a dog.

The Cause and Significance of Convulsions and Coma.—The immediate cause and the mechanism of production of these phenomena have not been determined. But it has been demonstrated that neither pituitary extract nor water alone [30] in similar, or even larger amounts, is capable of producing them. Edema of the brain, suggests itself as a logical explanation, but we have not succeeded in proving this to our own satisfaction. Table 6 presents the plasma and blood volume values as determined before and after water intoxication. From this it is apparent that increased blood volume has been excluded in at least some of our experiments. A marked increase in blood pressure is encountered in water intoxication. The rise is tardy in onset and

TABLE 7.—Blood Pressure Changes in Water Intoxication

Time	Water, C.c.	Weight, Kg.	Pituitrin, C.c.	Blood Pressure	Pulse	Respiration
11:00 a. m.	...	13.6	.....	140	84	..
11:20 a. m.	...	13.6	1 "0" Subcutaneously	140	..	..
11:30 a. m.	700	14.3	.....	140	..	..
11:45 a. m.	450	14.6	.....	160	..	..
11:50 a. m.	...	14.6	1 "0" Subcutaneously	150	72	22
12:00 m.	1,000	15.6	.....	140	..	..
1:00 p. m.	...	15.6	1 Subcutaneously	140	..	..
1:15 p. m.	1,000	16.4	.....	140	..	..
2:05 p. m.	500	16.9	1 Subcutaneously	150	70	24
3:05 p. m.	...	16.8	1 Subcutaneously	170	..	..
3:10 p. m.	500	17.2	.....	180	..	..
3:30 p. m.	...	0	1 Intravenously	190	..	..
4:00 p. m.	1,000	18.1	.....	206	72	26
4:30 p. m.	...	18.1	.....	...	..	..
4:40 p. m.	...	18.1	1 Intravenously	200	82	30
4:50 p. m.	...	18.1	.....	140	22	..

gradual in development and may reach a comparatively high level (Table 7; Fig. 9). However, the changes in blood pressure do not appear to be striking enough to account for the toxic manifestations.

Nausea, vomiting, muscle twitching, spasms, asthenia, convulsions, and coma developing in the presence of an obvious derangement of water excretion strongly suggest uremia, especially when death supervenes. But in the absence of increased values for blood urea, and in view of the rapidity of their appearance and disappearance, it does not seem at all probable. However, it is of more than passing interest to learn that the entire series of symptoms so frequently found in uremia can result from a common cause. From the standpoint of sudden onset and recovery eclampsia is also suggested.

30. Since this paper was submitted for publication, further experiments have been carried out and convulsions have been produced with water alone. The results of these further studies will be published later.

Convulsions of sudden onset characterized by a tonic and a clonic phase, associated with involuntary evacuations, and frothing at the mouth, followed by coma, and ending in complete recovery suggest epilepsy. On the other hand, nausea, vomiting, asthenia, and ataxia characterizing the earlier period of development of these phenomena have no resemblance to epilepsy. The possibility of reflex factors from the gastro-intestinal tract at least must be considered, since strangury and retching constitute marked features at times. A condition resembling status epilepticus and ending in death has also been observed.

In the absence of definite information relative to the seat, origin, and mechanism of production of these phenomena speculation is futile; it would be wiser perhaps to leave all such questions to the future.

CIRCULATORY COMPENSATION FOR DEFICIENT OXYGEN CARRYING CAPACITY OF THE BLOOD IN SEVERE ANEMIAS *

GEORGE FAHR AND ETHEL RONZONE
MADISON, WIS.

It is a well known fact that persons suffering from severe chronic anemias do not show the signs of anoxemia when at rest even when the oxygen carrying capacity of each cubic centimeter of blood is below the normal venous unsaturation, or, in other words, when the oxygen content of each cubic centimeter of arterial blood is less than the average amount of oxygen normally abstracted from the blood by the tissues during its passage through them. We recently studied a case of pernicious anemia in this hospital in which with a hemoglobin of 12 per cent.[1] and an oxygen carrying capacity of only 2.2 c. c. per hundred cubic centimeters of blood there was no dyspnea, no acidosis, no increased pulse rate and a normal basal metabolism or rate of oxygen consumption. As it has been frequently shown that the normal resting human organism abstracts an average of 5.5 c.c. oxygen from the blood in the capillaries, it was necessary to explain how anoxemia was avoided in this case, with normal basal metabolism or oxygen consumption, and an oxygen content per cubic centimeter of arterial blood less than half the amount normally abstracted in the capillaries for the processes of oxidation.

The explanation of this condition in our case contains the solution of the problem of the compensatory mechanism in severe anemias, and we feel that it is of sufficient interest to justify publication, especially as it emphasizes the necessity for bed rest in severe anemias and introduces a method of minute volume determination on man which may be of value in cardiovascular investigation.[3]

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* From the Bradley Memorial Hospital, University of Wisconsin.

1. All hemoglobin determinations were done by the method of Palmer.[2] In this method a standard blood is saturated with oxygen and its oxygen capacity determined. An oxygen capacity of 18.5 c.c. per hundred cubic centimeters blood is given a hemoglobin value of 100 per cent. Having determined the oxygen capacity and hemoglobin value for the standard blood, this blood is now colorimetrically compared to the patient's blood by means of the Haldane carbon dioxid method. In this way the percentage of hemoglobin always has a definite relation to oxygen carrying capacity and the values of different observers working in different clinics are based on the same 100 per cent. standard.

2. J. Biol. Chem. **33**:119, 1918.

3. This method was first suggested by Fick, Ges. Werke **3**:573.

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REPORT OF CASE

History.—A male, aged 49, entered the hospital complaining of pain in epigastrium and weakness, progressively increasing during past five years. He had a sore mouth two years ago. The skin had been yellow for years. He now complains of paresthesia in the legs.

Examination.—Lemon colored skin, with large pigment patches over neck and lower arms; no emaciation; petechiae on various parts of the body; mucous membranes pale; tongue smooth. Lungs normal. Heart apparently not enlarged to percussion. Systolic murmur present, loudest just inside apex. Systolic murmur at base is transmitted into carotids. Venous hum over jugulars. Spleen just at rib margin, moves 2 cm. below on deep inspiration. Tendon reflexes exaggerated, vibratory sense lost in legs. Sense of position questionable in legs.

Blood Findings on Entrance.—Red Cells, 1,600,000; hemoglobin, 42; index, 1.3; white cells, 3,600. Smears show many poikylocytes, anisocytosis, polychromatophilia and stippling, many megalocytes; no normoblasts, polymorphonuclears, 62 per cent.; lymphocytes, 33 per cent. No platelet count was made on entrance, later on when the hemoglobin had fallen to 12 per cent. the platelet count was 22,000; 4 per cent. reticulates. Normoblasts and megaloblasts were seen frequently in later smears.

Stomach Content After Boas Meal.—No "free acid" and a total acidity of 1 per cent.

Fragility test showed beginning hemolysis at 0.5 per cent. and complete at 0.35 per cent. The daily average of output of urobilin was 25,000 units.

Despite transfusions and regulation treatment, the patient's condition gradually became worse, and eight months after entrance the patient died with a hemoglobin content of only 8 per cent. Throughout a period of two months the hemoglobin content was 12 per cent. and the red count was about 550,000. It was during this period that the laboratory data were obtained. The necropsy confirmed the diagnosis of pernicious anemia.

Necropsy revealed a dilated heart with moderate increase in the thickness of ventricular musculature. Microscopic sections of heart muscle showed both hypertrophic and atrophic fiber. In certain areas there was vacuolization of this fiber. There was every evidence that death was due to circulatory failure. There was about one liter of transudate in each thoracic cavity. There was passive congestion of liver and spleen. The pathologist said that death was due to failure of the circulation.

April 3, 1921, two basal metabolism determinations were done with the Benedict unit apparatus and were found to be 1,454 calories, or 4 per cent., higher than the average normal value as predicted according to DuBois [4] and 15 per cent. higher than the basal metabolism as predicted according to Benedict.[5] Certainly the basal metabolism was not slowed up in this case. A few days later basal metabolism determinations were repeated and gave 1,451 calories. The oxygen

4. DuBois, D., and DuBois, E. F.: Arch. Int. Med. **17**:863 (July) 1916.

5. Benedict and Harris: Biometric Study of Basal Metabolism in Man, 1919.

consumption as determined by the apparatus was 213.5 c.c. per minute. If now we can find the oxygen abstracted from each cubic centimeter of blood leaving the lungs and passing through the peripheral circulation back into the right heart we can very easily calculate the number of cubic centimeters of blood passing through the lungs per minute or the number of cubic centimeters of blood leaving each chamber of the heart per minute. It is thus necessary to know the oxygen content of the arterial blood and the oxygen content of the venous blood. The oxygen content of the arterial blood is given by the hemoglobin determination according to the Palmer method. It is true the Palmer method gives the maximum oxygen content of the blood at atmospheric pressure of oxygen but this value has been shown by experiment to be only 5 per cent. above the value for arterial blood as actually determined. The Palmer determination on this blood, April 2, gave hemoglobin 12.2 per cent. The total combined and dissolved oxygen was 2.4 c. c. per hundred c. c. of blood. The determination of the mean oxygen content of the venous blood contains a slight error. We took the blood from the arm vein and determined its oxygen content according to the Van Slyke method.[6] We found this blood to contain 0.6 c. c. oxygen per hundred cubic centimeters blood.

The oxygen content of the venous blood varies slightly according to the part of the body from which it comes. During absolute rest in bed and before breakfast the blood coming from the heart will have more oxygen abstracted from it than blood which has passed through the capillaries of resting organs, like the arms, legs and trunk. The venous blood coming from the brain will also contain less oxygen than blood coming from an active organ like the heart. Metabolism in the portal area is not at its height during morning rest. It is safe to assume that although an active organ like the heart might possibly under the conditions of a very low oxygen content of the arterial blood abstract nearly all the oxygen, yet it is not very probable that this would occur, for a glance at the dissociation curve of oxyhemoglobin[7] shows that when the oxygen content has dropped to 10 per cent. of its normal maximum content[8] then the diffusion pressure is only 10 mm.[9] or about one tenth of the mean diffusion pressure in the capillaries and one fifth the average diffusion pressure in normal venous blood. The speed of diffusion is lowered to a point where oxygen must leave the blood in the capillaries very slowly and it is doubtful if under the conditions of increased velocity of flow in this case, which we shall prove in this paper, the last vestiges of oxygen can be

6. Van Slyke: J. Biol. Chem. **33**:127, 1918.
7. Bohr, Hasselbach and Krogh: Scand. Arch. f. Physiol. **16**:402, 1904.
8. In this case 0.4 c.c. per hundred centimeters blood.
9. Assuming that the partial pressure of oxygen in the tissues is zero.

to Rowntree's [16] method gave 5.2 per cent of body weight for plasma volume or a little more than the normal average for plasma volume. Because of the small corpuscular volume the total blood volume was only 5.4 per cent. of the body weight, or considerably less than the average normal. Therefore, the total blood content of the tubing was less than the normal, and it would seem hardly probable on first thought that the effective cross section of the tubing could be larger. Besides we know that the filling of the heart must be considerably greater in order to get the large output we have calculated. Moreover, frequent examinations of the finger capillaries with the method of Lombard [17] showed both a very marked contraction of the capillaries and fewer open capillaries. It is impossible to check up the lumen of all the vessels but the above observations do not mitigate against the assumption that the effective cross section of the vessels was greater, thus causing increased velocity, and at the same time the total volume content of the whole vascular tubing was diminished to correspond to the decrease in blood volume and the increased filling of the heart itself. For Poisseulle's formula for the velocity of blood flowing through tubing is $\frac{V = k.p.r^4.t}{l}$ where v is velocity, k is the reciprocal of viscosity, p is blood pressure, r is the radius of the section of tubing under consideration, t is the time and l the length of the tubing. As the radius is in the numerator in the fourth power and l is in the denominator in the first power it is easy to see how by increasing the diameter of the short capillary area and at the same time diminishing the lumen of the long arterial and arteriolar area both the effective resistance and the total volume of the tubing may be reduced at the same time.

Our capillary observations showed that some of the skin capillaries are remarkably reduced in diameter. We believe that this is one of the compensatory factors for securing increased flow of blood in more important organs where metabolism is greater. As observed by the microscope the flow in the skin capillaries was very slow but this is easily explained for the diameter of these capillaries was less than half of that of other patients and normals. Toward the end it was approximately one third the diameter of our own capillaries. On the other hand, the vital organs at necropsy impressed the pathologist as being more than normally filled with blood.

It is interesting to calculate the work done by the heart per minute and its oxygen consumption. In calculating the work of the heart we shall make use of Evans' [18] formula $W = \frac{7}{6} Q R + \frac{QV^2}{G}$, where Q is the minute volume, R is the combined aortic and pulmonic blood pressures

16. Rowntree, Geraghty and Keith: Arch. Int. Med. **16**:547 (Oct.) 1915.
17. Lombard: Am. J. Physiol. **29**:335, 1912.
18. Evans: J. Physiol. **52**:6, 1918.

in terms of a water column,[19] V is the linear velocity calculated from the aortic and pulmonic cross section, the minute output, and the actual time during which blood is flowing out of the ventricles, and G is the constant of gravity acceleration. We find that the heart performs 18.5 kg.m. of work per minute necessitating an oxygen consumption of 30.5 c. c. per minute,[20] or one seventh the total oxygen consumption of the body. If we assume that the venous blood leaving the coronary veins has an oxygen content of only 0.2 c.c. per hundred cubic centimeters, then we can reckon that the coronary circulation is 1.48 liters per minute, an enormous flow. Even if we assume that the oxygen content of the whole venous blood of our patient was 0 we are compelled to calculate a minute volume of 9.5 liters for the circulation and an oxygen consumption in the heart of 26 c. c. each minute. Even under these conditions the coronary flow would be 1,190 c. c per minute. It would be necessary to have a coronary circulation of 1.2 liters per minute to supply even this oxygen need. Evans has shown that the heart during the performance of very severe work must have a coronary circulation of about 850 c.c.[21] With blood of the viscosity of our patient's such a flow would become 1.87 liters, so that it is not at all impossible as at first it might seem. Of course, it is possible that the efficiency of the heart is greater than 30 per cent., but from Evans'[22] work we would assume that 30 per cent. is the highest mechanical efficiency of the human heart.

Our calculation shows that the heart may very easily suffer from lack of oxygen, especially if the patient is not at absolute rest. There is very good support in this paper for the pathologist's contention that the heart muscle changes of pernicious anemia are due to lack of oxygen.[23]

CONCLUSIONS

1. In severe anemias increased minute volume is the outstanding compensatory mechanism for loss of oxygen carrying power of the blood.

2. In a case of severe pernicious anemia the minute volume was increased about 250 per cent. and the systolic output in the same degree.

19. Evans uses 1.7 for R, in persons of normal blood pressure = 120. As the blood pressure in our patient was 105 we have used 1.5 for R.

20. Assuming that the mechanical efficiency of the heart is 30 per cent. and respiratory quotient 0.8.

21. Evans: J. Physiol. **47**:407, 1914.

22. Evans: J. Physiol. **52**:6, 1918.

23. Laboratory data of interest: CO_2 tension in alveolar air 37 mm.=5.2 per cent. Hydroxybutyric acid in blood 1.2 mg. per hundred cubic centimeters. Other acetone bodies, 0.53 mg. per hundred cubic centimeters. CO_2 combining power of blood, 62.6 c.c. per hundred cubic centimetres plasma. CO_2 content of blood, 51.3 c.c. per hundred c.c. plasma.

3. The increased blood velocity was very largely due to lowered blood viscosity, this being lowered to 45 per cent. of its normal value.

4. Another factor was increased effective cross section of the vascular tubing.

5. Microscopic examination of the skin capillaries showed that they were contracted down to half the normal diameter or less, thus determining a lessened blood flow through the skin and a larger flow through other organs. The lessened quantity of blood in the skin is certainly one factor in the degree of paling of the skin.

6. The coronary circulation is at the upper limit of the possible being about as large as that found in very severe work. There is a very great possibility that when a patient with severe anemia tries to work that anoxemia of the heart muscle is produced. The pathologic changes in the heart muscle in pernicious anemia may well be due to lack of oxygen.

A HITHERTO UNDESCRIBED TUMOR OF THE BASE OF THE AORTA*

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Tumors of the heart are not commonly met with and their clinical diagnosis up to the present time has been difficult, if at all possible, to make. Tumors of the aorta are much less frequent than those of the heart. Newer clinical diagnostic methods are promising much, however, in the early recognition of these cases. The tumor of the aorta attached to the heart which we found in our case has no counterpart in the literature. It became of interest, therefore, to describe this case not only from its clinical but also its anatomical aspects.

REPORT OF CASE

N. R., a white male, married, aged 54, was admitted to Barnes Hospital on the service of Dr. George Dock for the first time, June 26, 1918. The chief complaint at that time was shortness of breath occurring in paroxysmal attacks off and on for over fifteen years.

Family History.—This was unimportant, except that one brother, who had died of pneumonia, was supposed to have had "heart trouble."

Personal History.—The marital history was insignificant. The patient had been married eight years, he had one child, a boy of 6 years, living and well. His wife was living and well and had had one miscarriage.

Past History.—He had not had chorea, diphtheria, scarlet fever, pneumonia or tonsillitis. He had had measles, pertussis and typhoid fever in childhood but had recovered from these without complication. He had had gonorrhea at 28, and a "hard chancre" of the urinary meatus, with buho and inflammation of the testicles, at 29. He had been treated for syphilis by local applications and by mouth. No secondary lesions developed. "Smothering attacks" with shortness of breath, which he termed "asthma" had troubled him for fifteen years. These attacks would come on after exertion and were accompanied by palpitation and the appearance of a dusky gray color. He had taken three or four glasses of whisky, smoked two to three pipefuls of tobacco, and drank two to three cups of coffee daily for years.

Present Illness.—The trouble that brought him to the hospital was more or less dyspnea which gradually became exaggerated following an attack of "rheumatism" in February, 1918. He began to notice difficulty in breathing and wheezing, particularly at night, when lying in bed; no palpitation or pain was noticed and the symptoms were relieved by his getting on his feet. The attacks of dyspnea on exertion which he had had for years had grown more severe. His feet had been swollen for a week and there had been blueness of the lips and face during several of the attacks. The patient fainted once. He had also had pain in the epigastrium which radiated down into the abdomen.

Physical Examination.—The patient had a robust frame with moderately heavy musculature and thick panniculus, weighed 185 pounds and measured 70 inches in height. He walked into the ward but was very dyspneic. There

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was a dusky ashen pallor about his face while the rest of the body was cyanotic. On reclining the face became very cyanotic. Orthopnea was noted and the respiration was Cheyne-Stokes in type. The patient would drop off to what appeared to be sleep during the apneic periods. The veins of the neck were slightly engorged but there were no abnormal pulsations. The lungs were negative, except for many crackling râles at both bases posteriorly.

Heart: The heart was defintely enlarged. The apex impulse was not well localized but was felt best about 15 cm. to the left of the midsternal line in the fifth intercostal space. There was a general precordial heave without a strong impulse on palpation. No thrills were felt. The cardiac outline to percussion was 2.5 cm. to the right and 2.5 cm. to the left of the midsternal line in the first intercostal space; 3.5 cm. to the right and 4.5 cm. to the left in the second intercostal space; 4 cm. to the right and 9 cm. to the left in the third intercostal space. What was considered to be liver dulness was elicited on the right side below the third intercostal space, while to the left the figures of the outer cardiac dulness were: 14 cm. in fourth intercostal space; 16 cm. in fifth intercostal space, and 17 cm. in sixth intercostal space.

The contractions were regular and rapid. A systolic murmur was heard at the apex. This was transmitted toward the axilla, but not toward the sternum. Both sounds were accentuated at the apex. The pulmonary second sound was accentuated and louder than the aortic second sound. The blood pressure was from 110 to 120 mm. Hg. systolic, and from 100 to 85 mm. Hg. diastolic.

The pulse was regular and rather small. The radial and brachial artery walls were very much thickened, but not calcareous. The feet and legs were oedematous.

Abdomen: The abdomen was above the costal margin. There was distention of the superficial veins in the left hypochondrium. Tenderness was elicited in the epigastrium. The liver edge was found to be 8 cm. below the costal margin in the midclavicular line. Tenderness was noted all over the enlarged liver.

There was a linear 2 cm. scar of the old bubo in the left groin. The right lip of the urinary meatus was large and verrucous. The patient said that the "hard chancre" had been at this site. A small varicocele was found on the left side. The prostate was of moderate size, thickened throughout and adherent.

No abnormal reflexes or neurologic signs were elicited.

The patient was seen by Dr. G. Canby Robinson who found a general precordial heave in the region of the apex with no local heave but a definite tap. The heart borders extended 5.5 cm. to the right and 16.5 cm. to the left of the midsternal line. The heart sounds were blurred and distant. A faint nontransmitted systolic murmur was heard at the apex. The pulse was palpable with difficulty and counted 116 per minute. The pulmonary second sound was accentuated.

The electrocardiogram showed right ventricular preponderance and the chest plate showed right sided hypertrophy. Aside from these there were, however, no other signs of mitral stenosis.

A dose of 10 c.c. tincture of digitalis was administered and the regular rhythm became absolutely irregular within twenty-four hours. A slight pulse deficit was noted at that time and the difference in the force was more striking than the arrhythmia, but no pulsus alternans was ever demonstrated. The pulse later became regular and the edema disappeared. The liver, on the other hand, at the time of discharge remained 8 cm. below the costal margin in the parasternal line. The patient was given a prescription for 10 minims tincture of digitalis to be taken three times a day and discharged improved, July 20, 1918, to return to the Outpatient Department for observation.

Clinical Laboratory Findings.—Blood: The red blood cells numbered 4,472,000; white blood cells, 7,100; hemoglobin, 75 per cent. The differential smear showed polymorphonuclear neutrophils, 73 per cent; lymphocytes, 20 per cent., and large mononuclears and transitionals, 6 per cent. The blood Wassermann reaction was negative. The blood nonprotein nitrogen was 78 mg. per hundred c.c.

Urine: The specific gravity varied from 1.018 to 1.026. The volumes were small. Occasionally the night volume was increased over the day volume. There were also traces of albumin, and numerous hyaline and finely granular casts. Fifty-three per cent. of phenolsulphonephthalein was excreted in two hours.

Electrocardiograms:

1774; June 27; auricular flutter; well marked right sided preponderance.

1770; June 28; auricular flutter; well marked right sided preponderance.

1786; July 1; auricular fibrillation (24 hours after administration of 10 c.c. tincture digitalis).

1797; July 5; auricular flutter in part of the record; impure in another.

1801; July 7; auricular flutter; arrythmia suggesting varying degrees of block; auricular rate, 250; ventricular rate, 109.

1803; July 10; normal rhythm reestablished; right ventricular preponderance (suggesting mitral stenosis); S wave in Lead 1 very short again; negative T waves in all leads; diphasic P in second and negative P in third leads; rate, 102; P.R. 0.22 sec; Q R S, 0.08 second.

1815; July 11; one left ventricular extrasystole, otherwise as 1810. Depth of S wave in Lead 1 increasing.

There were no changes in the subsequent curves taken while the patient was in the hospital. The numbers and dates of these were as follows: 1824, July 13; 1831, July 15; 1837, July 16; 1843, July 17; 1849, July 19; 1855, July 20.

Record of Outpatient Department: The patient was seen at frequent intervals in the Outpatient Department where 10 minims tincture digitalis was ordered to be taken three times a day.

July 30: The cyanosis was marked. The heart action and the pulse were regular and equal.

August 15: The cyanosis remained the same. The heart action and the pulse were regular and equal.

September 3: The cyanosis was less, but there was puffiness about the eyes. The heart was regular at 84 per minute. The urine showed pus cells.

November 4, the patient was seen by Dr. Robinson, who found the outer cardiac dulness to be 4 cm. to the right and 17.5 cm. to the left of the midsternal line. He also noted an arrhythmia of a peculiar type associated with periods of regular rhythm. There was also a dropping out of beats without any evidence of premature contraction.

Electrocardiogram 2027, taken at this time, shows a curious type of arrhythmia suggesting a shift of the pacemaker in the junctional tissue, delayed auriculoventricular conduction and slight left ventricular preponderance.

December 9, Dr. Robinson noted that the patient was somewhat cyanotic. The point of maximum impulse was 14 cm. to the left in the fifth intercostal space. The limits of cardiac dulness were 4.5 cm. to the right and 14 cm. to the left of the midsternal line. A very faint systolic murmur was heard at the apex. The heart rhythm was irregular. It had a rate of 66 with groupings of three beats heard at times with regular periods. The liver was not felt and there was no edema of the ankles.

Jan. 13, 1919, another note by Dr. Robinson states that the ventricular rate is 74, there is no deficit of the pulse and that the patient complains of pain in the neck. Electrocardiogram 2163 shows: a tendency to left ventricular preponderance; delayed A-V conduction; P waves flat in Lead I, diphasic with deep negative phases in Lead II, negative and notched in Lead III; T waves upright in Leads I and II, inverted in Lead III; R waves notched in Lead III, becoming tall with the lowering of the diaphragm; Q R S interval lengthened; and periods of striking irregularity marked by changes in the P-R interval. Changes in the form of P waves are also noted. In two instances by changes in the form of R waves there is the appearance of a change from a right to a left ventricular preponderance. The P-R interval is 0.24 second. The rate is 78.

Second Admission.—March 4, 1920.

His complaint at the second admission, in addition to his shortness of breath, was pain in the lower part of the chest. He had been doing quite well until six weeks before admission when suddenly he had a "dizzy spell," his right leg became numb, and he fell to the ground. The attack lasted but a few minutes, his arm was not involved, there was no loss of consciousness or aphasia and he was able to walk within ten minutes. His dyspnea had been gradually getting worse and had been very severe for a week. After working hard, moving furniture, he had considerable difficulty in breathing. Often at nights he had to get up out of bed and sit in a chair for a few hours before he could recline and sleep.

Physical Examination.—This was very similar to that of the previous admission. The superficial veins, however, were much more prominent. They were engorged and tortuous over the manubrium below the right nipple and over the precordium. There were numerous varicosities over the right and left lower chest. Several large varicose veins were noted over the abdomen about the umbilicus and in the right hypochondrium. The leg veins were likewise varicose.

The findings in the lungs, heart and liver were as described previously. The heart was regular and rapid. The right cardiac border was found to be from 3.5 to 5.5 cm. to the right of the midsternal line until the seven-foot roentgenogram showed a large bulge 11 cm. to the right of the midsternal line. After this the percussion also routinely revealed a dulness from 10 to 11 cm. in this direction. According to the fluoroscopic examination made by Dr. Sherwood Moore and Dr. Frank N. Wilson there was also a clear space between the heart and the aorta in this region. This they thought ruled out an aortic aneurysm situated on the descending aorta behind the heart. This large shadow at the right border of the heart was seen to flicker but the movement was so slight that the observers could not be sure that it was not imaginary. This wide shadow to the right also gave the impression of a widely dilated right auricle suggesting the possibility of tricuspid stenosis, but there were no other signs to bear this out.

Dr. Robinson interpreted the roentgenogram as showing apparently a great dilatation of the right ventricle. This could not be reconciled, however, clinically with the signs and symptoms present. The latter were also different from those of aneurism of the heart.

Dr. Dock commented on the conspicuous wavy epigastric pulsation and the dilated superficial veins and suggested that a tumor could not be ruled out as other possibilities such as tricuspid stenosis and cardiac and aortic aneurism had been. An exploratory puncture was not made as had been suggested.

During the period of regularity the rhythm was shown by the electrocardiograms to be auricular flutter, with two to one block. Vagus experiments were done which showed the characteristic marked lability of the His bundle to vagus stimulation in this condition. Vagus stimulation by direct or ocular pressure stopped the ventricles for four to five series of four to twelve auricular beats. There was ventricular standstill for as long as three seconds (Fig. 2).

Dr. Robinson suggested a dose of 20 c.c. tincture of digitalis and repeated vagus tests. The digitalis at first produced irregular blocking with four to one rhythm. Vagus pressure caused a greater change than before digitalization. In one run the ventricles stood still for twenty-five auricular beats or about six seconds. Other series of long runs of 6, 8, 10 and 16 to one rhythm were obtained. Auricular fibrillation then appeared and persisted. The patient was discharged clinically improved, March 19, 1920.

Clinical Examination and Laboratory Data.—Blood: The red blood cells numbered 6,470,000; white blood cells, 6,950; hemoglobin, 100 per cent. The blood Wassermann was negative. Urine: The specific gravity varied from 1.020 to 1.038. The urinary output was small. No albumin or casts were found in any urine specimen. The phenolsulphonephthalein test showed 65 per cent. excretion in two hours.

The blood pressure was from 100 to 120 mm. Hg. systolic, and from 70 to 95 diastolic.

A seven-foot roentgenogram of the heart (Fig. 1) showed a large sharply outlined circular shadow projecting to the right of the midclavicular line.

The cardiac dimensions measured on the seven-foot teleroentgenograms were: Before digitalization, M. R., 11 cm.; M. L., 12.5 cm.; L, 22.5 cm.; A, 7 cm. After rest in bed and digitalization, M. R., 10 cm.; M. L., 12.5 cm.; L, 23 cm.; A, 6.5 cm.

Electrocardiograms (Fig. 2):

3716; March 7, 1920; auricular flutter; auricular rate, 266; ventricular rate, 128.
3725; March 8; auricular flutter; vagus experiments (Fig. 2).

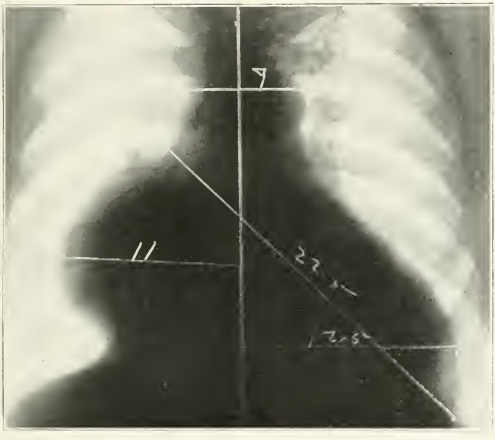
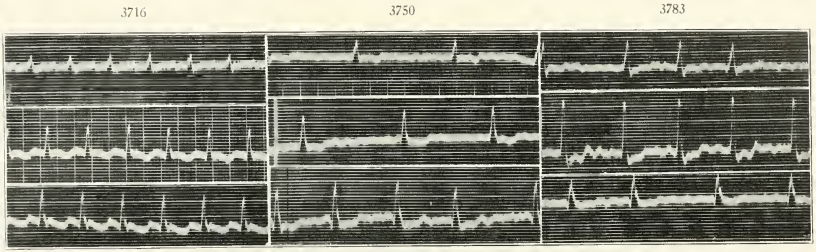


Fig. 1.—Seven foot roentgenogram of the chest made at the time of the second admission, March, 1920.

3739; March 9; three hours after digitalization, auricular rate, 256. Mixture 2 : 1, 3 : 1 and 4 : 1 block.
3740; March 9; six hours after digitalis; vagus experiments.
3741; March 10; fifteen hours after digitalis.
3750; March 10; auricular fibrillation twenty-eight hours after digitalis.
3769; March 12; auricular fibrillation.
3783; March 16; auricular fibrillation.

Final Notes April 3, 1920.—After leaving the hospital the patient, contrary to order, did rather heavy work. He had not been any more dyspneic than usual, but had some edema about the ankles each evening. He did not take the tincture of digitalis regularly as it had been prescribed. It was not known whether his pulse was regular or irregular. He had been complaining for a few days, but



Vagus Pressure Experiments

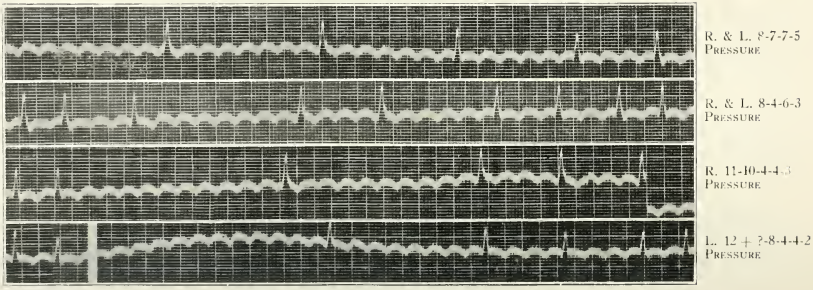


Fig. 2.—Electrocardiographic tracings.

refused to return to the hospital. April 2, he carried an iron range (stove) up three flights of stairs. In the evening he felt more "blue" than usual, but went to sleep apparently well. During that night he apparently did not struggle, at least his son sleeping with him was not awakened. On the following morning, however (April 3), he was found dead in bed. The body was slightly cool, quite cyanotic, especially the face, but rigor mortis had not set in.

NECROPSY REPORT

Permission for a complete necropsy could not be obtained. An examination of the heart alone was allowed. This was removed after the body had been embalmed. We saw it for the first time when it was brought to the laboratory. We are grateful to Dr. Robinson for his effort in gaining permission for us to examine this organ.

Heart: The organ is greatly enlarged, and a large tumor mass, the size of a large orange, is attached to the superior wall of the right auricle, to the tissue of the auricular septum, to the sides of the aorta and pulmonary artery. The attachments to the aorta and pulmonary artery are loose. The firm attachment is to the auricular wall. The fibrous tissue of the pericardium of the heart is continuous with the tumor. The muscle of the auricular wall beneath the tumor is atrophic and apparently not continuous with it. The attachment to the auricle does not appear to be a primary one but secondary to the irritation of the tumor lying on the auricle. The heart with the tumor weighs 945 grams.

The heart is enlarged, the hypertrophy being more marked in the left than in the right ventricle. The tricuspid valve measures 14.5 cm.; the mitral, 11 cm.; the aortic, 7.5 cm.; the pulmonary, 10 cm.; the muscular portion of the left ventricle wall measures 14 mm.; that of the right, 4 mm.

The mitral valve is uniformly thickened throughout and near its base are several fibrous and fatty placques, a few of which contain gritty material. The papillary muscles are much enlarged and there are several areas of fibrous thickening in the endocardium of the left ventricle. The aorta is normal in size. There are a few small fibrous and fatty placques in the intima of the aorta. The endocardium of the right ventricle and auricle show nothing of interest except at the attachment of the tumor. Here the endocardium is in close contact with the hard, gray, opaque wall of the tumor mass, which can be seen through it. The muscle fibers are largely missing in this region.

The myocardium of other portions of the heart, aside from the hypertrophy, show nothing of interest.

The epicardium over the whole of the heart contains a considerable amount of fat. The coronary arteries are straight and aside from the first few centimeters of their courses show nothing of interest. In the first centimeter of the left coronary there are numerous fibrous and fatty placques in the intima. Similar changes are seen in the first 5 cm. of the right coronary artery.

The orifices of these vessels are slightly constricted and there are several fibrous and fatty placques in the intima of the aorta immediately about them.

Just to the right of the orifice of the left coronary artery and in the aorta and just above the sinus of Valsalva is a cone-shaped pouch which extends inwards and appears to end blindly (Fig. 4a). It is 1 cm. deep and the diameter of the inner opening is 1 cm. Except for its shape it has the appearance of a small aneurism. There are several fatty and fibrous placques in the intima lining it.

Lifting the tumor away from the aorta reveals the outer wall of this pouch, which is seen to be continuous with a tough cylindrical shaped cord of tissue which passes directly to the wall of the tumor to disappear within it (Figs. 3 and 4b).

This slender cylindrical shaped cord is evidently the pedicle of the tumor, and on close inspection is found to be composed externally of a tough gray tissue like that of the aorta or one of the large arteries. It has, however, no evident open lumen, but its center is composed in places of a gelatinous and in other

places of a glistening gray material. It measures 4 cm. long and ½ cm. in diameter. It looks like an occluded anomalous arterial branch.

The tumor is ovoid in shape and measures 12×9 cm. It has a tough hard outer wall and is filled with a greasy necrotic material which everywhere glistens as if it contained crystals. A smear of this necrotic material shows large numbers of rhombic plates with notched corners. The outer tough wall is thickened at the point of insertion of the pedicle. Here there is a large necrotic fragile nodule which extends in and replaces a part of the soft greasy material (Fig. 4c).

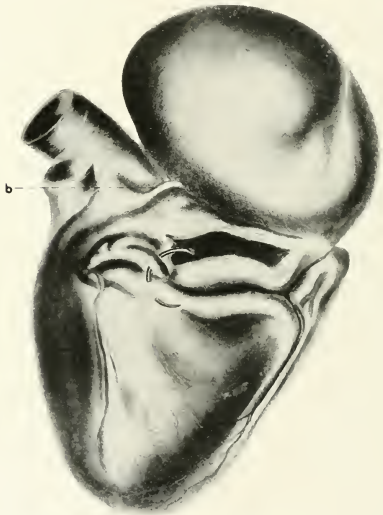


Fig. 3.—Semidiagrammatic drawing of the heart showing the tumor.

The remainder of the wall is thin. It measures from 1 to 2 mm. in thickness. This wall is seen to be divided into several layers. An outer one resembling muscle in many places, a second fibrous looking layer, and an inner layer which is in contact with the glistening greasy content. This last layer appears to be composed of a gelatinous material which in places is streaked and mottled with gray and yellow opaque lines and splotches.

From the gross description alone it was evident, therefore, that the tumor was not of auricular but probably of aortic origin. It had arisen from an anomalous arterial like branch of this vessel.

Microscopic Examination.—The microscopic examination of the heart shows muscular hypertrophy and nodular thickenings of the endocardium of the left ventricle. These nodules are fibrous and the centers of the larger ones are necrotic.

Atheromatous nodules of small size are present in the intima of the aorta. The media of the vessel appears normal but there are collections of lymphoid cells about a few of the vessels of the adventitia.

The wall of the aneurysmal-like pouch which marks the point of origin of the tumor pedicle (Fig. 5) is much like that of the aorta. It has a well formed intima, media and adventitia. The intima is irregularly thickened and fibrous

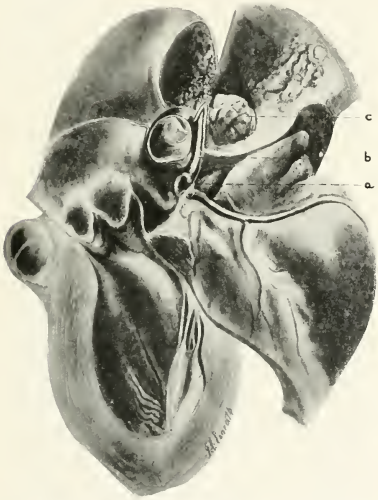


Fig. 4.—Similar drawing showing the heart and tumor opened. The lips of the aneurysmal pouch are exaggerated. They are flat and smooth.

in places. The outer portions of the media also show fibrosis and in one place this layer contains a large calcified placque. The muscle cells and the elastic tissue of the inner portions stain sharply. At the boundary between the adventitia and the media there are a few lymphocytes and there are also collections of these cells about a few of the larger vessels of the adventitia.

The pedicle has the structure of an artery with an excessively thickened intima which obliterates the whole of the lumen (Fig. 6 and 7). The media is well formed. It has a sharply defined internal and a poorly defined external elastic lamella. There is a slight increase in fibrous tissue within it but also

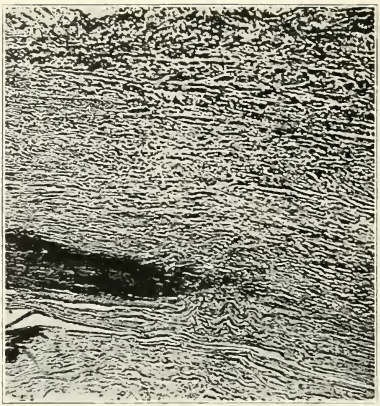


Fig. 5.—Photograph of a cross section of the wall of the aneurysmal pouch.

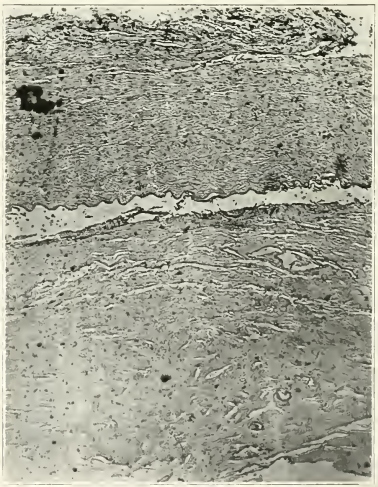


Fig. 6.—Low power photograph of one half of a cross section of the pedicle

sharply staining muscle cells and elastic fibers. The excessively thickened intima is composed of loose fibrous tissue with a finely granular intrafibrillar substance. In places it contains a few polyblastic cells and in other places it is degenerated and reduced to a homogenous granular mass containing numbers of open ovoid, circular and rhombic shaped spaces like those of the center of the tumor.

Sections from all parts of the tumor show the same general structure (Figs. 8 and 9), an outer tough sharply staining thin fibrous wall which grades off gradually or in places sharply into the large granular bluish and pink staining mass. This mass contains large numbers of open spaces which vary in shape. Many are spindle shaped (Fig. 10); others are ovoid, circular or rhomboid in shape.

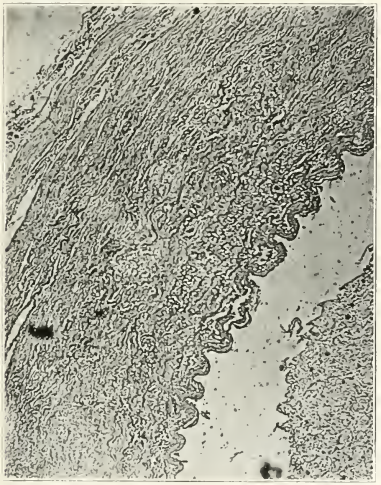


Fig. 7.—Higher power picture from another section of the pedicle.

The outer fibrous wall contains large numbers of polyblastic, plasma and small mononuclear cells (Fig. 8A). A few of these cells or shadows of them are seen deeper in the hyaline and necrotic portions (Fig. 8 and 9 B). Calcium deposits are also not uncommon in the hyaline portions of the wall (Fig. 8 B).

Sections through the auricular wall at the attachment of the tumor show no direct connection of the tumor with this part of the heart. The tumor wall is sharply defined and connected with the heart wall by loose fibrous tissue. In a few places atrophic and degenerating muscle fibers are seen between the tumor and the endocardium.

The picture as described in this tumor is one of a progressively degenerating fibrous wall of inflammatory origin. Leaving aside the inflammatory cells it is the picture of the ordinary atheromatous patch of the aorta. There is no evidence that it is or has been a neoplasm. It is rather a massive atheromatous tumor of what appears to be an atypical arterial branch of the aorta. This branch or pedicle has the appearance of an artery obliterated by an excessive proliferation of its intima.

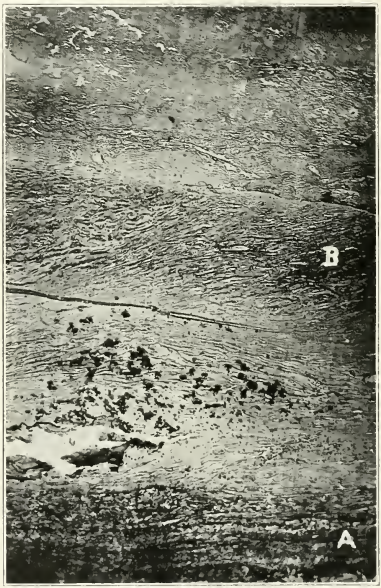


Fig. 8.—Photograph of a section taken through the wall of the tumor. A is the outer sharply staining area. B is the inner hyaline and fibrous layer.

The pouch at the origin of the tumor pedicle from the aorta has a well formed wall resembling that of the aorta. It looks like a simple dilatation of the wall of the aorta at this point rather than an aneurism. The changes in the wall of this pouch and in the aortic wall are suggestive of a generalized chronic degenerative and inflammatory disease of the vessels. The nodules as those described in the left ventricle have been also definitely associated with syphilis by some. It is possible in this case, however, that these changes in the aorta may have been secondary to the irritation of the tumor.

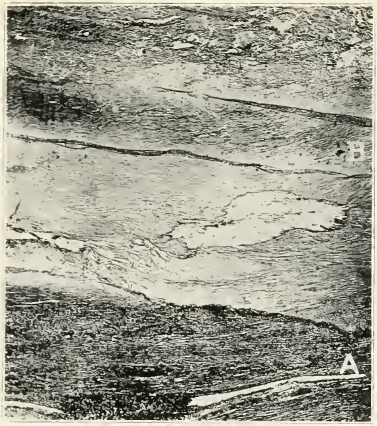


Fig. 9.—Photograph of a section of another part of the wall of the tumor. A is the outer sharply staining layer. B is the inner hyaline and necrotic layer.

Fig. 10.—Open spaces in the central part of the tumor mass.

CLINICAL SUMMARY

The case, as is evident, is a most unusual one. The clinical symptoms are largely those of a tumor of the heart while pathologically it is questionable whether the tumor is nothing more than a part of a more generalized inflammatory disease of this organ.

The patient was a chronic alcoholic. The supposed syphilitic infection at 28 years of age seemed to antedate any of the symptoms. The "smothering" and "asthmatic" attacks and mild cardiac symptoms followed this more or less closely. Aside from these facts, as well as the long duration of the disease, the symptoms might well have arisen entirely from the presence of a neoplasm. The symptoms were those of a gradually progressing myocardial change.

The reason for the insidious exaggeration of symptoms following "rheumatism" four months before admission is not clear. The dyspnea and the wheezing on reclining, relieved by arising, might well be explained as myocardial resulting from tumor pressure.

In the original physical examination, the observation of an ashen pallor, conspicuous cyanosis of the body and dilatation of the superficial abdominal veins on standing and the spread of the cyanosis to the face on reclining might have resulted from a tumor pressing on the venae cavae. Cheyne-Stokes breathing was present as a part of the cardiac syndrome. The dulness to the right and below the third rib which was taken to be that of the liver was probably due to the tumor. The roentgenogram of the chest taken at this time showed a shadow in this region which appears to be clearly the same enlargement that produced the striking teleroentgenogram which led to the special interest in the case and the provisional diagnosis of cardiac tumor.

On the second admission there was the added complaint of pain in the lower chest which might have been associated with the tumor. The sharply outlined shadow extending 11 cm., to the right of the midsternal line was considered one of three things: an aneurysm of the heart, a dilated right auricle from tricuspid stenosis or a tumor. The latter was not ruled out, while aneurysm and dilated auricle were considered improbable because of the patient's general condition and the physical findings. Fluoroscopic examination showed no definite movement or pulsation of this huge shadow.

The electrocardiograms in this case revealed interesting findings. The curves first showed auricular flutter which after digitalization changed to auricular fibrillation and later to normal mechanism with inverted P waves and delayed A-V conduction. On the second admission the auricular flutter was again present and vagus experiments were very successful in demonstrating a regular auricular activity with auriculo-ventricular blocking (Fig. 2). After a massive dose of digitalis auricular fibrillation began and persisted. These abnormal auricular

rhythms and mechanisms are associated with auricular muscle changes which in this case resulted from the pressure of the tumor, encroaching on the sinus area. The inverted P waves signify an abnormal course of the impulse through the auricles. The electrocardiographic findings point, therefore, definitely to pathology in the auricular muscle which, as the necropsy showed, was associated directly with a tumor pressing on the auricle and atrophy of the underlying auricular muscle.

In this case it was evident, therefore, as Dr. Dock pointed out, that there was but one possible diagnosis to make and that was tumor. The lack of expansile pulsation or any visible movement at all in the mass and the absence of a tracheal tug, reduplication of the heart sounds and pain ruled out in large measure an aneurism of the aorta. Again, there were no definite symptoms of sufficient gravity to indicate an aneurism of the right ventricle and the absence of symptoms and signs of tricuspid stenosis made a diagnosis of dilatation of the right auricle unjustifiable.

DISCUSSION

Tumors of the heart are not common but do occur in small numbers among the cases of any large clinic. The tumors which may be classed together into this group, as is well known from the literature may arise (1) from the heart itself, (2) from the pericardium, or from the adjacent portions of the great vessels or neighboring tissues of the mediastinum.

Link,[1] in 1909, collected ninety-one cases from the literature which he concluded were primarily of cardiac origin. Meroz,[2] 1912, selected fifty-five cases which he thought had their origin in the heart. Since that time Norton,[3] Gottel [4] and Weltmann [5] have each reported a case of a primary heart tumor.

According to the classification of Meroz the primary tumors of the heart may be (1) valvular; (2) intramuscular, and (3) intracavitary.

The tumor we observed belongs to none of these latter groups but must fall in its clinical aspects among those of the pericardium. It is questionable whether it was attached to the auricle in its earlier period of development. This attachment with the definite deterioration

1. Link, R.: Klinik der primärer Neubildungem des Herzens, Ztschr. f. klin. Med. **57**:272, 1909.

2. Meroz, E.: A Clinical Study of Three Cases of Primary Tumor of the Heart, Internat. Clin. **4**:231, 1917.

3. Norton, W. H.: Myoma of the Heart, Am. J. M. Sc. **158**:689, 1919.

4. Göttel, L.: Ein Fall von primären Herztumor, Deutsch. med. Wchnschr. **45**:937, 1919.

5. Weltmann, O.: Klinschr Beitrag zur Kasuistik primärer Herztumoren, Wien. klin. Wchnschr. **33**:537, 1920.

of the auricular muscle may have occurred in the later stages of the disease. Our tumor was definitely of aortic origin with secondary attachment to the heart.

The tumors decribed arising from the pericardium are (1) fibroma; (2) primary sarcoma; (3) myxoma; (4) parasitic cysts, and (5) dermoids. Fornia[6] recently made a collection of sixteen such cases. Secondary tumor metastases are not uncommon. These may arise from carcinoma, sarcoma, Hodgkins disease or lymphosarcoma situated in adjacent or distant regions of the body. Inflammatory nodules are also seen. Recently one of us [Burrows] observed such a case at necropsy. The nodules in this latter case were multiple. The largest measured about 1cm. in its longest diameter. The whole of the visceral pericardium was thickened. The nodules were striking histologically on account of the large number of foreign body giant cells which they contained. There were also similar inflammatory nodules in the lungs, pancreas, suprarenals and kidneys. The etiology was not determined. Diabetes mellitus was the cause of death.

These various cardiac tumors, as is well known, according to their position may simulate in their clinical picture any one of a great variety of grave cardiac diseases.[2] For this reason up to the time of the development of the roentgen ray their diagnosis was practically impossible, as has been stated by Oppolzer,[7] Gottel and others.

At the present time, as a few recent cases and our case illustrate, this may no longer be true for those tumors presenting on the surface of the heart. The cardiac cachexia not otherwise explained should, therefore, be most carefully studied by these means not only for the importance of improving these diagnostic methods but also from the standpoint of treatment.

The thorax is no longer a barrier to the surgeon. Tuffier[8] recently reported the successful partial removal of a dermoid the size of two fists which was adherent to the aorta and encroached onto the wall of the auricle and ventricle. The clinical symptoms were those of a grave angina pectoris. The case was diagnosed a cyst by Vaques. The tumor was partly calcified and was filled with greasy material. The incision, drainage and disinfection took six months. The patient recovered completely and is now free from the symptoms of angina pectoris and is in good health.

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6. Forni, G.: Primary Tumors of the Pericardium, Tumori **4**:523, 1914.

7. Oppolzer: Quoted by L. Krehl; Diseases of the Myocardium. Nothnagel's Encyclopedia of Practical Medicine. Diseases of the Heart, translated and revised by Dr. George Dock.

8. Tuffier: Tumors Primitives du Coeur. La Chirurgie du Coeur. (Piéce presentée a la Societe de Chirurgie, Paris) 1920.

Our case was brought to the attention of Dr. Evarts A. Graham who considered it an operative possibility had it been seen before the grave cardiac arrhythmias, irregularities and signs of heart failure (the so-called decompensation) had developed.

PATHOLOGY

Pathologically, as stated above, we have been unable to find any counterpart of this tumor in the literature of heart and aortic tumors. Tumors of the aorta are not common. The catalogue of the Surgeon General's Library reports but fifteen papers on this subject. Two of these were written in the eighteenth century before the time of careful histologic study of tissues. Three were cases of secondary carcinomatous metastases. One was a parasitic cyst in a dog, and one other was a blood cyst. Three were primary sarcomas, and one, reported by Threadgill, was a cartilaginous mass in the aorta of a negro child. The paper by Okada was not obtained, and another by Maixner adds nothing new to this subject.

Joel,[9] in 1890, reported the occurrence of a teratoma of the pulmonary artery. As stated above, our tumor is not a neoplasm but it is evidently of inflammatory origin. The pedicle has the structure of an arterial branch of the aorta which has undergone dilatation of its orifice and secondary atheromatous obliteration. The tumor has all the characters of an atheroma of a massive size.

We at first thought that similar tumors might have been observed and confused with dermoids or fibromata of the heart or pericardial tumors. A careful study of the gross and microscopic descriptions of such cases described in the literature has failed, however, to reveal any such similarities. (Morris,[10] Lambert and Knox,[11] Christian [12] and Dangschaat.[13])

Again, there is no evidence that it was primarily an aneurysm. It is more that of a granuloma undergoing secondary changes.

The etiology is obscure. It is impossible to be certain that it is related to other evidences of inflammatory disease of the heart and the aorta in this case and the supposed syphilitic infection. Levaditi

9. Joel, J.: Ein Teratom auf der arteria pulmonis innerhalbs des Herzbeutels, Virchows Arch. f. path. anat. **122**:381, 1890.

10. Morris, R. S.: Dermoid Cysts of the Mediastinum, Med. News **87**:404, 438, 494 and 538, 1905.

11. Lambert, S. W., and Knox, L. C.: Intrathoracic Teratoma, Tr. Assn. Am. Phys. **35**:17, 1920.

12. Christian, H. A.: Dermoid Cysts and Teratomata of the Anterior Mediastinum, J. M. Research, **2**:54, 1902.

13. Dangschaat, B.: Beiträge zur Genese, Pathologie und Diagnose der Dermoid Cysten und Teratom im Mediastinum Anticum. Beitr. z. klin. Chir. **38**:692, 1903.

stains were made of the tumor, of the nodules in the endocardium; of the left ventricle and of the aorta. The poor fixation of the tissue, however, made the negative results of no importance.

Its rarity cannot be accounted for. In this location it might be associated with the rarity of an artery arising from this part of the aorta. This does not explain, however, its absence of occurrence in other regions of the body.

It has been of interest, therefore, for us to report this case as a peculiarly rare clinical entity, the existence of the tumor of which is possible of diagnosis and which must fall, therefore, within the domain of the surgical treatment of the present and the future.

BACILLUS ACIDOPHILUS AND ITS THERAPEUTIC APPLICATION

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NEW HAVEN, CONN.

Bacillus acidophilus was first observed and described in 1900 by Moro.[1] It is a rather large gram-positive bacterium which is quite pleomorphic and which in many respects resembles Massol's *Bacillus bulgaricus* and Tissier's *Bacillus bifidus*. It was claimed by Moro to be the chief inhabitant of the intestine of infants that subsist entirely on mother's milk. This assertion was disputed by Tissier[2] who protested that *B. bifidus* holds the place of prime importance. *B. acidophilus* and *B. bifidus* are now known to constitute the main flora of the breast-fed child, the latter being, perhaps, the more prominent of the two. As the diet changes and becomes more and more complex, there is a corresponding change in the kinds and relative numbers of intestinal bacteria, until finally the intestinal population assumes the character of that of the ordinary adult. *B. acidophilus and B. bifidus* gradually disappear to such an extent that their presence can be demonstrated in the feces with considerable difficulty only. Their place has been taken by various other organisms, some of which are decidedly fermentative and putrefactive, and, according to Metchnikoff and others, assume a rôle harmful to the host.

B. acidophilus is practically indistinguishable from *B. bulgaricus* and has undoubtedly often been mistaken for the latter. There are, however, two well-known points of distinction between these two organisms. *B. acidophilus* produces relatively little acid in milk (less than 1 per cent.) even after continued incubation, whereas *B. bulgaricus* may produce as much as 3 per cent. Furthermore, *B. acidophilus* attacks maltose with acid formation, while *B. bulgaricus* has no action on this sugar. The most important mark of difference is that relating to intestinal implantation. *B. bulgaricus*, as numerous experiments have shown, is unable to live and multiply in the intestine of the white rat and of man, whereas *B. acidophilus* undergoes rapid development when administered by mouth, or as the result of milk, lactose or dextrin feeding.

Rettger and Horton[3] and Hull and Rettger[4] had shown that the feeding of milk or lactose to experiment animals, including the white

1. Moro, E.: Ueber den *Bacillus acidophilus*, Jahrb. f. Kinderh. **52**:38, 1900.
2. Tissier, H.: Réchérches sur la flore intestinale normale et pathologique du nourisson, Thése, Paris, 1900.
3. Rettger, L. F., and Horton, G. D.: A Comparative Study of the Intestinal Flora of White Rats Kept on Experimental and on Ordinary Mixed Diets, Centralbl. f. Bakteriol. **73**:362, 1914.
4. Hull, T. H., and Rettger, L. F.: The Influence of Milk and Carbohydrate Feeding on the Character of the Intestinal Flora, J. Bacteriol. **2**:47, 1917.

rat, tended to decrease the number of ordinary intestinal bacteria and to establish an organism of the *B. acidophilus* type. Hull and Rettger [4] demonstrated that an almost complete acidophilus flora may be obtained in the albino rat by the daily feeding of 2 gm. lactose. Cheplin and Rettger [5] confirmed these observations on white rats, and showed further that similar results may be had in man. They found that the daily ingestion of from 300 to 400 gm. lactose brought about a very profound change of bacterial types in which *B. acidophilus* greatly predominated, often to the extent of at least 90 per cent. of the viable organisms present. Torrey [6] had shown that in the treatment of typhoid fever patients with lactose from 250 to 300 gm. were necessary daily in order to establish an acidophilus flora.

It was not until the spring of 1919 that any serious attempts were made to administer cultures of *B. acidophilus* for the purpose of bringing about an implantation and proliferation of this organism in the intestine. Cheplin and Rettger [5] demonstrated that transformation of the flora may be brought about easily and within the course of four to six days in apparently normal human subjects by the daily administration of 300 c.c. pure whey-broth cultures of the organism. *B. acidophilus* was often present in the feces to the extent of from 85 to 90 per cent. of the cultivable bacteria. Similar results were obtained with all of these subjects when 150 c.c. of the culture and 150 gm. milk sugar were given in place of the requisite amount of culture alone.

Implantation of *B. acidophilus* may be brought about, therefore, by any one of the three methods just described. In fact, the results, as measured by the bacterial picture, were practically the same in each method, as is clearly shown in the curves and tables published at some length in book form.[7] The whey-broth culture was soon displaced, however, by the acidophilus milk culture which was devised by us early in 1920. On account of the extreme importance attached to the use of *Bacillus acidophilus* milk the following brief description is given of this product and of the method of preparation.

BACILLUS ACIDOPHILUS MILK

Fresh skimmed cow's milk is sterilized in one heating at 115-120 C., the time required being determined by the volume of the milk and the nature of the container. Quart lots in ordinary glass flasks are heated

5. Cheplin, H. A., and Rettger, L. F.: Implantation of *Bacillus acidophilus*, Proc. Nat. Acad. Sc. **6**:423, 704, 1920; Proc. Soc. Exper. Biol. & Med. **17**:192, 1920; **18**:30, 1921.

6. Torry, J. C.: The Fecal Flora of Typhoid and Its Reaction to Various Diets, J. Infect. Dis. **16**:72, 1915.

7. Rettger, L. F., and Cheplin, H. A.: A Treatise on the Transformation of the Intestinal Flora with Special Reference to the Implantation of *Bacillus acidophilus*, Yale University Press, 1921.

22-24 minutes. Properly heated milk should have a dark cream color, but should not be distinctly browned. After cooling to at least 37 C. the milk is inoculated with pure strains of *B. acidophilus* which have been grown, by repeated transfers, sufficiently long in milk to develop rapidly and bring about coagulation of the casein within twenty-four hours at a temperature of from 35 to 37 C. Viable milk cultures of the organism are employed as the inoculum, and at least 10 c.c. of the inoculum are transferred for each liter of milk treated. After thorough mixing, the newly inoculated milk is incubated for the period stated.

At the completion of the full incubation period the casein appears as a soft curd, with a thin layer of clear or almost clear whey over the surface. On thorough shaking the curd falls to pieces and the milk acquires a smooth consistency which resembles that of thick cream. Even during long standing there is no marked separation of whey from the curd, or collection of the curd into granules or lumps. The acidity of the acidophilus milk is never high, as compared with that of *B. bulgaricus* milk, seldom reaching more than 1 per cent., even after a week's incubation at ordinary room temperature. The odor and flavor resemble to some extent those of a high grade buttermilk and should be agreeable to persons who do not have a dislike for sour-milk products as such. The odor and taste are, however, decidedly characteristic, when the milk culture is pure. Contaminating organisms, if they have developed appreciably in the milk, owing to imperfect sterilization or subsequent contamination, change the character of the milk in such a manner as to be recognized readily by the odor and taste, and often by the physical appearance of the product. For example, the ordinary milk souring bacteria cause the usual sour milk fermentation and coagulation, and the common spore forming organisms of the *B. subtilis* type produce offensive products characteristic of the group. These are the main types of contaminants thus far encountered in the acidophilus milk by us.

THERAPEUTIC APPLICATION OF BACILLUS ACIDOPHILUS

In the first series of experiments with man, seventeen different subjects were employed. Fifteen were apparently normal and two had a long history of intestinal disturbances. Most of the subjects served in more than one experiment, bringing the total number of individuals up to forty-three. The entire work involved the bacteriologic examination of 580 stools. Implantation of *B. acidophilus*, with the predominance of this organism to the extent of at least 80 per cent. of the total flora of the feces, was brought about almost at will. Particular attention is called to the fact, however, that no two subjects required the same minimum amount of lactose, *B. acidophilus* culture or combina-

tion of the two, to yield to the transforming influence within a given period of time.

In all of the experiments the change in the intestinal flora was determined by the three following bacteriologic methods: (1) Plating of fecal suspensions (in physiologic sodium chlorid solution) in whey agar and the numerical study of *B. acidophilus*-like colonies; (2) preparation of deep whey-agar (Veillon) tubes for the determination of gas producing organisms of both the aerobic and anaerobic types; and (3) staining of slides by the Gram method and a differential study of bacterial types. These methods proved to be most valuable, and were employed also in the more recent work on intestinal flora in abnormal subjects. For a full description of these and all other methods employed in the earlier investigation, and for a full account of the results, the reader is referred to our monograph [7] on intestinal flora.

No difficulty was experienced in obtaining the cooperation of practicing physicians in our investigation of the therapeutic properties of *B. acidophilus* when administered by mouth, either alone as a pure milk culture or in combination with different amounts of lactose. It became apparent at the outset that the acidophilus milk is much to be preferred to the lactose broth or whey broth cultures of the organism for the following reasons: The milk is tolerated even by those who are unable to retain the simplest and most wholesome foods for convalescents; when properly prepared and preserved the acidophilus milk remains practically unchanged, and free from bacterial contamination and deterioration: it contains at least 4 per cent. lactose which in itself serves to stimulate *B. acidophilus* proliferation in the intestine; it is nutritious, and for those who cannot take or do not tolerate other foods it does much toward the maintenance of nitrogen balance and the prevention of tissue waste, when taken in the usual amounts, from 1 pint to 1 quart daily and finally, as a young culture of viable bacteria it is particularly potent in bringing about the desired transformation of bacterial types in the intestine.

PATHOLOGIC CASES

It is not our purpose here to present a detailed history of the individual cases, nor to dwell at any length on the treatment and the bacteriologic results. A full account of these studies will be published, however, at an early date. The subjects under observation may be subdivided into the following groups; (1) Chronic constipation with the symptoms of so-called autointoxication and other accompanying pathologic conditions, some of them acute, 20 cases; (2) chronic diarrhea following an attack of bacillary dysentery, 2 cases; (3) colitis,

at times bloody, and more or less mucous, 3 cases; (4) sprue, 2 cases; (5) dermatitis (eczema), 3 cases.

These thirty cases are exclusive of those which have come under our observation within the past few weeks. Nor do they include those which are being studied and treated in other institutions through our cooperation. Particular attention is directed to only a few of these thirty cases.

The subjects were requested to bring to the laboratory one or two specimens of stool before taking the acidophilus treatment, and for a while daily samples, when procurable, after the first administration of the acidophilus milk or of the milk plus stated amounts of lactose. Bacteriologic examinations were made of these specimens, and their results correlated with the clinical findings. It was the aim to obtain a pronounced transformation of the bacterial flora of the intestine in the shortest period of time; hence, so-called "maximum" treatment was given from the start. As lactose has a marked laxative effect when taken internally in sufficient amount, persons having a history of obstinate chronic constipation at first usually received 1 quart of the acidophilus milk plus 100 gm. lactose daily. The powdered lactose was added to the acidophilus milk in the flask and the contents thoroughly shaken. Subjects were instructed to take the daily supply in three equal portions, one in the forenoon, another in the afternoon, and the third immediately before retiring for the night, and in every instance at least two hours before and after meals. There were no regulations as to diet, except that the subjects were urged to refrain from the use of food which by experience or training they knew to prove injurious.

If, in the course of three or four days constipation was not relieved except by an enema, which was advised when the condition of the subject made it absolutely necessary, the daily amount of lactose was increased by 25 or 50 gm. On the other hand, when stimulation of peristalsis became too marked and a diarrheal condition resulted from the taking of the full amount (1 liter of acidophilus milk and 100 gm. lactose), the quantity of lactose was reduced by 25 or 50 gm. In a few instances the volume of milk taken daily was reduced to 500 c.c., with or without a reduction in the amount of lactose.

In the diarrheal cases (including colitis and sprue) the treatment consisted in the daily administration of 1000 c.c. acidophilus milk without any added milk sugar. The milk was easily tolerated by the patients; in one instance, however, the volume was reduced after the first few days to 500 c.c. owing to a feeling of fulness and partial loss of appetite of which the subject complained. Persons who could

not take other food in any form retained the acidophilus milk and complained of no distressing or otherwise injurous effect.

Chronic Constipation.—The two following cases of chronic constipation are briefly reviewed here, as they happened to be the first to take the treatment, and were among the most obstinate advanced cases of alimentary toxemia that have as yet come under our observation.

Case 1.—Subject D. had suffered from constipation for at least seven or eight years, and complained of fulness of the abdomen and of gas and pain in the epigastric region, also of an almost constant headache, visual disturbance, general discomfort after meals, loss of energy and initiative, general malaise, and what was most disturbing to him, melancholia and other indications of lessened mentality. He regularly required unusually large doses of laxative to induce bowel evacuation, and stated that he had been absolutely dependent on cathartics for at least two years for relief which was even then only partial and of very short duration.

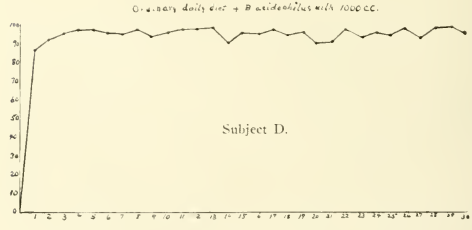

Fig. 1.—Results of addition of *B. acidophilus* milk to diet.

The subject was given 1 liter acidophilus milk daily, and instructed, as were all others, not to employ a cathartic, and to bring daily specimens (when possible) of stool. He reported almost daily at the laboratory for observation. Unfortunately, no sample of stool could be obtained before the beginning of the treatment. However, in none of the numerous experiments already conducted on man was *B. acidophilus* observed in the feces before treatment with *B. acidophilus* culture or special carbohydrates without much difficulty and then only rarely and in very small numbers; hence, it is safe to assume that in cases of constipation at least the per cent. of cultivable *B. acidophilus* cells is, without special stimulation, at or near 0.

Within forty-eight hours after the first ingestion of the milk culture the bacteriologic examination of the feces revealed a marked transformation of the flora with a preponderance of *B. acidophilus*-like organisms. By the end of the fourth day the gas producing organisms had apparently completely disappeared from the intestine, and the aciduric type reached a percentage level of at least 90 which it maintained throughout the course of the treatment (Fig. 1). The administration of the acidophilus milk had to be discontinued and the experiment ended after a period of thirty days, owing to the seasonal closing of the laboratory. The subject left very soon after for continued residence in the Orient.

On the third day after the subject began the treatment he reported a normal bowel evacuation, and continued to report at least one daily movement, barring one exception, for the remainder of the experimental period. There was an apparent change within the first three days in the patient's general condition. By the end of the first week he reported complete relief from gaseous distension and pain in the epigastic region. His appetite was good, and he was free from the usual intestinal disturbance following a substantial meal. Little by little he indulged his appetite more and ate heartily of meats, biscuits and pastries with apparent impunity, which hitherto he was forced to avoid. His headaches and mental disturbances disappeared, and he resumed his full daily duties with, as he stated repeatedly, new strength and endurance. These claims were fully borne out by his appearance and actions.

Case 2.—Subject W. was an almost exact duplicate of D. He had, however, marked dilatation of the descending colon. He received essentially the same treatment as Subject D., and though he responded more slowly at the beginning, the bacterial transformation was almost complete by the end of the first week, and the percentage of *B. acidophilus* remained at 85 to 95 throughout the course of observation. Gas-forming organisms disappeared early. On the third day after the first administration of the acidophilus milk he presented a natural specimen of stool which appeared normal, and thereafter, with very few exceptions, reported daily normal evacuations. His physical and mental condition had been such as to cause him considerable alarm. He had over a period of five or six years consulted several specialists and had been advised by two of them to undergo an operation for the colon dilatation.

This subject's general condition began to improve almost immediately. He reported constant improvement from day to day, which was apparent also in his facial expression and in his actions. He was under observation for eight months. After about three months of the treatment he was advised to take the milk less frequently and to continue its gradual elimination from the diet for the purpose of determining whether it could not be dispensed with eventually. Until early in May, and for a period of four weeks, he took only 1 or 2 quarts a week. During the succeeding six weeks he called twice for the acidophilus milk, stating each time that, while he still continued to be in very good condition, he thought it desirable to take a pint or a quart because of slight premonitions of returning trouble. He has not reported in person since, and in so far as the writers know there has been no recurrence.

Contrary to the rule, both these subjects responded readily to the use of the acidophilus milk, without any added lactose. Two other subjects have reacted similarly. On the other hand, most of the chronic constipation cases required 100 gm. added milk sugar, and one of them required as much as 200 gm. daily along with the quart of acidophilus milk. In no instance was there a failure to bring about relief when the treatment was not interrupted early.

Chronic Diarrhea.—Case 3.—Subject B. A Bohemian, male, 42 years old, residing in New Haven since April, 1921. He was seized in September, 1907, with an attack of acute diarrhea accompanied with tenesmus. The stools were bloody and contained mucus. Temporary recovery; no bacteriologic examination; recurrence in the spring of 1908; in hospital at Frankfurt a. M. for six weeks. Bacteriologic examination negative. In sanitarium at Meran in Tyrol. Limited diet; temporary recovery. Recurrence in summer of 1908. Diarrheal condition more or less constant till 1914, when *B. dysenteriae* was identified in the stools. Temporary recovery. Recurrence in January, 1915, while living in Silesia. In dysentery hospital six months. Shiga-Kruse bacillus again isolated from feces. Serum treatment. Left hospital as incurable. In 1915 in hospital in Hamburg; for six months exclusive diet of oatmeal gruel. Treat-

ment resulted in temporary cure. Normal formed stools for the first time since 1909. Recurrence after four weeks; acute abdominal pain and diarrhea. Feces examination negative. Condition much improved after four months' residence in Norway. Partial recurrence in England (December, 1920, to April, 1921). Took ship for America April 2, 1921. Apparently normal on ship and for a few days after arrival in New Haven.

Within a week after subject B. reached New Haven he was suddenly seized with an attack of profuse diarrhea and acute pains in the descending colon. Presented himself for treatment in April. Stools were watery, very dark, and of pronounced putrefactive odor. By the third day the stools appeared lighter (yellowish) in color and less watery. After one week's treatment the abdominal pains had practically disappeared, the feces rapidly approached the normal and the diarrheal condition had almost completely ceased. During the second week's treatment he pronounced himself fully recovered. He continued apparently normal for about three weeks when owing to dietary indiscretion there was a slight return of the disturbance. The night before the partial recurrence he attended a banquet and indulged freely in all that was set before him, including two courses of meat. This setback lasted only two or three days.

Subject B took one quart of acidophilus milk daily from the first without any intermission. Except for the above mentioned and a second slight recurrence early in June brought on apparently by bathing in cold sea water, he was, according to all appearances and his own claims, in normal condition for two months and to the time when the experiment was interrupted owing to the closing of the laboratory (July 1). The subject has on several occasions since then informed the writers that he has suffered no recurrence.

Another subject whose case in some respects was similar to this reacted favorably to the treatment. A full history of this case, with results, will be given in a later paper.

Colitis.—The two cases of colitis which came under our observation were of the acute type. One was apparently uncomplicated, but had a long history of intestinal disturbance. The other was complicated with nephritis. The former responded completely to the milk treatment (800 c. c. daily) and after about one month returned to his work. He continued in apparently good health for about two months when he experienced a partial reversion, due to overconfidence in his improved condition and indulgence in late shore dinners.

The second patient gave every indication of physical improvement when, owing to his serious nephritic condition, he required special hospital treatment and was compelled to discontinue the use of the acidophilus milk. His severe abdominal pains had almost completely disappeared, however, and he was suffering apparently very little from the colitis.

Both of these cases will be presented more fully at a later date.

Sprue.—Case 4.—Subject Wr had contracted sprue while in China. Though the affection was not of an acute type, it was serious and compelled him to return to the United States where for at least two years he was constantly under its annoying and debilitating influence. He took one quart of the acidophilus milk daily for six weeks during which time the character of the feces changed completely from the clay-colored, soft and extremely offensive type to the yellow, almost formed and almost odorless. The gas disappeared from the colon, and the subject stated from day to day that he thought he

was for the time at least in perfectly normal condition. The bacteriological results of fecal examination are shown in Figure 2.

A second case of sprue was that of a returned missionary who had contracted the disease during twenty years of service in China. When seen by the senior author he had been confined to his bed for several months with the characteristic symptoms in their most acute form, including tetany. He was emaciated and subject to abdominal pains and gaseous distension.

This patient has been under observation for almost six months, during which period he has taken, with very few brief intermissions, one quart of acidophilus milk daily (the milk being sent to him by special messenger). He has shown from almost the beginning gradual improvement in his condition, though he has from time to time suffered relapses.

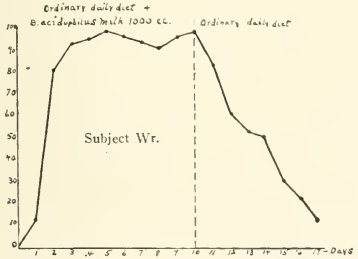

Fig. 2.—Results of addition of *B. acidophilus* milk to ordinary diet and then returning to ordinary diet.

Dermatitis.—All of the three cases of dermatitis were those of eczema. Treatment of two of them was discontinued before any definite results could be obtained. The third patient (Subject Q) responded completely to the treatment, and for five months has been free from the eczema which for at least twelve years had been a source of constant annoyance and embarrassment. When first seen practically the entire face was involved, as well as other parts of the body.

Transformation of the intestinal flora was effected with considerable difficulty, and required fully a month. However, by increasing the daily amount of added lactose from 50 to 100 gm. a high aciduric flora was established and maintained throughout the remainder of the experiment. Concomitant with this change there began a clearing of the skin which continued until after another month almost all traces

of the dermatitis had vanished. At the present time there are no indications of a return of the affection.

GENERAL COMMENTS ON THE THERAPEUTIC APPLICATION OF BACILLUS ACIDOPHILUS

The work of the past two years has shown conclusively that *B. acidophilus* can be implanted in the intestine of man almost at will, and that its colonization there may be such as to displace at least 80 per cent. of the usual mixed flora. This transformation is brought about by the administration of at least minimum amounts of lactose or of living acidophilus culture or of a combination of both. The most practical and effective method is by means of the acidophilus milk or of the milk plus definite amounts of lactose given daily. Cases of obstinate constipation almost invariably require some added lactose.

B. acidophilus is, according to all available information, an organism which does not elaborate toxic or other harmful products. It is classed as a strictly nonfermentative and nonputrefactive micro-organism. It is present in the intestine of nursing infants in relatively large numbers, and at all times is an inhabitant of the intestine of children of all ages and of the adult. It is demonstrated with difficulty, however, in the feces of persons subsisting on the usual mixed diet of which protein forms a large part, owing to its being suppressed by the other intestinal micro-organisms which flourish on the usual mixed diet. Administration of sufficient lactose (or dextrin) stimulates the proliferation of the relatively few aciduric bacilli. Ordinary milk accomplishes the same result, but enormous amounts of the milk are usually required to bring about the change. Pure viable cultures of *B. acidophilus* accomplish the same thing, with or without added lactose, but when applied alone definite minimum quantities of the cultures or suspensions, which must be determined for each individual, are necessary.

Viable cultures of *B. acidophilus* when used in sufficient amounts and under the right conditions have important therapeutic properties. They are of particular merit in the treatment of chronic constipation and of diarrheas, as the numerous experiments thus far conducted by the writers conclusively show. Furthermore, *B. acidophilus* should be of marked benefit in the treatment of other ailments which are directly or indirectly referable to disturbed function of the digestive system and of the chief organ of elimination; the results already obtained on several individuals bear out this promise.

A word of warning should be sounded at this time. The principle on which the acidophilus treatment is based has been clearly set forth in the various publications from this laboratory. It is only when these principles are adhered to that favorable results are to be expected.

In the first place, this is not a cure for all kinds of ailment, nor will all cases of disturbances falling within its category necessarily respond to the acidophilus treatment. In the second place, it is not an elixir in the sense that Metchnikoff's *B. bulgaricus* was for a while supposed to be. The ingestion of relatively few acidophilus bacilli will not lead to implantation and bodily improvement. A minimum amount of bacterial culture is necessary to bring about these results, and for this reason the writers have adopted the acidophilus milk culture as the surest and most effective means of attaining the desired results. So-called acidophilus tablets and powders can be of no use whatever in effecting transformation of flora and relief from trouble, either when taken as such or when used for the production of acidophilus milk. As has been fully pointed out elsewhere, the preparation of viable and satisfactory acidophilus cultures is impossible without the absolute sterilization of the medium to be used, and without the aseptic use of pure cultures of the organism as inoculum.

The fullest benefit from the acidophilus treatment can be derived only when the patient is under practically daily observation and when thorough bacteriologic examinations of the feces are made at frequent intervals. These examinations are of extreme importance in determining the amount of acidophilus milk or milk and lactose that are to be taken from day to day. Unless at least a reasonable degree of transformation of the intestinal flora to the aciduric type is effected little should be expected from the clinical standpoint. In any application of the principle of acidophilus treatment immediate results must not always be expected. In a number of instances in which the treatment became effective we have failed to obtain a favorable reaction until after one to two weeks' application, and in certain few cases there was no favorable response until a month after the initial administration of the acidophilus milk or the milk and lactose. This is to be expected when the results to be sought must of necessity be indirect, as in the positive eczema case. Yet, such cases may clear up and in the end prove to be some of the most satisfactory.

Various plans are now being considered for making *B. acidophilus* milk generally available and under such conditions as to assure its viability and purity.

THE EFFLUX OF BLOOD FROM THE CAROTID ARTERY OF THE DOG AND ITS EXPRESSION BY A GENERAL EMPIRICAL FORMULA*

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The study of the normal and pathologic significance of the blood pressure has been a subject of interest for many years. It was not until mechanical instruments were available, however, that any accurate measurements of blood pressure were taken. Ludwig, in 1847, first obtained a blood pressure tracing. In 1882, almost forty years later, V. Basch invented the tonometer. Roy and Adami in 1890 modified this for external use and Riva Rocca in 1896 manufactured the first practical clinical instrument for taking blood pressures.

During the last two decades, the clinical literature has been filled with blood pressure observations on both man and animal. The normal blood pressure of man has been established by a score of investigators; Alvarez,[1] Barach and Marks,[2] Cook,[3] Dawson,[4] Fisher,[5] Frau Wolfensohn-Kriss,[6] Goepp,[7] Greene,[8] Kammerer,[9] Lee,[10] MacKenzie,[11] Michael,[12] Sallom,[13] Smith,[14] Sorapure,[15] Weysse,[16] and Woley.[17] The

* From the Physiology Department, University of Minnesota.

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series by Goepp included 9,996 determinations; that of Fisher, 12,647; and that of MacKenzie, 31,934. A recognized normal blood pressure has been established also by several large insurance companies. The Northwestern National Life Insurance Company, for instance, uses an average scale ranging between 120 systolic pressure at 20 years to 136 systolic at 60 years. Much has been done to correlate high blood pressures with certain diseases, for instance, the toxemias of pregnancy, hypertension and arteriosclerosis.

Although blood pressure has been studied extensively, no attempt has been made to establish a correlation between it and blood flow. The present work is an effort to secure such a correlation. By means of quantitative methods and the graphic analysis of the results, a relationship between the arterial blood pressure and the efflux of blood from a cannula of known size was obtained. The data of this work are entirely from dog experiments. Any application of this relationship to direct arteriovenous transfusion can be used only after further observations on human material are made. This work was done under the physiology department at the University of Minnesota and material assistance was rendered by Dr. F. H. Scott and Dr. R. E. Scammon. Credit is also due to Mr. J. F. Borg and Mr. H. R. Smithies, who assisted in some of the experiments.

In addition to obtaining the relationship of blood pressure to blood flow, the total blood volume of each dog was determined. These data are reserved for a later publication.

MATERIAL

The dog was selected as the best laboratory animal to be used for the experiment. Eighteen dogs were used, differing in sex, variety, and size. No distinction was made between sex and variety since these factors did not bear on the problem. The size of the animal was important, however, since it was necessary for the carotid artery of the dog to be larger than the lumen of the cannula used for the experiment. The dogs were all in good health and had not been used for previous experimentation of any kind. The cannules used for the problem were manufactured by the Wilson and Wilson Company, Boston. These cannules are made from the same material as are their nickle plated steel needles and they correspond to them in gage size. The ends of the cannules are made blunt, however, to eliminate experimental error.

METHODS

A uniform technic was employed for all of the experiments. From twenty to thirty beakers were prepared for the collection of the blood of the animal. Into each of these 5 c. c. of sodium citrate solution were

measured by means of a buret. A bulb, T-shaped cannula was inserted into the left carotid artery and one arm connected to a mercury manometer for recording arterial blood pressure.

The internal surface of the metal cannula was coated with liquid petrolatum to prevent the formation of a blood clot. All but a thin film of the petrolatum was washed out by hot water. A rubber tube was fastened to the cannula in order to convey the blood from the carotid artery to the beakers. This tube was filled with a solution of physiologic sodium chlorid solution so that the blood flow for the first ten seconds would not be inaccurate. After finishing all the preliminary preparations the last thing done before starting the experiment was to insert this cannula in the right carotid artery. The kymograph was started and a normal curve of blood pressure was taken. Then the clip was removed from the right carotid and the blood was permitted to flow through the cannula. At the end of each ten seconds the blood flow was deviated to another beaker and the time was indicated on the kymograph tracing. When the animal ceased to bleed the arteries were cut and all of the blood was drained from them. No attempt was made to perfuse the animal. The amount of blood in each beaker was accurately measured to 0.5 c. c. The mean blood pressure for the respective intervals of ten seconds was obtained from the tracings. The determinations for all the data necessary in the experiment were now complete, except for the estimation of the area of the cannula lumen. The diameter of the lumen of the cannula was measured by means of a vernier caliper, accurate to one hundredth millimeter. The cross section area of the lumen was calculated by using the formula for the area of a circle: Area$=3.1416\ (r^2)$ in which r is the radius in mm.

ACCURACY OF THE DATA

. It is essential to estimate the accuracy of the data in order to obtain a relationship between the three variables, blood pressure, blood flow and the size of the lumen of a cannula. The cross section area of the lumen of the cannula can be determined with considerable exactness. All the cannules were measured in the same manner. The diameter of each was obtained by averaging thirty readings of the vernier caliper. By this means an accurate determination of the cross section area of the cannula was obtained. The blood flow per ten seconds is also an accurate measurement since it is not distorted in any way by experimental error. The blood pressure, however, is not as exact an observation. The necessity for an absolutely accurate baseline was not obvious while the experiments were being carried out. The error in its determination occurred because the third arm of the three way cannula was not kept horizontal to the carotid artery. The variation ranged from 2 to 10 mm. Hg.

TREATMENT OF THE DATA

The accuracy of the data is very important for the successful interpretation of the physiologic relationship between the blood pressure and the blood flow. The significance of the results, however, can be obtained only by an application of graphic and mathematical analysis to the data. The methods used in this series of experiments are three in number: (1) the construction of field graphs and drawing curves by inspection; (2) the determination of a general empirical formula, and (3) the comparison of the inspected absolute curves to the respective curves derived by the general empirical formula.

1. The construction of field graphs, together with the establishment of curves showing the central tendency of the data, was the first method of graphic analysis which was attempted. Each graph (Figs. 1, 2, 3, 4, 5 and 6) includes the data which were obtained by the use of a certain cannula. In each figure the abscissa represents blood flow in c. c. per ten seconds, while the ordinate is the blood pressure of the animal in mm. of Hg. The curve drawn by inspection does not signify a curve of mathematical accuracy but merely represents the best expression of the judgment of the author as to the central tendency of the data.

Figure 8 is also a field graph. In this instance the abscissa represents the area of the lumen of the cannula. The ordinate shows the average blood flow per ten second interval for the respective cannules.

2. After the field graphs were made and the inspected curves were drawn for each, a general formula was calculated expressing the blood flow in terms of the blood pressure and the cross section area of the cannula. This general formula was obtained by the method of trial and error. In determining the equation, the values of the cross section area of the cannula were kept unchanged. Blood pressure values were also kept as nearly similar to the respective observed determinations as the nature of the data would permit. The best general formula can be expressed as follows: Blood flow (c. c.) $=0.17$ (area [sq. mm.]) (Blood pressure [mm. Hg.]) in which blood flow is the efflux of blood from a cannula per ten seconds of time, area is the cross section area of the lumen of the cannula in sq. mm., blood pressure is the average blood pressure in mm. of Hg., and the number 0.17 is an empirically determined constant.

3. The comparison of the absolute values of the curves drawn by inspection with the corresponding determinations of the general formula is demonstrated graphically and numerically. On each absolute graph (Figs. 1, 2, 3, 4, 5 and 6) both the inspected and the calculated curve are inserted, the former by a solid line and the latter by a broken line.

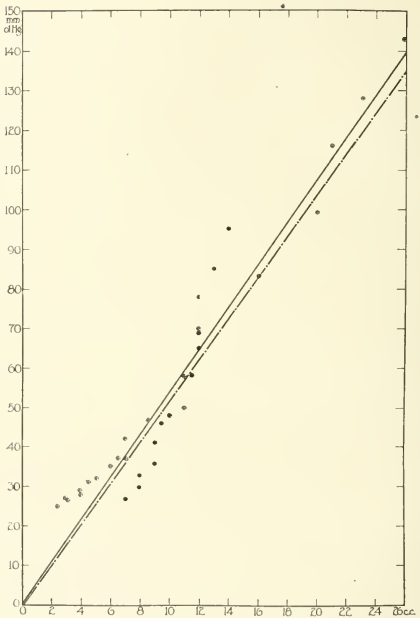

Fig. 1.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had outlet 1.131 sq. mm. in area. Abscissa: efflux of blood in cubic centimeters per 10 seconds of time. Ordinate: blood pressure in millimeters of Hg. Individual cases are indicated by solid dots (for Experiment 1) and by circle-crosses (for Experiment 2). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

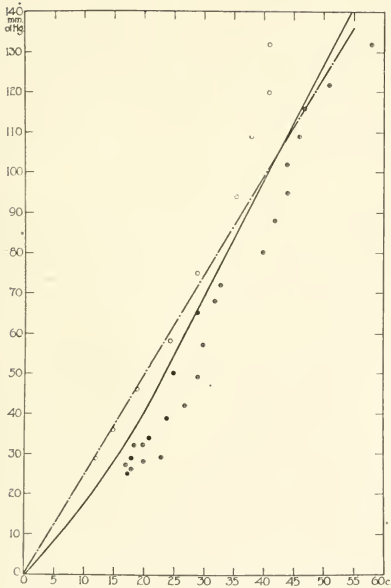

Fig. 2.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 2.378 sq. mm. in area. Abscissa: efflux of blood in c. c. per 10 seconds of time. Ordinate: blood pressure in mm. Hg. Individual cases are indicated by solid dots (for Experiment 3), by circle-crosses (for Experiment 4) and by open circles (for Experiment 5). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

In Figure 7 these curves are grouped to a uniform scale. The curves drawn by inspection are paired with those which were calculated and the corresponding pairs numbered according to the respective graphs.

The numerical comparison of the respective values which are taken from the curves drawn by inspection and those calculated by the general empirical formula is seen in Tables 1 and 2.

Table 1 contrasts in parallel columns the observed and the calculated values of both the average blood flow and the average blood pressure for each experiment.

Table 2 shows the observed and the theoretical values of the average blood flow and the average blood pressure for each graph.

EXPERIMENTAL OBSERVATIONS

A summary of the observations made on the data is divided for convenience into four subdivisions: (1) a consideration of the absolute data which are presented by means of field graphs and tables; (2) an enumeration of averages obtained from this absolute data; (3) a comparison of the observed and calculated values, and (4) the significance of the relationship between the blood flow and the size of the cannula outlet.

1. The absolute data available for this study are set forth in the field graphs (Figs. 1, 2, 3, 4, 5 and 6) and in Table 1.

Figure 1 is a field graph based on two experiments. Each of the dogs selected weighed 4.54 kg. The cannula used was gage 16 and had an opening 1.131 sq. mm. in area. The curve, drawn by inspection, shows that 26 c. c. of blood flows from the cannula in ten seconds when the blood pressure is 140 mm. of Hg. This amount of blood outflow steadily decreases until at 25 mm. of arterial pressure only 3 c. c. of blood flows from the cannula per ten seconds of time. The curve indicated by dashes is the general empirical formula: Blood flow (c. c.) = 0.17 (area [sq. mm.]) (Blood pressure [mm. Hg.]). It is slightly lower than the curve drawn by inspection.

Figure 2 is a field graph based on three experiments, the dogs weighing 5.67, 13.4 and 7.72 kg., respectively. The cannula used in these experiments was gage 14 in size and had a cross section area of 2.378 sq. mm. The curve drawn by inspection shows that 55 c. c. of blood leave the cannula in ten seconds when the blood pressure is 140 mm. of Hg. The arterial pressure descends rapidly to 40 mm. at which point the efflux of blood in ten seconds is 20 c. c. The curve drawn by calculation from the general formula is a straight line which falls slightly below the inspected curve at a blood pressure above 100 mm. of Hg. and slightly above the inspected curve at an arterial pressure below 100 mm. of Hg.

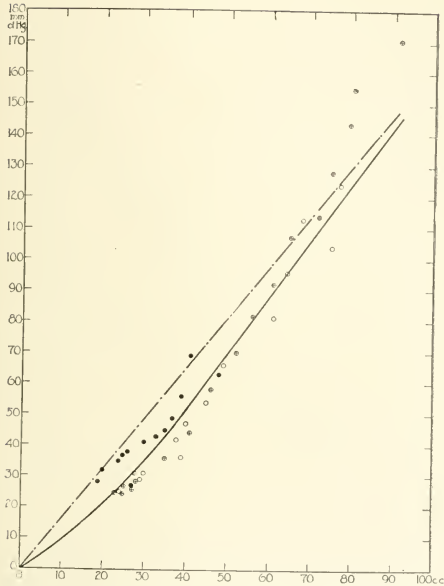

Fig. 3.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 3.597 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 6), by circle-crosses (for Experiment 7) and by open circles (for Experiment 8). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.)=0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

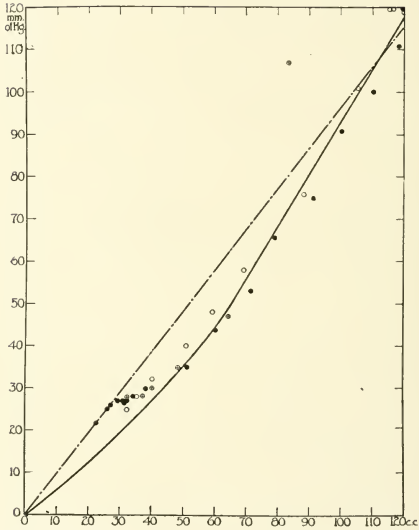

Fig. 4.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 5.2 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 9), by circle-crosses (for Experiment 10) and by open circles (for Experiment 11). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

Figure 3 expresses the absolute relationship between blood pressure and blood outflow per interval of time when the cannula has a cross section area of 3.597 sq. mm. Three experiments were carried out to establish this relationship, the dogs weighing 9.54, 20.45 and 15.2 kg., respectively. The blood pressure decreases more rapidly in amount than does the blood flow per unit of time. At 127 mm. of arterial pressure there is approximately 80 c. c. of blood flow from the carotid in ten seconds. The blood pressure decreases rapidly to 25 mm. and the blood flow to 23 c. c. per ten seconds. The calculated curve is at all times higher than the curve drawn by inspection.

The absolute data set forth in Figure 4 varies more widely from the empirical formula than do those of any other field graph. Three dogs, weighing 28.1, 10.13 and 21.8 kg., respectively, were used to establish this relationship. The cross section area of the cannula was 6.07 sq. mm. The inspected curve is distinctly concave descending rapidly from a blood pressure of 118 mm. of Hg. and a blood outflow of 120 c. c. per ten seconds of time to a blood pressure of 50 mm. of Hg. and a blood outflow of 68 c. c. per ten seconds. The descent is then more slow until the efflux of blood per ten seconds of time reaches 37 c. c. at 25 mm. of arterial pressure. The curve of the general empirical formula is definitely higher than the inspected curve although it is approximately correct for the higher blood pressures.

Figure 5 shows the relationship of blood pressure to the efflux of blood when a cannula with an outlet area of 7.548 sq. mm. was employed. Four dogs weighing 12.3, 22.7, 20.4 and 27.3 kg., respectively, were used. The individual cases are scattered in this figure although the central tendency is quite obvious and is expressed by the curve drawn by inspection. This curve shows that 220 c. c. of blood leave the cannula in ten seconds of time when the blood pressure is 159 mm. of Hg. The curve descends steadily to 37 c. c. of blood outflow at 25 mm. of arterial pressure. The curve drawn by the general empirical formula is slightly higher than that drawn by inspection.

The experiments set forth in Figure 6 were made on three dogs weighing 26.4, 20.0 and 25.1 kg., respectively. The cannula used to drain off the blood had a cross section area of 9.512 sq. mm. The central tendency of the individual cases in this figure is expressed by the inspected curve. This curve shows that 200 c. c. of blood flows from the cannula in ten seconds when the arterial pressure is 135 mm. of Hg. and that the amount of blood outflow per ten seconds of time descends steadily to the amount of 35 c. c. at a blood pressure of 25 mm. of Hg.

The absolute data for each experiment are summarized in Table 1. The number of observations on each dog and the number of experiments for each figure are given. The body weight of the dog before

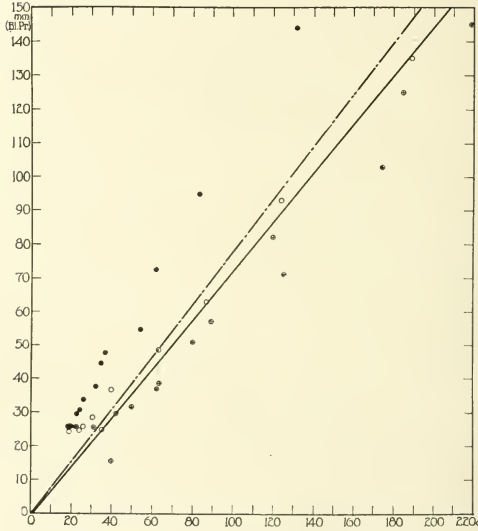

Fig. 5.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 7.548 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 12), by circle-crosses (for Experiment 13), by open circles (for Experiment 14) and by circle-dots (for Experiment 15). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.)=0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

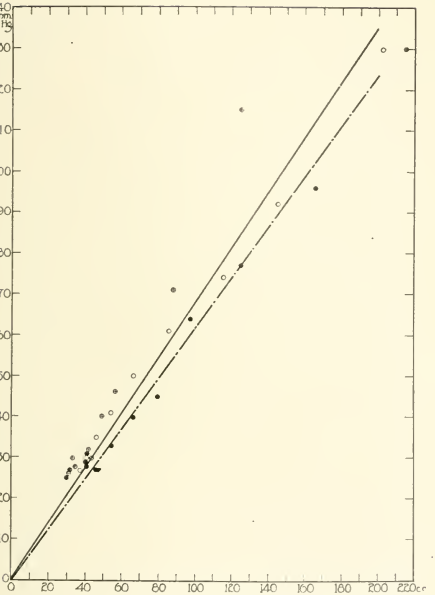

Fig. 6.—A field graph and curves expressing the relationship between blood flow and blood pressure. A cannula was used which had an outlet 9.512 sq. mm. in area. Abscissa: efflux of blood in c.c. per 10 seconds of time. Ordinate: blood pressure in mm. of Hg. Individual cases are indicated by solid dots (for Experiment 16), by circle-crosses (for Experiment 17) and by open circles (for Experiment 18). The solid line represents a curve drawn by inspection. The broken line is a curve drawn to the general empirical formula: Blood flow (c.c.) = 0.17 (area [sq. mm]) (blood pressure [mm. Hg.]).

TABLE 1.—Absolute Data for Individual Experiments
Blood Volume (C.c.)=0.17 (Area [Sq. Mm.]) (Blood Pressure [Mm. of Hg.])

Number of Graph	Number of Experiment	Number of Observations in Experiment	Weight of Dog, Kg.	Total Volume of Blood, C.c.	Average Blood Flow, C.c.		Average Blood Pressure, Mm. of Hg	
					Observed	Calculated from Observed Average Blood Pressure	Observed	Calculated from Observed Average Blood Flow
1	1	13	4.54	209	10.30	10.58	55.0	54.0
	2	20	4.54	234	10.05	10.98	57.2	52.3
2	3	6	5.67	329	22.30	16.30	40.3	55.4
	4	19	13.40	806	33.60	27.85	69.0	83.5
	5	9	7.72	381	28.30	31.12	77.0	70.3
3	6	12	9.54	488	31.40	27.35	44.7	51.4
	7	17	20.45	1,074	52.00	47.90	78.3	84.7
	8	15	15.20	825	46.40	36.90	60.4	75.8
	9	17	28.10	1,333	61.70	55.80	54.0	59.7
4	10	6	10.13	408	50.70	47.40	45.8	49.0
	11	11	21.8	1,215	75.50	72.10	69.8	73.0
5	12	11	12.3	633	48.00	71.90	56.0	36.9
	13	7	22.7	948	83.00	69.40	54.0	64.8
	14	9	20.4	790	67.00	68.50	53.4	52.4
	15	9	27.3	1,204	86.10	73.40	57.2	67.2
6	16	14	26.4	1,509	77.60	78.40	48.5	48.0
	17	9	29.2	737	56.30	75.0	46.4	34.8
	18	9	25.1	1,206	88.30	97.0	60.0	54.6

TABLE 2.—Absolute Data for Each Graph
Blood Volume (C.c.)=0.17 (Area [Sq. Mm.]) (Blood Pressure [Mm. of Hg.])

$$\text{Blood Pressure (Mm. of Hg.)} = \frac{\text{Blood Volume (C.c.)}}{0.17 \text{ Area (Sq. Mm.)}}$$

Numbers of Graphs	Cannula			Average Blood Flow, C.c.		Average Blood Pressure, Mm. of Hg	
	Radius of Lumen, Mm.	Area of Lumen, Sq. Mm.	Approximate Gage	Observed	Calculated from Observed Average Blood Pressure	Observed	Calculated from Observed Average Blood Volume
1 and 2	0.60	1.131	16	10.2	10.8	56.2	53.0
3 and 4	0.87	2.378	14	30.2	26.7	66.1	74.7
5 and 6	1.07	3.597	13	44.4	38.6	63.0	72.5
7 and 8	1.39	6.070	11	64.2	59.5	57.0	62.2
9 and 10	1.55	7.548	—	69.1	70.9	55.2	53.7
11 and 12	1.74	9.512	—	74.6	82.6	51.1	46.1

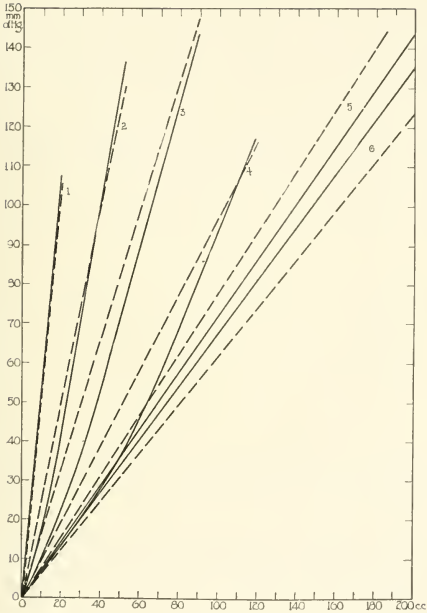

Fig. 7.—A series of curves illustrating the relationship between blood pressure and the efflux of blood per 10 seconds of time. These curves are taken from Figures 1, 2, 3, 4, 5 and 6. Abscissa: Blood flow in c.c. per 10 seconds. Ordinate: blood pressure in mm. of Hg. The solid lines indicates curves drawn by inspection. The broken lines are curves drawn to the general empirical formula: Blood flow (c.c.)=0.17 (area [sq. mm.]) (blood pressure [mm. Hg.]).

the operation is indicated in kilograms and the total amount of blood drained from the arteries during the experiment is noted in c. c.

2. An enumeration of arithmetic means obtained from this data has been carried out for the individual experiments (Table 1) and for these experiments grouped according to the cannula used (Table 2).

3. A comparison of the observed and the calculated absolute values can be made by a survey of the collected absolute curves (Fig. 7) or by inspection of the adjoining columns of observed and calculated determinations in Figures 1 and 2.

4. The curves taken from the field graphs are collected for the purpose of comparison in Figure 7. Considering the variability of the blood pressure due to experimental error, the inspected curves from

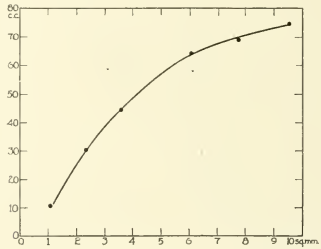

Fig. 8.—A curve to show the relationship between blood flow and the size of the cannula outlet. Abscissa: average efflux of blood in c.c. per 10 seconds of time. Ordinate: the area of the cannula outlet in sq. mm. The solid line is a curve smoothed by inspection.

four field graphs (Fig. 1, 2, 5 and 6) fit closely the general empirical formula. The inspected and the absolute curves from Figures 3 and 4, however, show a marked deviation, especially in the intermediate values of the curve.

In Table 1 the observed absolute values of both blood flow and blood pressure can be compared to the calculated values of blood flow and blood pressure respectively.

Table 2 demonstrates the correlation of the observed blood flow and the observed blood pressure with the respective calculated blood flow and blood pressure values.

5. The significance of the relationship between blood flow and the size of the cannula outlet is portrayed in Table 2 and Figure 8. The absolute averages of observed blood flow per ten seconds of time (Table 2) increases with the size of the cannula. In Figure 8 this

relationship is expressed graphically. The abscissa represents the cross section area of the opening of the cannula in sq. mm.; the ordinate gives the average efflux of blood per ten seconds of time. The curve based on this absolute data is logarithmic in type. The amount of blood flowing from the cannula in a given length of time increases rapidly at first as a larger cannula is used. When cannula gage 11 is employed (which has a cross section area of 6.07 sq. mm.) the blood flow per unit of time increases at a slower rate. The efflux of blood reaches a maximum average quantity of 75 c. c. per ten seconds when a cannula, 9.512 sq. mm. in area, is used.

The significance of this relationship between the flow of blood and the lumen of a cannula is not understood at the present time. It may be explained in several ways, none of them entirely satisfactory. At any rate, the general empirical formula is definitely influenced by this factor. A point is reached at which the size of the cannula makes little difference in the amount of blood flowing from an artery.

SUMMARY

The relationship of the blood pressure, the efflux of blood from the carotid artery of a dog, and the lumen of a cannula, the cross-section area of which ranges between 1 and 10 sq. mm., can be expressed by the general empirical formula:

Blood flow (c. c.)=0.17 (Area [sq. mm.]) (Blood pressure [mm. Hg.]).

STUDY OF BLOOD SUGAR CURVES FOLLOWING A STANDARDIZED GLUCOSE MEAL*

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ST. LOUIS

The following study is concerned with the effort to demonstrate the main factors which influence the duration of hyperglycemia after a glucose meal. More than 200 cases have been studied critically. There is extensive literature on the subject of blood sugar curves after various sorts of carbohydrate meals. In some studies standardized meals were given, in others not. Many clinicians have assigned diagnostic importance to an increased hyperglycemia following glucose ingestion.

The interpretation of the value of sugar curves depends on the following factors: (1) The technic of the administration of the glucose meal; (2) the collection of blood samples; (3) the method of doing the blood sugar determination, and (4) the wide application of the test so as to learn the many factors which influence these curves.

We believe it necessary, in order to support our conclusions, to discuss the first three of these points in detail.

Standardized Glucose Meal.—The standardized Janney[1] glucose meal was used. Glucose is the sugar of choice because it is most readily absorbed and because there are data as to the rate of its absorption from the gastro-intestinal tract. Fisher and Wishart[2] and Janney[3] have shown, by different methods, that from 66 to 80 per cent. of injected glucose is absorbed in the course of two hours.

The question of absorption is an important one. The curves here studied would indicate that absorption is fairly constant for the individual. This is brought out by the similarity of repeated curves (Table 1) on the same individual. The constancy of these curves is rather striking, especially where the symptoms and signs have not greatly changed. It is probable, therefore, that the absorption rate is fairly constant, at least for each individual. Again, in analyzing two hundred curves only six were found with a sudden increase in hyperglycemia at the end of the second hour, there having been no hyperglycemia the first hour. In other words, nearly all curves reach the maximum at the end of the first hour and the second hour levels are usually lower, or only slightly higher, than the first hour ones. This would show that absorption is quite rapid.

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1. Janney: Proc. Soc. Exper. Biol. & Med. **15**: 1917-1918. Janney and Isaacson: J. A. M. A. **70**:1131 (April 20) 1918.
2. Fisher & Wishart: J. Biol. Chem. **13**:49, 1912.
3. Janney: J. Biol. Chem. **22**:191, 1915.

Sansum and Woodyatt [4] have shown that the maximum intravenous tolerance rate of man and animals without glycosuria is 0.85 gm. per hour per kilo of weight. Intravenous tolerance methods, although scientifically desirable, are not practical. The known facts for determining a standard alimentary dose are: The above noted intravenous tolerance and the average absorption rate of 66 per cent. in two hours. The theoretical dose would be $(2 \times 0.85 \times \frac{100}{66})$ or about 2.5 gm. sugar per kilo. Janney has recommended 1.75 gm. per kilo as a

TABLE 1.—Repeated Curves

Diagnosis	Date	Blood Sugar Values, per Cent.				Curve Classification
		Fasting	1st Hr.	2d Hr.	3d Hr.	
Dyspituitarism	12/21/20	0.092	0.124	0.085	0.075	S
	2/ 4/21	0.092	0.120	0.085	0.093	S
Neuritis of sciatic nerve	2/ 8/21	0.085	0.190	0.150	0.130	III
	2/14/21	0.085	0.185	0.175	0.150	III
Hypothyroidism	10/14/20	0.090	0.110	0.095	0.095	S
	10/19/20	0.090	0.110	0.085	0.095	S
Manic-depressive psychosis	12/13/20	0.090	0.160	0.170	0.140	III
	1/10/21	0.100	0.183	0.195	0.175	III
	1/20/21	0.140	0.192	0.140	0.140	III
Lethargic encephalitis	12/ 8/20	0.100	0.110	0.090	0.080	S
	12/13/20	0.090	0.087	0.080	0.090	S
Exophthalmic goiter	6/ /20	0.168	0.280	0.220	0.113	II
	10/27/20	0.175	0.440	0.220	0.095	II

TABLE 2.—Showing Composition of Glucose Meal

Weight, Pounds	Glucose, Gm.	Lemon Juice, C.c.	Water, C.c.
90	72	54	126
100	80	60	140
110	88	66	154
120	96	72	168
130	104	78	172
140	112	84	196
150	120	90	210
160	128	96	224
170	136	102	238
180	144	108	252
190	152	114	266
200	160	120	280
210	168	126	294
220	176	132	308
230	184	138	322
240	192	144	336

standard dose. This amount of glucose for a man weighing 150 pounds, for instance, would amount to 120 gm. of glucose, or 480 calories. Such a man in basal state plus 10 per cent. increase for the specific dynamic action of glucose would be burning from 70 to 75 calories per hour. This dosage of glucose is, therefore, greatly in excess of caloric needs under ordinary circumstances and would show, with an absorption efficiency of 66 per cent., the glycogenic function of the individual or his ability to store the excess of an amount of sugar, commensurate

4. Sansum and Woodyatt: J. Biol. Chem. **30**:155, 1917.

with his weight, absorbed in a unit of time. Sansum and Woodyatt [4] have also shown that injecting animals in excess of the tolerance rate with varying concentrations of glucose made no difference in the amount of glucose in the urine, but that it did make a difference in the height of the blood sugar. It is, therefore, better technic to use a 40 per cent. solution of glucose using water and lemon juice as a solvent.

It seems obvious that one should not give 100 gm. glucose to an individual weighing 200 pounds and a like amount to one weighing 100 pounds and expect duplicate results in blood sugar concentration. It has been fairly well established that blood volume varies approximately with weight. Normally sugar is stored both in the liver and in the muscles. Palmer [5] found that in the diabetic animal the amount of glucose in the tissues varied with the hyperglycemia. It is possible, therefore, that sugar storage might take place in some abnormal conditions in other tissues besides the liver and muscles, and it would seem that the weight of the individual is our best index to his available space for storing glucose.

TABLE 3.—SHOWING THE ABSENCE OF RELATIONSHIP BETWEEN WEIGHT AND THE TYPE OF CURVE

Weight in Pounds *	Number of Individuals	
	Normal Curve	Subnormal Curve
90–100	4	3
100–110	8	5
110–120	2	6
120–130	6	5
130–140	6	2
140–150	6	5
150–160	3	2
160–180	1	3
180–200	5	2
200 plus	2	

* What the average weight of all hospital patients is, is not known, but the table shows the size of the patient does not influence the curve.

In some of the latest work in blood sugar determinations [6] after a glucose meal, a constant amount of glucose was used for all individuals. The results would have been more constant if the weight of the individuals had been taken into consideration (Table 3). The same can be said for the amount of water given with the meal.

Blood Sugar Determinations.—The blood was drawn with a 5 or 10 c.c. syringe and introduced into a test tube containing a few crystals of potassium oxalate and gently shaken. The first specimen was taken with the patient in a basal state, twelve hours after the last food. After the collection of the blood, the standardized meal was given. The blood was drawn again at the end of one, two and three hours. The third hour specimen was found to be of great importance. It is necessary that the blood should be precipitated immediately after taking the sample.

5. Palmer: J. Biol. Chem. **30**:79, 1917.

6. Allen, Wishart and Smith: Arch. Int. Med. **24**:523 (Oct.) 1919. Boothby: J. A. M. A. **77**:252 (July 23) 1921.

Meyers and Bailey's[7] modification of Benedict's first method was used: 3 c.c. blood was added to 12 c.c. saturated picric acid solution and a few crystals of picric acid. The blood was thoroughly shaken and filtered after five minutes. The standard glucose solution was made up of 1 mg. glucose to 5

TABLE 4.—Comparison of Blood Sugar Values by Benedict's and Shaffer's Methods

Case	Fasting 1st, 2d and 3d Hours		Classification	
	Benedict's Method, per Cent.	Shaffer's Method, per Cent.	By Benedict	By Shaffer
1	0.089 0.155 0.123 0.100	0.077 0.149 0.125 0.094	N*	N
2	0.087 0.159 0.136 0.117	0.096 0.171 0.143 0.125	II	II
3	0.103 0.169 0.135 0.095	0.088 0.138 0.119 0.074	N	N
4	0.104 0.089 0.113 0.094	0.090 0.090 0.099 0.095	S	S
5	0.086 0.163 0.156 0.117	0.099 0.143 0.138 0.127	II	III
6	0.095 0.148 0.167 0.137	0.090 0.157 0.166 0.109	III	II
7	0.143 0.195 0.138 0.142	0.115 0.195 0.142 0.114	III	III
8	0.098 0.190 0.296	0.096 0.176 0.181	III ?	III ?
9	0.102 0.096 0.088	0.095 0.082 0.088	S	S
10	0.089 0.118 0.091	0.079 0.106 0.093	S	S
11	0.126 0.236 0.154 0.139	0.113 0.191 0.156 0.135	III	III
12	0.082 0.224 0.226 0.143	0.072 0.230 0.189 0.101	III	II

* N, normal; S, subnormal; II, 2 hour sustained; III, 3 hour sustained.

c.c. saturated picric acid; this solution being part of the same sample of saturated picric acid that was used to precipitate the blood.

Cowie and Parsons[8] have shown how much more sensitive picric acid solutions are to such substances as acetone, diacetic acid and epinephrin than

7. Meyers and Bailey: J. Biol. Chem. **24**:147. 1916.
8. Cowie and Parsons: Arch. Int. Med. **26**:333 (Sept.) 1920.

to sugar itself. This work explains the very high blood sugars obtained in the cases of diabetes mellitus, but in the absence of acetone bodies the method is fairly accurate.

Since the publication by Shaffer and Hartmann[9] of their iodometric method, a considerable number of curves have been determined by both methods. In only minor respects has the classification of curves been changed by values obtained by the Shaffer method. In fifty blood sugar determinations done by both methods varying from 0.06 to 0.30 per cent., the averages at different levels by the two methods agree within a few per cent.

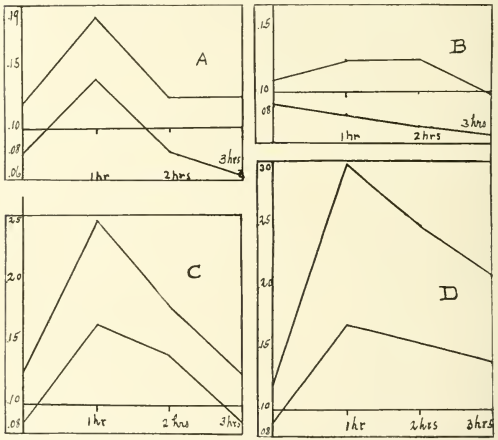

Fig. 1.—In each curve the two lines represent the limits between which the curves of that type falls. Ordinates show percentage of blood sugar. A, Normal curve; B, subnormal curve; C, Type II curve; D, Type III curve.

Classification of Curves.—In dealing with a considerable number of curves some sort of classification is necessary. This introduces the question of terminology. Sugar tolerance work began by feeding sugar by mouth and watching for its appearance in the urine. If an individual could take 100 gm. glucose and show no sugar in his urine, his "tolerance" would be considered normal; if he could take more than 100 gm. without glycosuria his "tolerance" was increased, and if he showed glycosuria on taking 100 gm. his "tolerance" was decreased.

9. Shaffer and Hartmann: J. Biol. Chem. **45**:365, 1921.

It is impossible to transpose this term "tolerance" into the terminology of blood sugar because a higher "tolerance" means a low blood sugar curve and a low "tolerance" means a high blood sugar curve. It has been our experience that the use of the word "tolerance" only leads to confusion and it would, therefore, seem to be better to use the term "blood sugar curve after glucose meal" or "blood glucose curve."

In consideration of the classification of curves it has not been considered important to include fasting hyperglycemia because it has been found that a fasting hyperglycemia is not a common condition, except where there is a loss of power to oxidize glucose, or in the presence of ashyxia or severe toxemia. As a rule, fasting hyperglycemia has not been found in endocrine or neurologic cases.

Normal curves were constructed on five normal individuals and also on about forty patients in the hospital who showed no demonstrable cause for a disturbed glycogenic function. These normal curves agree with those of other observers [10] in that after the normal fasting level there is a hyperglycemia at the end of the first hour of from 0.14 to 0.19 per cent. and at the end of the second hour the blood sugar level is within normal limits, or from 0.08 to 0.12 per cent. The third hour is still within normal limits from 0.06 to 0.12 per cent. We have assumed a higher normal hyperglycemia at the end of the first hour than other observers. However, this seemed justified when the procedure was so well controlled and the clinical data carefully studied. Many of the normal curves show a marked hypoglycemia at the end of the second and third hours. This hypoglycemia may be to the extent of from 0.06 to 0.08 values—so low that mere changes in blood volume would scarcely account for them. We cannot offer an explanation but have observations to show that by the end of the fourth hour the blood sugar values return to normal levels.

Abnormal curves have been divided into two main classes. The sustained curve, showing an abnormally sustained hyperglycemia, and the subnormal curve, which shows no normal hyperglycemia and even a hypoglycemia after a glucose meal. The curves showing sustained hyperglycemia we have divided into two groups: those showing hyperglycemia the second hour but with a return to normal levels the third hour; and those showing hyperglycemia at the end of three hours. The reason for this division of sustained curves into two groups will appear later.

Subnormal curves show a hypoglycemia or a normal fasting blood sugar. No hyperglycemia follows the administration of a glucose meal. The failure of the appearance of hyperglycemia may be due to one or both of two possibilities: Either a delayed absorption rate or an

10. Hammon and Hirschman: Arch. Int. Med. **20**:761 (Dec.) 1917.

increased glycogenic function. There are data [11] to show that in one condition, hypothyroidism, there is no delayed absorption in spite of the subnormal curves. Delayed absorption may occur in some conditions, such as hypopituitarism.

DISCUSSION OF MATERIAL

In the cases studied we noted age; weight; pulse rate and temperature; diagnosis (as obtained from the history sheet); gonads; children; menses; sexual power and desire; sympathetic symptoms; sweating; vasomotor instability; emotional tendencies, fear, anxiety; reflex excitability; gastro-intestinal symptoms; pituitary: sella (roentgen ray); bones; hair; eyegrounds; visual fields; secondary sexual characters; thyroid: vascular activity in gland itself; tremor; external ocular movements; size; exophthalmos; skin; special tests: basal metabolism; goetsch; hemoglobin.

In this study emphasis has been laid particularly in the selection of cases, on the so-called suspected endocrine disturbances of the thyroid and the pituitary; on the fatigued states, and on the hysterias and true dementias.

Many other conditions show abnormal curves, but the nature and constancy of their influence on the glycogenic function is even more uncertain than the above mentioned conditions. Such conditions are any mild toxemia, such as that in low grade bacterial infection; malignancy, etc., acidosis of any origin; drugs, such as opium and its derivatives, or salicylates. It is probable that these conditions can disturb blood sugar curves; certainly they affect general metabolism to some degree.

In this type of case the curves presented are not as numerous as one would wish. A few furunculosis cases (Fig. 2) show sustained curves. Some carcinomas of the gastro-intestinal tract, especially when metastases have taken place, show the same curve. Others with localized carcinoma show a normal curve. A normal curve is usually found in arthritis, but in the presence of fever or after foreign protein injections there is a high curve. If sugar curves are to be of value from an endocrine or a neurologic point of view, such conditions as may disturb glycogenic function should be avoided. Too little is known about them and there is no reason to believe their influence on the glycogenic function is a constant one. It seems more probable that a sustained curve in such conditions is a part of the general effect of incidental toxemia rather than a specific characteristic of a definite metabolic disturbance.

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11. Janney and Isaacson: Arch. Int. Med. **22**:160 (Aug.) 1918. Janney and Henderson, Arch. Int. Med. **26**:297 (Sept.) 1920.

Focal Infection.—Pemberton [12] has shown the effects of low grade inflammatory infection on delaying glycogenesis. Not only in cases of arthritis, but in other focal inflammatory processes, he found higher curves than in his normals. He did not use the standardized glucose meal. In a few cases he observed a return to normal curves after the removal of the foci of infection.

The manner in which toxins may influence the height of blood sugar curves is open to much speculation.

1. The toxin may directly stimulate the action of the diastase of the liver and muscles, or it may inhibit their glycogenic power.[13] Langfeldt [14] has recently shown in vitro the optimum p_H at which liver diastase works in the presence of thyroid extract and epinephrin. Toxins from foci may possibly disturb the hepatic acid-base equilibrium.

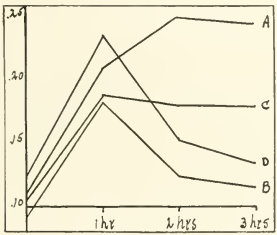

Fig. 2.—A and B curves are of arthritis cases. Curve A was taken two days following the intravenous injection of foreign protein. B, normal curve obtained in most cases of arthritis. C and D, curves of cases of furunculosis.

2. Focal toxins may act on glycogenolysis through their effect on suprarenal medulla directly or through autonomic reflex.

3. Focal toxins may also act on higher cerebral centers.

The association of fatigued state with focal infection is often noted. The curves of such conditions will be discussed later. Again, the focal toxins may disturb the mixture of food stuffs burned in the cell. The well known protein-sparing property of carbohydrate, especially in long sustained fevers, suggests that carbohydrate is burned most readily and possibly is mobilized to protect protein. The possibilities of the effects of toxins on glycogenesis and glycogenolysis have not

12. Pemberton and Foster: Arch. Int. Med. **25**:243 (Feb.) 1920.
13. Lusk: Science of Nutrition, p. 522, quoting Rosenthal, who showed that injection of diphtheria toxin prevented glycogen formation.
14. Langfeldt: J. Biol. Chem. **46**:381, 1921.

been exhausted, but enough has been mentioned to show the complexities of the possibilities. Certainly at present it is better to suppose that disturbance of glycogenic function in focal infection is a manifestation of the effects of infection just as hyperpyrexia or esthenia. The rationale of restricted diet in these cases can be questioned: Why deprive these patients of the protein sparing property of carbohydrate? Why feed typhoid fever patients carbohydrate and deny it to the arthitic? The great losses of weight seen in chronic arthitis would suggest that such patients are greatly in need of carbohydrate in abundance. The metabolism of arthitis does not differ from that of any other chronic focal infection. Certainly there is no loss of power to oxidize glucose, nor is there reason to believe that products of carbohydrate oxidation have a deleterious effect on periarticular inflammatory processes. Even if the toxins of the agent of infectious arthitis do cause sugar mobilization, that in itself should not suggest carbohydrate denial as a therapeutic indication. The experience of this clinic with low carbohydrate diet in arthitis has been quite disappointing.

Thyroid Diseases.—The influence of the thyroid gland on sugar curves has long been appreciated. The internal secretion of the thyroid excites two influences: (1) the delaying of glycogenesis, or an increased glycogenolysis; (2) an increased or stimulated metabolism.

When thyroid is fed carbohydrate is burned rapidly. One would therefore suppose that curves of exophthalmic goiter patients (Fig. 3) would be high but fall quickly, the rapid fall being associated with the increased metabolism. This is brought out by the fact that in spite of the height of the curves, normal blood sugar levels were reached by the end of three hours. Basal metabolism was performed on many cases. As found by Janney, there is no relationship between the height of metabolism and the height of the blood glucose curve. If the metabolism were extremely high one would suppose that the glycogen stores would be exhausted continually and the sugar, which with a lower metabolism would remain mobilized, is burned up; the result being a lower curve than is found in milder cases. We found this to be the case. One of the lowest curves in Figure 3 is from a patient having a basal rate of + 100 per cent. The reverse also is true; patients showing the highest curves had basal rates of about + 50 per cent.

The curves in exophthalmic goiter cases clearly indicate the nature of the dietetic treatment of hyperthyroidism: (1) To protect protein, a high carbohydrate intake; (2) to avoid hyperglycemia, the feeding in hyperthyroid cases should consist of many and small meals.

With clinical evidence of lack of thyroid secretion, curves were obtained which substantiate those already published [11] (Fig. 4). Janney did not find the constancy in hypoglycemia after the glucose meal that is shown in Figure 4. Cases under treatment are not included in this

chart. In some cases the curves very quickly become high under treatment, while others remain low. It has been shown experimentally in animals whose thyroids have been removed that there is no delay in intestinal absorption.[11] If this be true, the low curves in hypothyroidism must be due to increased sugar storage.

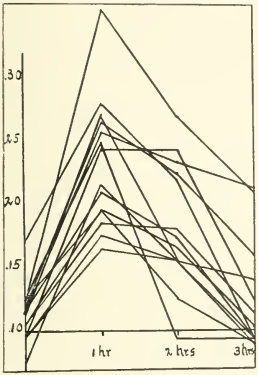

Fig. 3.—Curves of hyperthyroidism.

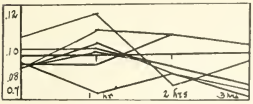

Fig. 4.—Curves of hypothyroidism.

Pituitary Cases.—The posterior lobe of the pituitary gland has been shown to affect the glycogenic function;[15] in acromegaly there is a low "tolerance" while in hypopituitary disease the "tolerance" is high.[16] Glycosuria following experimental stimulation of the pituitary has been shown to take place reflexly to the splanchnic area and also after all known nervous paths have been cut, indicating a true hormone glycogenolysis. No cases have been observed clinically or metabolically

15. Cushing: The Pituitary Body and Its Disorders, Lippincott, 1911.
16. Weed, Cushing and Jacobson: Bull. Johns Hopkins Hosp. **24**:40, 1913.

showing high curves, but a large number of cases diagnosed "hypopituitarism," "dyspituitarism" and "polyglandular syndrome" show low curves. It is in this type of case that the factor of delayed absorption may play a part. We have observed delayed water absorption in some of these cases.

Mild Diabetes.—The necessity of pancreatic hormone for glycogen formation was early demonstrated in perfusion experiments.[14] It is not known whether an increased secretion by the islands of Langerhans ever occurs, but a decrease in pancreatic hormone has two effects; loss of glycogenic power and loss of ability to oxidize glucose. It would, therefore, be reasonable to suppose that even if there is loss of oxidative power to a small degree, or, in other words, a very mild diabetes, the hyperglycemia would be sustained to a more marked degree than any other condition affecting glycogenesis.[10] That such is the case is shown by the curves in Figure 5. One of the greatest uses for blood sugar curves is in doubtful cases of mild diabetes. With a normal fasting blood sugar and a carbohydrate tolerance of from 150 to 200 gm. the curves following a glucose meal are quite distinctive, and differ from any other curve seen in cases of glycosuria. At the end of three hours the hyperglycemia is commonly above 0.3 per cent.

Renal Diabetes.—The so-called "renal" diabetic shows glycosuria with normal fasting blood sugar levels. Two cases have been studied carefully. Both gave subnormal curves. In one case the threshold glycemia seemed to be 0.075. Great care must be taken to distinguish between the emotional glycosuria and this type of glycosuria. The emotional patient's curve rises to above normal limits the first hour and may be sustained still longer. The curves of the "renal diabetic" here observed are quite flat (Fig. 5).

Mental States.—It is not proposed here to enter into discussion as to whether disturbances of the higher cerebral centers act on glycogenic function through reflex action on the chromafin-sympathetic system. It is simpler to accept Cannon's [17] hypothesis that there is a reflex stimulation of epinephrin formation in some mental conditions. The purpose here is to make clear the very considerable influence of various disturbances of the mental state on blood sugar curves. There is, however, one condition which would give distinct evidence of the effect of suprarenal medulla on sugar curves; namely, Addison's disease. With hypofunction of the suprarenal medulla and the absence of other factors influencing them, low curves should be obtained. Two cases have been followed for several months. The first patient had tuberculosis of the lungs and gave a normal curve; the second patient,

17. Cannon: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton, 1920.

the pathology of whose suprarenal was unknown, gave a subnormal curve (Fig. 6). The first case shows the effect of the bacterial intoxication as well as the deficiency of medullary-adrenal secretion.

Cannon found that pain, rage and fear in animals caused, in a considerable number of cases, the appearance of glycosuria. The same

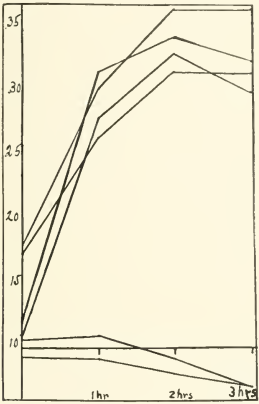

Fig. 5.—The upper curves are those of mild cases of diabetes mellitus. Compare with Figures 3 and 8. The lower curves are of "renal" diabetes. Compare with Figures 7 and 8.

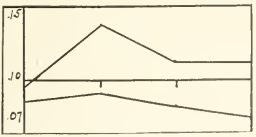

Fig. 6.—Curves of two cases of Addison's disease. The upper of the two is from a patient who had an active tuberculous lesion which would tend to raise the curve.

has been observed in man, especially in states of excitement and after severe mental effort. We have studied the blood sugar curves of a considerable number of cases diagnosed as neurasthenia after a search was made for organic lesions; cases of hypochondriasis; hysteria;

epilepsy, both of organic origin and ordinary type; dementia praecox and manic depressive insanity,[18] and the outstanding fact is that no prediction can be made as to the nature of the curve from diagnosis alone. It may be possible for the psychiatrist or neurologist to determine what the particular mental condition is that stimulates glycogenolysis. Some of the interesting facts are as follows:

Hysterical individuals usually give a normal curve (Fig. 7) in spite of their intense emotional state. Hypochondriacs and manic depressive patients (Fig. 8) show, in the majority of cases, high curves. Neurasthenics and dementia praecox patients may show any type of curve. The uncertainty of the response in these cases makes the interpretation of blood sugar curves difficult.

Summary of Factors Influencing Curves.—To summarize these factors influencing glycogenesis and glycogenolysis in muscle and liver the following outline may help.

Glycogenesis; necessary hormones:

1. Pancreas,
2. Parathyroid (?)

Glycogenolysis; increased by:

1. Increased p_H of muscle, liver or blood. Found in such pathologic conditions as starvation acidosis, nephritic acidosis, etc.
2. Increased secretion of thyroid hormone.
3. Increased secretion of pars nervosa of the pituitary.
4. Increased activity of sympathetic-chromafin system may occur with:
   (*a*) Reflex stimulation from cerebral, peripheral or splanchnic areas.
   (*b*) Blood born stimuli, such as infections, malignant, in pernicious anemia, leukemia, etc.
5. Substances in the blood acting directly on glycogen stores in the muscles and liver, such as any of 4b.

So far as known the pancreas has the most definite and profound influence on formation of the glycogen. The evidence for the parathyroids lies in the fact that their removal causes glycosuria.[19] There seem to be many more factors stimulating sugar mobilization. Anything increasing H ion concentration of blood or locally in the tissues seems to stimulate glycogenolysis. This has been shown by intravenous injections of acids and in perfusion experiments.

18. For permission to study these cases we are indebted to Prof. Sidney I. Schwab.

19. Underhill and Hilditch: Am. J. Physiol. **25**:66, 1909. Underhill and Blatherwick: Am. J. Chem. **18**:87, 1914.

The livers of experimental animals can be almost freed from glycogen by feeding thyroid.[20] Although respiratory quotients show no decrease in burning power for glucose during feeding,[21] it is undoubtedly the strongest stimulus known to sugar mobilization. The increased metabolism accompanying thyroid feeding tends to lessen

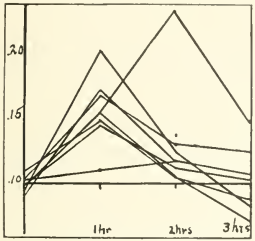

Fig. 7.—Cases of hysteria, many of which show intense emotional excitement. Seventy-five per cent. of uncomplicated cases of hysteria give normal curves.

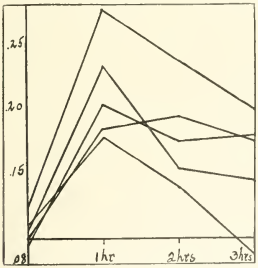

Fig. 8.—Cases of manic depressive insanity. Compare these curves with those of hyperthyroidism.

the glycemia by the rapid burning of sugar. Hyperthyroid blood sugar curves are high but steep, and show an interesting distinction from the high curves due to psychic disturbance which are not high but tend to be sustained. The explanation of increased glycogenesis when thyroid

20. Cramer and Krause: Quart. J. Exper. Physiol. **11**:59, 1917.
21. Cramer and McCall: Quart. J. Exper. Physiol. **12**:81, 1918.

hormone is decreased is only guesswork. If one considers the hormones of thyroid and suprarenal as opposed or balanced against the pancreatic hormone, disturbance of this balance increases or decreases glycogenesis. The increased glycogen storage coincident with thyroid deficiency might be taken as evidence that the pancreatic hormone overacts when not counterbalanced by thyroid.

TABLE 5.—SUMMARY OF CASES

Curves are classified thus: N, normal curve; S, subnormal curve; II, second hour sustained hyperglycemia; III, third hour sustained hyperglycemia. *

Diagnosis	Total No. of Cases	Curve Classification			
		N	II	III	S
Endocrine:					
Hyperthyroidism and exophthalmic goiter	19	1?	12	4	2?
Hypothyroidism and myxedema	10	1	0	0	9
Dyspituitarism; hypopituitarism; polyglandular syndrome	15	9	1	0	5
Addison's disease	2	1	0	0	1
Neurologic:					
Neurasthenia	15	4	4	2	5
Hysteria	16	8	1	3	4
Hypochondriasis	3	2	0	0	1
Organic Central Nervous System Lesions:					
Encephalitis	2	0	1	0	1
Tumor of brain (not pituitary)	4	2	1	0	1
Syphilis	9	4	2	2	1
Neuritis	2	0	1	1	0
Epilepsy	12	3	5	1	3
Constitutional inferiority	4	0	1	2	1
Psychoses:					
Dementia praecox	12	5	3	3	1
Manic depressive insanity	7	0	3	4	0
Senile dementia	2	0	0	2	0
Focal Infection:					
Arthritis, chronic	4	2	1	0	1
Arthritis, acute	1	0	0	1	0
Prostatitis, chronic	2	0	2	0	0
Appendicitis, chronic	2	2	0	0	0
Sinusitis	1	1	0	0	0
Keratitis	2	1	0	0	1
Furunculosis	2	0	0	2	0
Neoplasms:					
Carcinoma, stomach	1	0	1	0	0
Carcinoma, intestinal	2	1	1	0	0
Hodgkin's Disease	1	0	1	0	0
Miscellaneous:					
Goiter	3	3	0	0	0
Lead poisoning	1	0	1	0	0
Arteriosclerosis	..	0	2	1	0
Myocarditis	..	0	1	0	1
Nephritis	..	1	0	0	0

* Diagnoses with only one curve are not included.

In the above outline nervous effects on glycogenolysis are indicated as reflex through the agency of adrenalin. It must be borne in mind that this question is still a disputed one. It is also to be remembered that blood borne stimuli to glycogenolysis may act through adrenalin. These possibilities are quite hypothetical and are mentioned only as such. Again it is not known whether the many toxic substances disturbing the glycogenic balance toward the side of increased sugar mobilization act directly on the liver and muscles; on the nervous system or on the suprarenal medulla. All are possibilities.

CONCLUSIONS

1. The basis for the standardization of the technic of the administration of the glucose meal is pointed out. The necessity for such standardization is made clear.

2. The discussion of the many known factors which influence blood glucose curves shows the importance of the consideration of all of them when such curves form part of any study.

3. The pathologic conditions in which the form of blood glucose curve is usually (within certain limits) constant, are: (1) hyperthyroidism and hypothyroidism; (2) hypopituitarism, and (3) diabetes mellitus.

4. There are certain conditions which, in general, show increased curves after the glucose meal. The curves obtained in such conditions do not even approximate the fair degree of constancy found in the above mentioned conditions. Our present knowledge of glycogenic function in these conditions is rather meager. In this class belong the effects of infectious toxins; those of cancerous origin; those supposedly found in pernicious anemia and leukemia; Hodgkin's disease, etc. Here also belong conditions of the mental state. "Functional" disturbances, usually spoken of as neurasthenia, very definitely disturb the height of blood sugar after glucose meal.

CORRECTION

In the paper by Killian and Kast on "A Study of Significant Chemical Changes in the Blood Coincident with Malignant Tumors" in the ARCHIVES OF INTERNAL MEDICINE, December, 1921, the statement is made, page 813, that "the comparative decrease in the amounts of these (nonprotein nitrogen compounds) has been ascribed to an increased need for nitrogen for the new growth, whether it be malignant tumor or embryo." This statement follows a reference to the work of Theis and Stone, so that many would infer that the above explanation of the low nitrogen figures was offered by these writers. It should be stated that Theis and Stone offered no such explanation of the figures in this connection, but that the explanation was advanced by several workers verbally to us, and we inadvertently included it in our paper without proper explanation.

JOHN A. KILLIAN AND LUDWIG KAST.

BOOK REVIEWS

ACUTE EPIDEMIC ENCEPHALITIS (LETHARGIC ENCEPHALITIS). An Investigation by the Association for Research in Nervous and Mental Diseases. New York: Paul B. Hoeber, 1921. 258 pages, 36 illustrations. Price, $2.50.

This little book is worthy of attention for two important reasons: First, on account of its form, as it embodies a novel idea in the organization of centralized effort by a large body of investigators focused on one disease, and in the method of presentation of the subject to the reader. The book consists of the papers read at the first meeting of the Association for Research in Nervous and Mental Diseases held in New York in December, 1920, together with discussions and the final conclusions of a commission of distinguished neurologists who conducted the meeting and edited the book. At the meeting each reader of a paper was questioned by the commission to which the papers had been submitted beforehand. Anyone interested in the method of conducting scientific meetings and reporting their proceedings will be benefited by glancing over this volume, even if he is not especially interested in the subject.

Secondly, this is the first book which covers all phases of this new disease in a readable manner. The history of the disease, etiology, symptomatology, diagnosis and morbid anatomy are presented by well-known investigators. There are altogether thirty-six contributors but, thanks to the good editorial work of the commission, the subjects are presented in logical sequence and without needless repetition. A bibliography of eighteen pages of the most important articles is appended. As the literature already has grown to unwieldy proportions, the appearance of this book is timely, placing all essential data at the elbow of anyone desirous of authoritative and condensed information.

The commission which edited the book was composed of W. Timme, Pearce Bailey, L. F. Barker, C. L. Dana, Ramsay Hunt, Foster Kennedy, G. H. Kirby, H. T. Patrick, B. Sachs, W. G. Spiller, Israel Strauss, E. W. Taylor, F. Tilney and T. H. Weisenburg.

DIABETES: A HANDBOOK FOR PHYSICIANS AND THEIR PATIENTS. Philip Horowitz, M.D. Published by Paul B. Hoeber, New York. July, 1920. Pp. 1-186.

For convenience in handling his cases, the author has recognized four clinical types of diabetes, "mild, moderately severe, severe and juvenile." The diagnostic symptoms of each type are enumerated so that a given case of diabetes could readily be classified. The diet the author recommends is given, and the subsequent additions follow. The book contains very complete analytical tables showing the composition of foods, and lists of such ménus and recipes as are valuable in handling diabetics. In another chapter questions of hygiene and exercise are discussed briefly. The book is closed with a description of tests which are necessary in following intelligently the progress of the patient. No generalizations of the principles used in the formulation of the diets are given. Hence, the reader has no way of judging whether a given diet is adequate in protein or calories or whether the proper relationship between fats and carbohydrates has been maintained. It can be seen that such a collection of diets falls short of giving either the physician or patient an adequate conception of the fundamentals of diabetic management. Within the last year studies directed towards the rationalization of diet formulation have appeared. If these be accepted, then the present hand book may be regarded as out of date.

DISEASES OF THE DIGESTIVE ORGANS, WITH SPECIAL REFERENCE TO THEIR DIAGNOSIS AND TREATMENT. By CHARLES D. AARON, Sc.D., M.D., F.A.C.P. Lea & Febiger, 1921.

The third edition of this book is a comprehensive volume devoted to disorders of the entire gastro-intestinal tract—the plan of work following the physiologic path from the mouth downward. The usual diseases are treated clearly and fully, with full descriptions of the various laboratory and chemical procedures and their interpretation, many of which the general practitioner has never heard of—but with many of which he should be familiar. In general, the material is presented in a form resembling that of Osler's "Principles and Practice of Medicine," with definitions, etiology, pathology, symptoms, prognosis and treatment under separate headings. Colored plates, engravings and roentgenograms are used liberally to augment descriptions. Dietetic principles in health and disease, the high caloric feeding for typhoid; vitamins—their importance and distribution, and the functional disturbances of the nervous system, vagotonia and sympathecotonia, are clearly and fully discussed. Throughout the book are tables and paragraphs giving a type of information often desired and difficult to find—the analyses of various springs and waters, as compared with the more famous European Resorts; the composition of many proprietary preparations, both of food and from the various pharmaceutical houses. The book commends itself to both the specialist in diseases of the digestive tract and to the general practitioner and surgeon.

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OBSERVATIONS ON PAROXYSMS OF TACHYCARDIA *

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1. *The Frequency of Paroxysms of Auricular Fibrillation.*—The widespread use of instruments of precision in the diagnosis of cardiac arrhythmias during the past few years, and the resulting improvement in diagnosis, have demonstrated that paroxysmal auricular fibrillation is by no means a rare clinical condition. That it is encountered in a certain variable proportion of hospital patients has been pointed out by a number of observers, most of whom have expressed their belief that the condition occurred more commonly than was recognized, but the highest percentage of cases yet recorded is that of Levine,[1] who found that 14.1 per cent. of his group of patients with auricular fibrillation had shown at some time the transient form. This author includes in his series four patients who showed auricular fibrillation only during the transitional stage between auricular flutter and normal rhythm; if these be excluded, his percentage becomes 10.9, which still remains the largest published figure.

In sharp contrast to this comparatively infrequent occurrence, it is our experience that paroxysmal auricular fibrillation is found in private practice with almost the same frequency as the permanent form, and about as often as paroxysmal auricular tachycardia. In a recent series of 250 cases with cardiac symptoms or with signs of heart disease (consultation case of one of us), there were fifteen cases of paroxysmal auricular tachycardia, seventeen cases of paroxysmal auricular fibrillation, eighteen cases of permanent auricular fibrillation, and four cases of paroxysmal flutter. One of the cases of paroxysmal flutter showed also on occasion the coarse type of paroxysmal fibrillation, and is included in both groups.[2] The total number of patients with auricular

* From the Cardiographic Laboratory, Massachusetts General Hospital.

1. Levine, S. A.: Auricular Fibrillation: Some Clinical Considerations, Am. J. M. Sc. **154**:43, 1917.

2. It seems highly probable that paroxysms of flutter and of fibrillation may occur in the same patient at different times more commonly than reports would indicate. Theoretically, such variations might be expected, in view of

fibrillation in this group is thirty-five, and seventeen of these, or 49 per cent., showed the transient form.[4]

Eleven of the seventeen patients with paroxysmal auricular fibrillation were more than 50 years of age (eight were past 60 years). The age incidence in this series is thus in general accord with the observations of Levine,[1] Heard and Colwell,[5] Fox[6] and Robinson.[7] Krumbhaar[8] reported six cases, the patients aged 53, 38, 40, 18, 33 and 35 years, respectively. Our two youngest patients were aged 22 and 27 years, respectively; the etiology of their paroxysms is not clear. Both showed cardiac enlargement on roentgen-ray examination. In contrast to the age incidence of this group of cases, we find that more than two thirds of the patients with paroxysmal auricular tachycardia (eleven out of fifteen) were under 50.

The common types of heart disease in which we have seen the paroxysmal or transient form of auricular fibrillation are the same as those in which the permanent form of arrhythmia is commonly seen. They are most frequently arteriosclerotic (ten of seventeen); less often rheumatic (three of seventeen) and thyroid (two of seventeen). A recent article by Smith[9] has emphasized this close correspondence. Rarely, this paroxysmal type of fibrillation may be found during the course of acute pericarditis; we have seen three such cases (only one included in the present group of 250 cases) and Krumbhaar has reported one case. Severe acute infections (particularly pneumonia), hyper-

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the ready transitions from flutter to fibrillation after digitalis, and from fibrillation to flutter after quinidin. The recent work of Lewis and his associates,[2] which has demonstrated the common origin of the two conditions in a circus movement in the auricle, lends further support to the belief that one patient may exhibit both mechanisms.

3. Lewis, T.: Observations on Flutter and Fibrillation: Part 2, The Nature of Auricular Flutter, Heart **7**:191, 1920. Observations on Flutter and Fibrillation: Part 9, The Nature of Auricular Fibrillation as It Occurs in Patients, Heart **8**:193, 1921.

4. It is to be remembered that this figure represents the incidence of transient auricular fibrillation among patients seen in a consulting practice, where opportunity has been afforded of seeing them earlier in disease than in the usual hospital practice. It is not, therefore, to be compared with previous reports based on hospital records of patients who presented themselves, as a rule, only when forced to do so by a failing heart. Perhaps in general private practice the ratio of paroxysmal to permanent auricular fibrillation would be found even greater.

5. Heard, J. D., and Colwell, A. H.: Transient Auricular Fibrillation, Penn. M. J. **24**:59 (Nov.) 1920.

6. Fox, G. H.: The Clinical Significance of Transitory Delirium Cordis, Am. J. M. Sc. **140**:815, 1910.

7. Robinson, G. C.: Paroxysmal Auricular Fibrillation, Arch. Int. Med. **13**:298 (Feb.) 1914.

8. Krumbhaar, E. B.: Transient Auricular Fibrillation, Arch. Int. Med. **18**:263 (Aug.) 1916.

9. Smith, F. M.: Clinical Observations on Paroxysmal Auricular Fibrillations and Flutter, Am. J. M. Sc. **162**:13, 1921.

thyroidism and digitalis in large doses, may be responsible for the onset of the new mechanism. It seems highly improbable that nervous stimulation alone may be responsible for the clinical condition; no clear-cut case is on record, although three of our cases were somewhat suggestive when first seen.[10] In our experience, and in the present series, permanent damage or severe toxicity have been the basis for paroxysms of auricular fibrillation.

The one patient mentioned above who showed at various times paroxysms of auricular flutter and of coarse auricular fibrillation has been under observation for a period of seven years, during which time she has been followed carefully by clinical, roentgen-ray and electrocardiographic observations. One of her electrocardiograms has been published.[11] This patient has shown no important symptoms at any time except during the attacks, she has no murmurs that can be distinguished, and she has worked as a nurse for six years with only four days off duty because of her cardiac condition in spite of very frequent paroxysms. She is now in good health. A cervical rib was removed from the right side of the neck in 1915 and was followed by considerable improvement. A teleroentgenogram of the heart in 1915 showed considerable enlargement; a similar plate taken six years later showed the same degree of enlargement, in the same chambers, notwithstanding frequent paroxysms of tachycardia in the interval.[12]

2. *The Diagnosis of Paroxysmal Tachycardia of Ventricular Origin.*—Within the past few years there has been considerable interest manifested in the subject of paroxysmal tachycardia due to ectopic impulses arising in the ventricular tissue. Although a number of reports of such instances have been published, Robinson and Herrmann[14] in a recent review were able to find only six undoubted instances, and six which were probable, in which the pacemaker responsible for the new rhythm lay in the ventricles. These authors have called attention to the necessity of obtaining electrocardiograms,

10. Nervous stimulation may be and often is, of course, the exciting factor in producing paroxysmal auricular fibrillation in a diseased heart.

11. White, P. D., and Stevens, H. W.: Ventricular Response to Auricular Premature Beats and to Auricular Flutter (Fig. 5). Arch. Int. Med. **18**:712 (Nov.) 1916.

12. Another patient who has shown paroxysmal auricular tachycardia very frequently between 1914 and 1921 has not been incapacitated at all, and is in good health at the present time. He also shows cardiac enlargement of unknown cause. He has been reported as an unusual case of paroxysmal auricular tachycardia,[13] an exception to the general rule of an absolutely abrupt onset and offset of the attack, but nevertheless an undoubted instance of paroxysmal auricular tachycardia, possibly of nomotopic type.

13. White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**:420 (April) 1920.

14. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, Heart **8**:59, 1921.

and have included in their list only those cases from which such curves have been published. In order that the diagnosis may be established beyond question, they direct attention to the following requirements:

(1) The electrocardiogram must give definite indications that the cardiac impulses producing the high ventricular rate are arising in the ventricles, and this can be shown most clearly when a succession of auricular impulses can be made out, occurring independently of, and at a slower rate than, the complexes of ventricular origin. (2) The ventricular complexes must be abnormal in form. (3) The presence of isolated ectopic ventricular beats between paroxysms is in favor of the tachycardia being of ventricular origin, especially if the ectopic beats and those composing the paroxysms are of similar form.

To the six cases previously reported, Robinson and Herrmann have added four, bringing the total number of undoubted cases to ten. It has seemed to us worth while to report a further instance of this comparatively rare type of tachycardia, partly to increase the number of recorded cases, but chiefly to call attention to the possibility of error in making the diagnosis, even with electrocardiograms, unless control records have been obtained from the patient between paroxysms. Under a certain condition, which we shall illustrate, it is possible to obtain records of auricular paroxysms which resemble closely those of ventricular origin.

The patient from whom the electrocardiograms shown in Figures 1, 2, 3 and 4 were obtained was a young woman, aged 21, whose past history was uneventful, except for the occurrence of diphtheria and pneumonia in early childhood and occasional mild attacks of tonsillitis during several successive winters. There had been no symptoms of cardiac disease whatever preceding the onset of the paroxysms of tachycardia; the patient had been attending business school for two years and had taken daily walks of several miles for exercise. Her first paroxysm occurred six weeks prior to her entry to the hospital, as she was stooping to pick something from the floor. It lasted for approximately two minutes, during which time she felt dizzy, her head seemed "hot and swollen," and she was conscious of the tachycardia. The attack ended as suddenly as it had begun, but a second one occurred two hours later and lasted for approximately fifteen minutes. During this second attack her symptoms were as before, but in addition there was marked shortness of breath, which was a feature of all subsequent attacks. After the first day there was a period of freedom for about two months, when the attacks recommenced, and it was during this second period of paroxysms that the following records were obtained.

Figure 1 is an electrocardiogram obtained April 7. Leads I, II and III are shown, and the only abnormality in the curves is a single premature beat arising in the ventricle, which is recorded in Lead II. April 21, we were fortunate in securing the onset of one of her numer-

ous paroxysms (Fig. 2). The plate shows three strips of Lead II, and satisfies in itself all the requirements mentioned by Robinson and Herrmann for the diagnosis. Isolated ectopic beats of ventricular origin are seen in A and B, and these are similar in form to the beats which compose the succeeding paroxysm. The ventricular complexes are highly abnormal in form. Finally, auricular complexes occur in B after every second ventricular beat, the rate of the ventricles being 262.5 per minute and that of the auricles one half this rate. Similar curves, in which the auricles beat at exactly half the rate of the ventricles, P waves appearing at corresponding points on every second ventricular complex, have

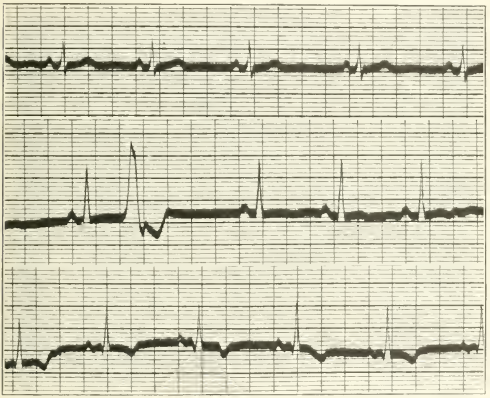

Fig. 1.—Electrocardiogram of M. R. Leads I, II and III. Normal complexes throughout except for one ventricular premature beat in Lead II. (In this and all succeeding electrocardiograms, distances between ordinates represent 0.2 second, distances between abscissae 10^{-4} volts.)

been published by Hart,[15] and more recently by Robinson and Herrmann [14] (their Figs. 9, 11 and 13). There is a close resemblance between Hart's Figure 4 and our Figure 2, except that the R waves in our illustration show notching at the tip and the P waves are more prominent than in Hart's case. It is to be noted that during the brief part of the paroxysm shown in B the rate is not absolutely regular, nor are the complexes precisely alike. The time intervals, as measured from peak

15. Hart, T. S.: Paroxysmal Tachycardia, Heart 4:128, 1912.

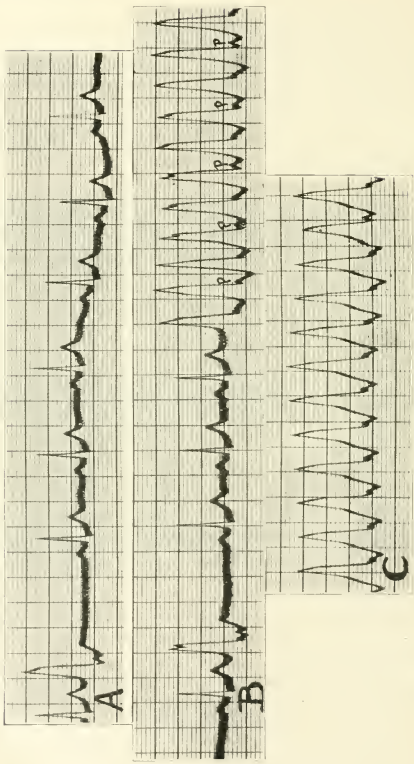

Fig. 2.—Electrocardiogram of M. R. Lead II. Ventricular premature beats in A and B. Onset of ventricular paroxysm in B. Note the presence of auricular waves (P) after every alternate ventricular beat in B. Rate in B, 262 per minute; in C, 220.

to peak of the R waves in seconds are as follows: 0.257, 0.198, 0.212, 0.237, 0.243, 0.243, 0.243, 0.253, 0.245, 0.248. The variation in rate, as shown by these intervals, is largely confined to those beats which initiate the new rhythm; from the fourth beat onward the greatest variation from cycle to cycle is 0.010 second. Thus the rate for the entire stretch of the paroxysm is 262.5, but the rate for the last eight beats is 250. The difference in form of the complexes is apparently of a progressive nature; the second and third beats, for instance, are practically free from notching or slurring of the ventricular complex, the succeeding five beats show very definite slurring of the upstroke of R and notching of the beginning of the downstroke, while the last

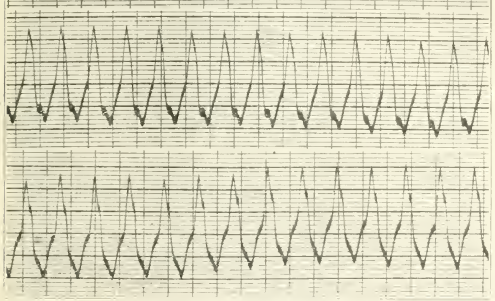

Fig. 3.—Electrocardiogram of M. R. Leads I, II and III, taken during a paroxysm of tachycardia of ventricular origin, in which the rate is 209 in Leads I and III, and 225 in Lead II.

three recorded complexes apparently foreshadow the final form which is to be assumed, in which a heavy slurring of the upstroke and a slighter degree of slurring of the downstroke of R appear as the prominent features.

The lower part of the figure, marked C, was taken within a few seconds after B and shows the form of ventricular complex which characterized the second lead in all subsequent electrocardiograms. It will be noted that the P waves, which appeared so prominently after every second ventricular complex in B, have now almost disappeared.

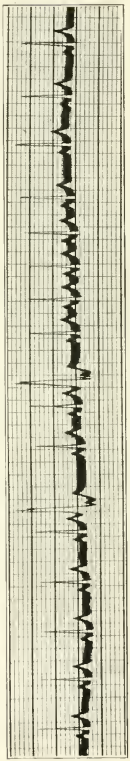

Fig. 4.—Electrocardiogram of M. R. Lead II. First half of curve shows normal rhythm interrupted by two ventricular premature beats. Just after the second premature beat there is a series of five beats constituting a paroxysm of auricular tachycardia, in which the rate is 125 per minute. Rate of normal rhythm, 75 per minute.

The last feature of the ventricular paroxysms to which attention should be directed is shown in Figures 2 and 3, and consists of the change of rate between the early and later parts of the paroxysm. Thus in Figure 2 the rate in B is 250 or 262.5, according as we include or exclude the first three beats, while in C, taken a few seconds later, the rate is only 220. Similarly, in Figure 3, the rate in Lead II is 225 per minute, while in Leads I and III the rate is from 209 to 211. These two figures are from different paroxysms on the same day.

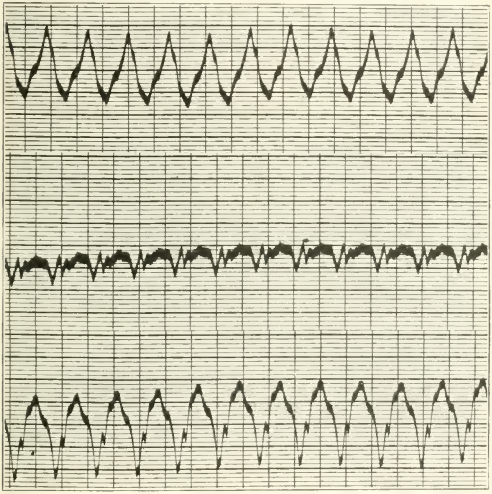

Fig. 5.—Electrocardiogram of L. K. Leads I, II and III. Taken during a paroxysm of tachycardia, in which the rate was 190 per minute. Note the general resemblance between Leads I and II of this figure and Leads II and I, respectively, of Figure 3.

The same patient showed also unusual paroxysms of auricular origin. A plate taken just after that reproduced in Figure 2 and just before that in Figure 3 recorded two such paroxysms, only one of which is here shown (Fig. 4). This curve is from Lead II, and shows in its early part complexes of normal form, with a rate of 75 per minute.

In the middle of the curve are seen two exactly similar premature beats arising in the ventricle. Immediately following the second of these premature beats there occurs a short paroxysm of tachycardia consisting of five beats, in which the normal sequence of chamber contraction is

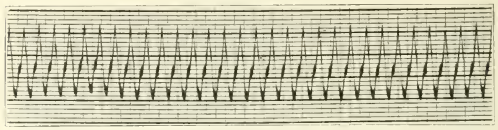

Fig. 6.—Electrocardiogram of L. K. Lead I, taken with plate traveling slowly. Same paroxysm as that shown in preceding figure.

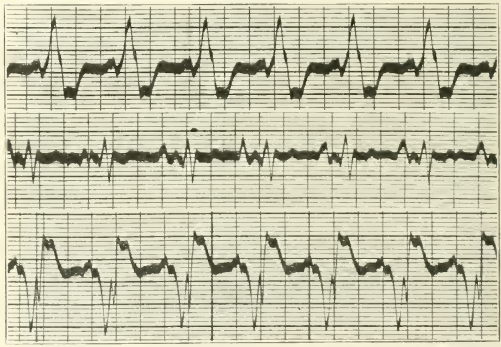

Fig. 7.—Electrocardiogram (Leads I, II and III) of L. K., showing normal rhythm, the ventricular complexes of which are typical of those associated with defective conduction along the right branch of the A-V bundle. Rate, 100 per minute. Ventricular complexes are similar to those in Figure 5.

maintained.[16] The rate is 125 per minute. After the conclusion of the paroxysm, the rate falls at once to its original level.

This case, then, is one in which there have been recorded at different times isolated ectopic beats of ventricular origin, paroxysms of tachycardia of ventricular origin, and paroxysms of tachycardia in which

16. The P wave of the paroxysm is slightly higher than the normal P.

the pacemaker lay in the auricles. In at least one instance, the rate for the first few beats of the ventricular paroxysms was higher than the rate subsequently maintained. In the only instance where the onset of the new rhythm was recorded, there was a slight, progressive change in the form of the first eight ventricular complexes.

By way of contrast to the above example of paroxysms of tachycardia arising in the ventricle, is an electrocardiogram (Fig. 5) from another case which at first sight appears also to be of ventricular origin. Leads I and II of this figure, for example, are quite similar in form to Leads II and I, respectively, of Figure 3. (Corresponding leads cannot be compared because of obvious gross differences.)[17] The general outline of each complex is that of an ectopic beat arising in the ventricle. This appearance is even more striking in Figure 6, which is from Lead I of the same patient, taken with the plate traveling at a slower rate.

That this paroxysm does not owe its origin to impulses arising in the ventricle, however, is made apparent at once by inspection of

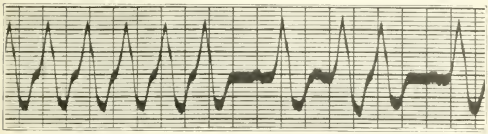

Fig. 8.—Electrocardiogram of L. K. Lead I. The end of a paroxysm is recorded. Note that the first, second and fourth ventricular beats after the end of the tachycardia are in response to impulses from the normal supraventricular focus, yet are similar in all details to the beats composing the paroxysm.

Figure 7, which was obtained about five minutes after Figure 6, and shows the normal rhythm. The three leads are given, and a comparison of this curve with that in Figure 5 shows that the ventricular complexes in both are similar in all three leads and we know them to be of supraventricular origin because in Figure 7 each ventricular beat is preceded by an auricular wave. This electrocardiogram is of the type associated with defective conduction along the right branch of the A-V bundle.

Further proof of the auricular origin of the paroxysm is obtained from Figure 8, in which the termination of a paroxysm is shown. The first, second and fourth beats after the end of the tachycardia are preceded by waves due to auricular activity, and are clearly to be

17. As a matter of fact these very differences would help to differentiate the two conditions, Figure 5 being much more likely an example of intraventricular block.

considered as ventricular responses to impulses from the auricles, yet these ventricular responses are in all respects similar to the beats composing the paroxysm.

It would be impossible to assert with confidence that the paroxysmal tachycardia shown in Figure 5 is of auricular origin without the further knowledge obtained from other records. From the standpoint of accurate diagnosis and a more complete understanding of the electrical events in the heart associated with tachycardias of paroxysmal nature, it is important to make this differentiation.

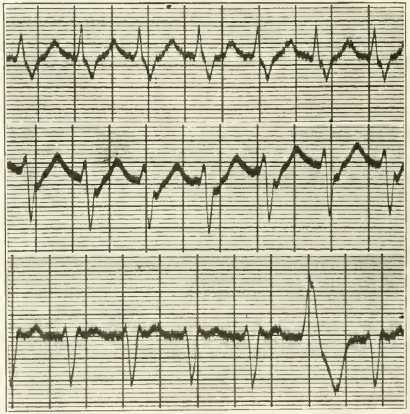

Fig. 9.—Electrocardiogram of E. J. H. Leads I, II and III. Paroxysmal auricular tachycardia. An ectopic beat arising in the ventricle is shown in Lead III. Note that it does not disturb the dominant rhythm.

Lewis [18] has called attention to the possibility of sudden interference with conduction in one branch of the A-V bundle during the period of rapid heart action, and has published a record illustrating aberration only during the paroxysm. Such curves, of course, are similar to those obtained from patients with pre-existing bundle branch block, for the mechanism of their production is exactly alike. Lewis concludes that "in the human subject, paroxysms presenting anomalous ventricular

18. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat. New York, R. Hoeber, 1921, p. 259.

complexes may be produced in one of two ways; these paroxysms either arise in the ventricle itself, or, arising in the auricle, the excitation wave pursues an abnormal ventricular course." This abnormal ventricular course may be due to transient interference with conduction, as in his case, or to permanent interference, as in the case reported above. Reference has already been made [11] to an electrocardiogram published by one of us in 1916, which shows the sudden development of aberration of the ventricular complexes during a paroxysm of auricular flutter.

3. *The Occurrence of Ectopic Ventricular Beats in Auricular Paroxysmal Tachycardia.*—The interruption of paroxysms of auricular tachycardia by ectopic beats arising in the ventricle is of rare occurrence; we have been able to find but one published electrocardiogram illustrating such an event.[19] We have recently seen a case exhibiting ectopic beats with such frequency as to make it one of considerable interest.

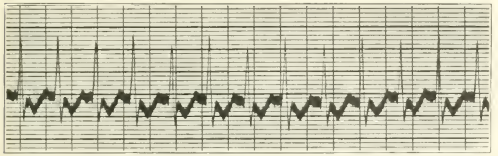

Fig. 10.—Electrocardiogram of J. D. S. Paroxysmal auricular tachycardia. Rate 200. Alternation in size of the QRS complexes is shown.

The patient from whom the curve shown in Figure 9 was obtained was a laborer, aged 57 years, who had been subject to attacks of tachycardia for about three years. The paroxysms occurred usually three or four times a day, for from two minutes to several hours. His only symptom during the attacks was slight palpitation, which had never been of sufficient severity to cause him to stop his work for even a few minutes. An electrocardiogram taken between attacks showed ectopic ventricular beats similar to those which appeared during the attacks, and indicated also partial A-V heart block (the P-R interval measuring 0.233 seconds) and intraventricular block.

Figure 9 was taken during an attack in which the heart rate was 166.6 per minute. It shows one ectopic ventricular beat. Several such beats were recorded during the paroxysm. It is to be noted that the ectopic beat does not disturb the rhythm; it occurs almost at the precise

19. Agassiz, C. D. S.: Paroxysmal Tachycardia Accompanied by the Ventricular Form of Venous Pulse, Heart **3**:193, 1912.

instant when a beat was to be expected, and the beat which follows falls at its proper point. In other words, the same features mark a ventricular premature beat in paroxysmal auricular tachycardia as in the normal rhythm arising in the sino-auricular node; in both instances, the distance between the complexes embracing the ectopic beat measures the same as that between any two rhythmic beats.

This case is recorded because of the rarity of such published curves and because it is of some importance to recognize that the finding of

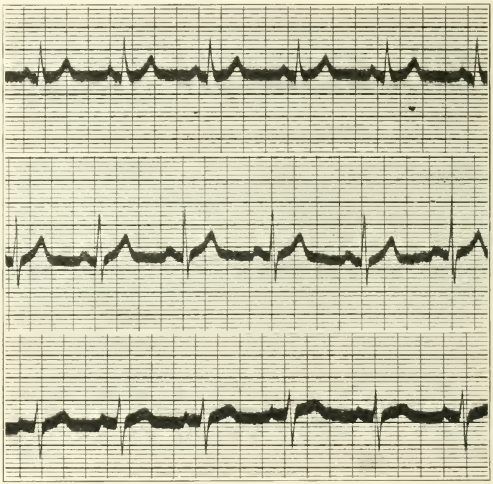

Fig. 11.—Electrocardiogram of J. D. S. Normal rhythm from same patient whose previous record is shown in Figure 10.

ventricular premature beats in a case which presents the features of auricular paroxysmal tachycardia does not militate against that diagnosis. Among the records of more than thirty cases of auricular paroxysmal tachycardia in the files of our laboratory, this is the only instance in which ventricular ectopic beats have been found in the midst of a paroxysm.

4. *Alternation of the R Waves in Paroxysmal Tachycardia.*—Alternation in the amplitude of the radial pulse in cases of paroxysmal

tachycardia occurs with such frequency that it is no longer regarded as unusual or important. Alternation in the height of the R waves in this condition, however, is not common, in so far as one may judge by published records. There have been many curves showing variation in amplitude without alternation, although the vast majority of cases exhibit complexes which are precisely alike in size and shape over long periods. Lewis has placed on record an excellent example of simultaneous alternation of the R waves of the electrocardiogram and the radial pulse, in which the large ventricular complexes correspond to the small pulse waves.[19] Hart[15] has recorded a striking instance of this condition, his curves being obtained from a case of paroxysmal tachycardia of ventricular origin.[20]

The electrocardiogram shown in Figure 10 represents Lead II. The rate is 200 per minute. The patient from whom it was obtained was subject to paroxysms of the usual description, and the only feature of interest in the curve, other than the alternation, is its close resemblance to auricular flutter. A tracing taken after the paroxysm showed curves which were normal in all respects (Fig. 11 showing Leads I, II and III).

SUMMARY

1. Paroxysmal auricular fibrillation is a common type of paroxysms of tachycardia, and is seen in practice as frequently as paroxysmal auricular tachycardia and permanent auricular fibrillation.

2. Paroxysmal auricular fibrillation is found most frequently in old age, the result of cardiosclerosis. It is also found in rheumatic and thyroid hearts, in acute pericarditis, severe acute infections, and following digitalis.[21]

3. Paroxysms of tachycardia may occur at frequent intervals for years without incapacitating the subject and without increasing the degree of cardiac damage appreciably.

4. Paroxysmal tachycardia of ventricular origin is very rare. Another case is added to the ten undoubted cases already reported.

5. Electrocardiographic study is essential in the accurate diagnosis of ventricular paroxysmal tachycardia, and even with electrocardiograms the condition must be differentiated from auricular paroxysmal tachycardia with bundle branch block.

6. Ventricular ectopic beats may occur in auricular paroxysmal tachycardia without disturbing the dominant rhythm.

7. Rarely, alternation of the Q R S complexes of the electrocardiogram may be found in paroxysmal tachycardia. (Alternation of the radial pulse in this condition is common.)

20. Lewis, T.: Mechanism of the Heart Beat, 1911, p. 274.
21. It also has been reported after other poisons.

RENAL GLYCOSURIA *

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There are four cardinal points in the diagnosis of this interesting anomaly: (a) a glycosuria without hyperglycemia; (b) little, if any, relationship between the carbohydrate intake and the amount of glucose excreted in the urine; (c) the absence of the signs and symptoms characteristic of diabetes mellitus, and (d) a long period of observation during which the patient shows no tendency to develop diabetes mellitus. Joslin [1] lays particular stress on the last criterion, which is the most difficult to carry out. A critical review of the literature is made by Goto,[2] Bailey,[3] Strouse [4] and Lewis and Mosenthal.[5] When preparing data connected with the report in 1915, Lewis and Mosenthal found less than ten cases which were described in sufficient detail to warrant their acceptance as instances of true renal glycosuria, but since that time at least nine other cases [6] have been noted. With the more careful observations of the blood sugar this depression of the "leak point" for glucose is being recognized with greater frequency.

In this paper a further note is recorded on the case reported in 1915 [5] and studies of two other instances observed in the metabolism clinic of the Royal Victoria Hospital are presented in some detail. The clinical findings in the first patient may now be said to fulfill all four requirements as he has been observed for a period of six years; the second and third cases which have been observed for twelve and fifteen months, respectively, can be regarded as answering the first three tests, but a final decision will not be possible without a further period of observation.

Methods Employed.—Sugar identified as glucose, by fermentation; osazone crystals; and synchronous determinations of the amount of sugar by polariscopic and copper reduction methods. Urinary sugar: Benedict's standard quantitative methods. Blood sugar: Lewis-Benedict method, unless otherwise stated in the text.

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* From the Metabolism Clinic of the Royal Victoria Hospital.

1. Joslin, E.: Treatment of Diabetes Mellitus, Philadelphia, 1917, p. 64.
2. Goto, K.: Alimentary Renal Glycosuria, Arch. Int. Med. **22**:96 (July) 1918.
3. Bailey, C. V.: Renal Diabetes, Am. J. M. Sc. **157**:221, 1919.
4. Strouse, S.: Renal Glycosuria, Arch. Int. Med. **26**:768 (Dec.) 1920.
5. Lewis, D. S., and Mosenthal, H. O.: Renal Diabetes, Bull. Johns Hopkins Hosp. **27**:133, 1916.
6. Beard, H., and Grave, F.: Renal glycosuria, Arch. Int. Med. **21**:705 (June) 1918. Allen, F. M.: Wishart, M. B., and Smith, L. M.: Three Cases of "Renal Glycosuria," Arch. Int. Med. **24**:523 (Nov.) 1919. Paullin, J. E.: Renal Glycosuria, J. A. M. A. **75**:214 (July 24) 1920. Marsh, P.: Renal Glycosuria, Arch. Int. Med. **28**:54 (July) 1921.

REPORT OF CASES

Case 1.—W. P. W.[5] (medical No. 34774), was first studied in September, 1915. On admission to the Johns Hopkins Hospital his urine contained 2.06 per cent. sugar, and the daily output averaged 25 gm., with a blood sugar ranging from 0.08 to 0.11 per cent. He gave a normal curve following the ingestion of 100 gm. glucose. Further studies by Mosenthal, in 1916, confirmed the findings. In August, 1921, the patient reported that he had continued in excellent health since his discharge from the hospital. He had gained 12 pounds in weight; he had survived a severe "flu" infection, and was taking a full and unrestricted diet. His urine still contained about 2 per cent. sugar, but he had no thirst, polyuria, or any other symptoms of diabetes mellitus.

The following data of recent studies on this individual have been supplied by Dr. F. M. Hanes of Winston-Salem, N. C., and prove that his condition has shown no essential change. The diagnosis made in 1915 has been verified by the subsequent course of the case.

The functional condition of the kidney has attracted considerable attention in renal glycosuria. Klemperer [7] in his first description of what he termed "renal diabetes," stated that the sugar always disappeared from the urine with the onset of a nephritis. On the other

TABLE 1.—Response of Blood Sugar to 132 Gm. Glucose

June 8, 1921	Blood Sugar, per Cent.	Remarks
Fasting	0.09	After 24 hours fasting
First hour	0.15	
Second hour	0.12	
Third hour	0.10	

The urine passed during the twelve hours preceding the test contained 3.5 per cent. sugar (Benedict).

hand, Lüthje,[8] Tachau [9] and Naunyn [10] suggested a direct causal relationship between the nephritis and the glycosuria, and the first two gave examples of proved renal glycosuria in which the onset seemed to be associated with the appearance of a nephritis. Frank [11] has described a glycosuria following the toxic nephritis produced by mercury, uranium, chromium and cantharadin, but there has been little evidence of severe kidney disease in a majority of the reported cases. Bailey [3] described one case of severe parenchymatous nephritis, with a renal glycosuria. The blood sugar was comparatively high, and after 75 gm. glucose it rose to 0.4 per cent., returning to the fasting level

7. Klemperer, G.: Ueber regulatorische Glykosurie und renalen Diabetes, Berl. klin. Wchnschr. **33**:571, 1896.

8. Luthje, H.: Beitrag zur Frage des renalen Diabetes, München. med. Wchnschr. **38**:1471, 1901.

9. Tachau H.: Beitrag zum Studium des Nierendiabetes, Deutsch. Arch. f. klin. Med. **104**:448, 1911.

10. Naunyn, B.: Der Diabetes Mellitus, Wien., 1906, p. 136.

11. Frank, E.: Ueber experimentelle u. klinische Glykosurien renalen Ursprungs, Arch. f. exper. Path. u. Pharmakol. **72**:387, 1913.

six hours after the meal. This, he states, is a type of curve often seen in nondiabetic cases of nephritis. In this patient the sugar output was remarkably constant, and there was no sign of a true diabetes. Mosenthal and Lewis [12] also report a case of arteriosclerosis and primary contracted kidney, in which a glycosuria appeared while under observation. This patient excreted 22 per cent. of phthalein in two hours, and his blood urea was 0.749 gm. per liter. With a fasting blood sugar of 0.10 per cent., the urine contained 0.13 per cent. sugar, and after the ingestion of 100 gm. glucose the blood sugar rose to 0.26 per cent. in 90 minutes, and returned to the fasting level at the end of three hours.

The following cases are examples of this type of renal glycosuria.

Case 2.—May 5, 1920, T. C., (metabolism No. 50), Chinese boy, aged 18.

History.—About four weeks before admission he had a chill and fever. He passed very little urine. His legs began to swell, and he had to stop work. The swelling gradually spread to his trunk, arms and face. No further history was obtainable. He was admitted to hospital May 9 and transferred to the Metabolism Clinic May 21.

Physical Examination.—Temperature, 98; pulse, 70; respiration, 20 (on admission). Patient was an adult Chinese of about stated age. He lay comfortably in bed. There was marked general anasarca; pupils equal and active; teeth in fairly good condition; tonsils not enlarged; tongue coated; no general glandular enlargement; thyroid not enlarged; no signs of hyperthyroidism. The chest wall was edematous. There was a bilateral hydrothorax and many moist râles were heard over both lungs. The heart was regular in rhythm, and extended 7 cm. to the left of the midline. The sounds were well heard. There were no murmurs or accentuations. The vessel walls were not thickened. Blood pressure: 110/65. The abdomen was tense; the walls were edematous; there was a marked ascites; the liver and spleen were not palpable. The genitalia were much swollen, there was no urethral discharge. The reflexes were active. The eyegrounds were normal.

Urine: Acid; cloudy; specific gravity, 1.026; albumin, 20 gm. per liter; no sugar. Microscopic Examination: Granular, hyalin and fatty casts. White blood cells and an occasional red blood cell.

Tests of Kidney Function.—Blood urea, 0.585 gm. per liter; plasma chlorids, 5.65 gm. per liter; phthalein tests, 8 per cent. in two hours.

Blood: Wassermann test negative. Red blood cells, 5,910,000; white blood cells, 5,600; hemoglobin, 85 per cent. (Talquist).

Diagnosis.—Chronic diffuse nephritis; general anasarca.

Diary.—In view of the severity of the nephritis the patient was kept in bed on a salt-poor diet, with an average daily carbohydrate intake of 125 gm. His condition gradually improved, and he lost 16 kilos in weight, but with an increased diet his edema returned and his general condition became much worse. At this time an estimation of the blood proteins showed a globulin-albumin ratio of 3.61 : 1.30, which is a complete reversal of the usual proportions. In view of Epstein's [13] reports, the diet was changed September 10, to one with

12. Mosenthal, H. O., and Lewis, D. S.: The D : N Ratio in Diabetes Mellitus, Bull. Johns Hopkins Hosp. **28**: 187, 1917.

13. Epstein, A. A.: Oedema in Chronic Nephritis, Am. J. M. Sc. **154**: 638 (Nov.) 1917.

low fat and relatively high protein values. There was little change in the water balance, but the total nonprotein nitrogen of the blood mounted from 40 mg. per hundred c.c. to 89 mg. per hundred c.c. in six days, and the diet was discontinued soon afterward. Suddenly, September 22, a glycosuria appeared. The first day the output was 6.99 gm.; the next day it was 7.39 gm., and for the succeeding eight months sugar was absent in only five twenty-four-hour specimens, and in individual specimens of six other days. During this entire period the output has never exceeded 16.8 gm., and it has been between 5 and 10 gm. 151 times in a total of 230 determinations (Table 2), while the concentration in the urine has been from 0.5 to 0.75 per cent. in two of every three examinations. In other words, the output and concentration have shown a high degree of constancy.

TABLE 2.—Range of Concentration and Total Excretion of Sugar in Urine

Concentration in Urine, per Cent.	Number of Analyses	Per Cent. of Total No.	Output in Gm. per Day	Number of Analyses	Per Cent. of Total No.
Above 0.75	38	16.5	Above 10.0	38	16.5
0.75 – 0.50	151	65.7	10.0 – 5.0	151	65.7
Below 0.50	41	17.8	Below 5.0	41	17.8

TABLE 3.—Independence of Carbohydrate Intake and Output

Date, 1920	Diet			Sugar in Urine	
	Protein	Fat	Carbohydrate	Per Cent.	Gm.
Nov. 2	41	42	174	0.86	6.45
3	49	57	209	0.51	3.82
4	39	39	144	0.52	3.74
5	20	21	87	0.60	2.70
6	46	53	204	0.45	2.79
7	46	53	204	0.40	6.68
8	46	53	204	D. 0.28	1.12
				N. 0.09	0.00
9	46	53	204	0.34	5.71
10	28	30	138	0.65	6.82
11	54	61	135	0.43	3.01

D., day specimen; N., night specimen.

Again, the total output of glucose seems to be independent of the carbohydrate intake, the higher rates of excretion often being associated with the lower diets and vice versa. Table 3 will serve to illustrate the independence of intake and output.

Similarly, his excretion varies from 0 to 8.16 gm. during the period from November 16 to December 16 with an unchanged diet which contained protein, 50 gm.; fat, 57 gm., and carbohydrate, 234 gm. Throughout the period of observation the changes in the output are featured by their sudden onset and disappearance. In Table 3 the output is 6.68 gm. one day, 1.12 gm. the next day, then sugar free for twelve hours, and on the following day is reestablished at its old level of 5.71 gm. On the other hand, during any particular day the rate of

excretion from hour to hour seems to be very constant. Two hourly collections are presented in Table 4, and show a maximum variation in concentration of only 0.16 per cent., and an hourly output from 0.50 to 0.36 gm.

In September, 1921, he was studied again, and at this time he was fasted for three days before becoming sugar free. On a gradually increasing carbohydrate diet traces of sugar reappeared with 30 gm. carbohydrate given as green vegetables, and a measurable quantity (0.18 per cent.), with a diet containing 40 gm. of carbohydrate in the form of potato.

A glucose curve was also carried through with the following results, which are quite typical of those seen in nondiabetic cases of nephritis. There is a relatively slow rise to the maximum (0.241 per cent.), at one

TABLE 4.—RATE OF SUGAR EXCRETION FROM HOUR TO HOUR

March 7, 1921. Diet: Protein, 70 gm.; fat, 81 gm.; carbohydrate, 250 gm.

Time	Volume in C.c.	Spec. Gr.	Per Cent.	Gm.	Gm. per Hour
8 a. m. – 10 a. m.	116	1.022	0.71	0.82	0.41
10 a. m. – 12 m.	138	1.020	0.63	0.87	0.43
12 m. – 2 p. m.	152	1.021	0.66	1.00	0.50
2 p. m. – 4 p. m.	142	1.022	0.69	0.98	0.49
4 p. m. – 6 p. m.	170	1.020	0.56	0.95	0.47
6 p. m. – 8 p. m.	140	1.021	0.67	0.94	0.47
8 p. m. – 8 a. m.	775	1.019	0.55	4.26	0.36
Total	1,633			9.82	

TABLE 5.—RESPONSE OF BLOOD AND URINE TO 100 GM. GLUCOSE

Time	Blood Sugar*	Urine					Remarks
		Vol., C.c.	Sp. Gr.	Per Cent.	Gm.	Gm. per Hr.	
9:00 a. m.	....	95	1.019	0.35	....	....	100 gm. glucose
9:30 a. m.	0.092	...	....	....	....	..	in 300 c.c. of
10:15 a. m.	0.208	...	...	....	....	....	lemonade at
10:30 a. m.	.....	80	1.029	0.60	0.48	0.32	9:30 a. m.
11:00 a. m.	0.241	...	.....	....	....	....	
11:30 a. m.	0.151	88	1.016	0.91	0.80	0.80	
12:30 p. m.	0.096	167	1.011	0.32	0.54	0.54	
2:30 p. m.	0.087	202	1.013	0.20	0.40	0.20	

* Folin, O., and Wu, H.[14]

and a half hours and the normal level is reached again in three hours. The specimen of urine passed before the ingestion of glucose showed that sugar passed through the kidney with a blood concentration in the vicinity of 0.092 per cent. A previous determination had shown a glycosuria of 0.11 per cent. with a fasting blood sugar of 0.068 per cent.; therefore, no question can be raised as to the extreme depression of the renal threshold.

In the course of ten months during which the glycosuria has been observed in hospital, there have been periods during which the patient

14. Folin, O., and Wu, H.: A System of Blood Analysis, Suppl. 1, J. Biol. Chem. **41**:367 (March) 1920.

has shown large changes in his body weight. A study of the fluid exchange and the rate of sugar excretion has shown no constant relation between the total fluid excreted and the amount of sugar in the urine. During one period there was a considerable fall in the sugar output with a retention of water, while during a subsequent period of diuresis the sugar showed no corresponding increase. This independence of sugar and fluid output has been noted in a majority of the published cases.

Case 3.—C. M., (metabolism No. 56), aged 74; bookkeeper.

History.—This man was admitted on account of a severe attack of scurvy occasioned by a deficient diet, the result of his financial straits. The sugar was found during the routine analysis of the urine. Subsequent questioning failed to reveal any of the usual symptoms or signs of diabetes mellitus. There was no thirst; no craving for sweets; no polyuria; no loss of weight. Nothing suggesting hyperthyroidism, and beyond a mild eczema of the hands, he had been very healthy. The family history was negative as regards metabolic disorders.

Physical Examination.—Temperature, 98 F.; pulse, 80; respiration, 20 (on admission). A well nourished man; who appears much younger than stated age. There is fluid in both knee joints, and the right olecranon bursa is filled with blood-stained fluid. There are intramuscular hemorrhages in the thighs and calves of both legs. The gums are much cut up where several teeth have been extracted recently on account of "pyorrhea" and are quite spongy around the remaining teeth. The pupils react to light and accommodation. The chest shows a moderate emphysema and bronchitis. The heart is slightly enlarged, there is an extrasystolic arrhythmia, the sounds are well heard, and there is a soft apical systolic murmur, poorly transmitted to the axilla. The vessel walls are definitely thickened. Blood Pressure: 160/84. The abdomen is negative, the genitalia are negative.

Urine: Acid; specific gravity, 1.021; albumin, faint trace; sugar, 2.5 per cent. Acetone and diacetic acid are absent. Microscopic examination shows a few leukocytes and occasional hyalin and granular casts.

Tests of Kidney Function.—Blood urea, 0.435 gm. per liter; uric acid, 5 mg. per hundred c.c.; creatinin, 1.64 mg. per hundred c.c.; plasma chlorid, 6.19 gm. per liter. The nephritic test diet gives a normal curve, and the phthalein excretion is 64 per cent. in two hours.

Blood: Erythrocytes, 4,900,000; leukocytes, 7,200; hemoglobin, 90 per cent. (Talquist). Wassermann test negative.

Diagnosis.—(1) Scurvy, (2) arteriosclerosis and arteriosclerotic kidney, (3) glycosuria.

Diary.—The scurvy cleared up rapidly with the ordinary anti-scorbutic foods, and the glycosuria was then studied. On ordinary diets with no limitation of carbohydrate he excreted from 33.2 to 53 gm. sugar daily, with a fasting blood sugar of 0.115 per cent., and a digestion sugar [15] of 0.133 per cent. Four days of a low calory diet (protein, 43 gm.; fat, 46 gm., carbohydrate, 29 gm.), followed by starvation for two days and three days of protein 40 gm., only sufficed to reduce the daily sugar excretion to 15.6 gm. The attempt to render the urine sugar free was then abandoned. On subsequent days, with a

15. Blood taken one and one-half hours after food.

gradually increasing diet, his output ranged from 20 to 57.5 gm. and the blood sugar from 0.112 to 0.129 per cent. when fasting, and from 0.121 to 0.161 per cent., one and half hours after food. In Table 6 a summary is presented of the diets, sugar excretion and blood sugars, fasting and digestion, during his first admission.

This table shows the independence of carbohydrate intake and output. The highest excretion being immediately after the starvation period, when the intake was at its lowest level. Allen[16] has directed attention to this apparent inability of the organism, be it normal or diabetic, to handle a sudden increase in the carbohydrate intake after a period of starvation or of low carbohydrate feeding. This also is

TABLE 6.—SUMMARY OF DIET, URINE AND BLOOD SUGAR OF C. M. (CASE 3)

Duration of Period	Diet			Urine Sugar		Blood Sugar	
	Protein	Fat	Carbohyd.	Per Cent.	Gm.	Fasting	Digestion
		House diet		2.2-3.8	33.2-53.4	0.115	0.133
5 days	0-40	0	0	0.6-1.2	16.0-23.1	0.158	0.144
12 days	90	131	90	1.0-3.1	20.3-57.5	0.112	0.141
8 days	100	130	100	1.2-3.7	22.3-38.1	0.116	0.161
5 days	100	125	150	0.8-1.6	28.7-39.0	0.117	0.121
4 days	101	125	200	1.6-1.7	25.3-48.8	0.114	0.136

TABLE 7.—REACTION OF SUGAR IN BLOOD AND URINE TO SPECIAL DIETS

Duration of Period	Diet			Urine Sugar		Blood Sugar*	
	Protein	Fat	Carbohyd.	Per Cent.	Gm.	Fasting	Digestion†
3 days		House diet		1.40-2.80	30.1-32.3	0.086	0.141
15 days	80	80	250	0.90-2.80	37.7-42.0	0.088	0.136
6 days	40-80	0	0	1.02-1.70	17.4-20.7	0.088	0.093
						0.046	0.061
3 days	0	100	0	0.92-2.01	13.3-16.1	0.078	0.087‡
4 days	80	80	250	1.00-5.40	37.5-54.0	0.089	0.242

* Blood sugars, Folin Wu method.
† Blood 1½ hours after food.
‡ Severe acidosis. Van Slyke 33.2 at end of third day, but rose to 60.5 volumes per cent. after two days of balanced diet.

shown in Table 7, where the sudden change from a pure fat diet to a liberal régime containing 250 gm. of carbohydrate is associated with a marked digestion hyperglycemia (0.212 per cent.) and one of the highest sugar outputs (54 gm.) ever found in this case. During the second admission studies were made of the effects of high carbohydrate, high protein and high fat intakes, with the following results.

After a preliminary period the patient was given a fixed diet for fifteen days with increasing fluid intakes of 1,000, 2,000, 3,000 and 4,000 c.c. per diem, but under these conditions the output showed only minor variations, an evidence of the lack of relation between the diuresis and the sugar leakage. With a pure protein dietary, there was a gradual drop in the blood sugar to the extremely low level of 0.046

16. Allen, F. M., and Associates: Three Cases of "Renal Glycosuria," Arch Int. Med. **24**:523 (Nov.) 1919.

per cent., but even on this day he excreted 19.42 gm. sugar. So far there had been no sign of acidosis, but on the third day of a pure fat diet he developed an alarming acid intoxication. The bicarbonate reserve dropped to 33 volumes per cent., and he became drowsy. The diet was changed at once to a more varied one, and in two days all sign of the acidosis had disappeared (bicarbonate reserve 60.5 volumes per cent.)

Response to Added Glucose.—Three blood sugar curves were carried out, in each case the usual dose of 100 gm. was given in lemonade.

TABLE 8.—RESPONSE OF URINE AND BLOOD SUGAR TO 100 GM. OF GLUCOSE

Hour	Blood	Urine				
June 16, 1920	Sugar	Vol., C.c.	Per Cent.	Gm.	Gm. per Hr.	Remarks
8:45 a.m.	0.119	...	....	....	....	Test taken after two days
9:00 a.m.	.....	...	2.60	....	....	of fasting and three of
9:30 a.m.	0.200	...	....	....	....	carbohydrate-free diet.
10:00 a.m.	0.200	85	2.17	1.85	1.85	100 gm. glucose at 9:00
10:30 a.m.	0.204	...	....	....	....	a.m.
11:00 a.m.	0.200	125	3.02	3.78	3.78	
12:00 m.	0.188	120	4.50	5.40	5.40	
2:00 p.m.	0.150	125	4.50	5.62	2.81	
4:00 p.m.	0.158	125	5.70	7.25	1.18	
6:00 p.m.	0.150	120	2.50	3.00	1.50	
March 16, 1921						
8:45 a.m.	0.088	...	....	....	....	After two weeks of pro-
9:00 a.m.	.....	86	1.50	....	....	tein, 80 gm.; fat, 80 gm.;
9:30 a.m.	0.122	...	....	....	....	carbohydrate, 250 gm.
10:00 a.m.	0.136	134	2.07	2.77	2.77	100 gm. glucose at 9:00
10:30 a.m.	0.178	...	....	....	....	a.m.
11:00 a.m.	0.170	72	2.60	1.87	1.87	
12:00 m.	0.083	166	2.40	3.98	3.98	
2:00 p.m.	0.061	126	1.40	1.76	0.88	
March 23, 1921						
8:45 a.m.	0.064	...	....	....	....	After three days protein,
9:00 a.m.	.....	150	2.70	....	....	40-80 gm.; carbohydrate
9:30 a.m.	0.127	...	....	....	....	free. 100 gm. glucose
10:00 a.m.	0.192	50	1.31	0.65	0.51	at 9:00 a.m. Voided at
10:30 a.m.	0.160	...	....	....	....	10:15 a.m.
11:00 a.m.	0.194	...	....	....	....	
12:00 m.	0.206	300	2.38	7.14	4.08	
2:00 p.m.	0.104	250	2.29	8.01	4.00	

The second curve is the one most nearly approaching normal. The maximum rise in blood sugar is a little high and its appearance is slightly delayed, but this can be accounted for by the arteriosclerosis and low grade nephritis [17] as shown by the albuminuria, casts, etc. The slow return to normal levels (three hours) can also be explained on the same grounds.

The first and third curves are decidedly abnormal, but are similar to those reported in other cases in which the test period was preceded by starvation or restricted carbohydrate intake. The fact remains, that in each case the kidney excretes sugar, while the glycemia is within normal limits, and in the third test the urine contained 2.7 per cent. sugar with a blood sugar of 0.064 per cent.

17. Janney, N.: Discussion, J. A. M. A. **75**:217 (July 24) 1920.

In this case the urine was collected in two hourly specimens during the day and a single specimen at night, and the hourly output was found to be remarkably constant. It was highest in the morning, fell during the afternoon and reached its lowest point during the night, showing in this regard a close resemblance to the output of albumin in that other anomaly of kidney action, orthostatic albuminuria.

TABLE 9.—RATE OF SUGAR EXCRETION FROM HOUR TO HOUR

March 7, 1921	Volume in C.c.	Specific Gravity	Sugar			Remarks
			Per Cent.	Gm.	Gm. per Hr.	
8-10 a.m.	95	1.034	4.59	4.36	2.18	Blood sugar: a. c., 0.104; p. c., 0.134
10-12 a.m.	150	1.030	2.86	4.29	2.15	
12- 2 p.m.	335	1.030	1.74	5.82	2.91	Diet: protein, 80 gm.; fat, 80 gm.; carbohydrate, 250 gm.
2- 4 p.m.	185	1.028	1.99	3.68	1.84	
4- 6 p.m.	155	1.029	2.02	3.13	1.57	
6- 8 p.m.	145	1.030	2.40	3.48	1.74	
8 p.m.-8 a.m.	1,050	1.021	1.36	14.28	1.19	
Total	2,115			39.05		

SUMMARY

Notes are presented on three cases of renal glycosuria. The first patient, after six years of observation, still presents a marked glycosuria without symptoms and with a normal amount of sugar in the blood. He is apparently in excellent health.

The second is a severe case of chronic diffuse nephritis, in which a glycosuria appeared while under observation. The glycosuria has been practically continuous since its onset twelve months ago. It is small in amount, the largest quantity being 16 gm.; it is largely independent of the carbohydrate intake, it required three days starvation before its disappearance, and reappeared on an intake of 30 gm. carbohydrate as green vegetables. The amount of glucose does not show any constant relation to the urinary volume. Synchronous sugar determination on blood and urine show the presence of a glycosuria with 0.068 per cent. sugar in the blood. The response to 100 gm. glucose falls within the limits of a nondiabetic case of nephritis. There are no other signs of a diabetes mellitus.

The third patient, aged 74, has a marked arteriosclerosis, (arteriosclerotic kidney), and was first seen on account of scurvy. The duration of the glycosuria is unknown. The glycosuria has been continuous for the past fifteen months, the usual output varying from 30 to 50 gm., and the ordinary changes in the diet had very little effect on the amount of sugar excreted. The sugar output was found to be independent of the urine volume. Synchronous studies of the blood and urine showed 2.7 per cent. sugar in the urine, with only 0.064 per cent. in the blood. The blood sugar curve following ingestion of 100 gm. glucose is somewhat atypical, but can be explained by the presence of arteriosclerosis and nephritis. There are no signs of diabetes mellitus.

It is generally recognized that there are two types of renal glycosuria [17]: the one of unknown or idiopathic origin in which the blood sugar curve is of a strictly normal order, the other, is associated with a chronic diffuse nephritis or an arteriosclerosis, in which case the patient shows a remarkably high and prolonged rise in the blood sugar, which is probably a retention phenomenon, or may be connected with the high diastatic activity of the blood, so often seen in severe nephritis. The first case is an example of the idiopathic type, while the second and third are examples of the second group.

Acknowledgment is due to Dr. E. H. Mason who has kindly placed at my disposal much of the data connected with the second and third cases; also to Miss Lane for technical assistance.

CHEMICAL STUDIES OF THE BLOOD AND URINE OF SYPHILITIC PATIENTS UNDER ARSPHENAMIN TREATMENT

WITH A NOTE ON THE MECHANISM OF EARLY ARSPHENAMIN REACTIONS *

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The chemical analyses of the blood and urine of five cases of tertiary syphilis form part of an investigation conducted in collaboration with Schamberg, Kolmer and Raiziss [1] on the subject of the causes and mechanism of the severe reactions occasionally observed after the intravenous administration of alkaline solutions of arsphenamin. Since the clinical and pathological literature on arsphenamin reactions has frequently been reviewed, we will concern ourselves here with a small number of available papers that deal with strictly chemical investigations made by modern acceptable methods.

REVIEW OF THE LITERATURE

Very little literature is available concerning the effects of arsphenamin on metabolic processes. Marischler and Schneider,[2] who were among the first to investigate this problem, unfortunately used the subcutaneous route of administration. Since the journal in which their paper is published is inaccessible, a brief summary of their work will be of interest. They investigated three cases of syphilis: one primary, one secondary and one tertiary. The patients were kept on a constant diet. An increased excretion of calcium oxid and phosphorus in the urine and feces was found in all three cases, and in one case there was an increase in the phosphorus to nitrogen ratio, with a correspond-

* From the Dermatological Research Institute.
* Investigation aided by funds accruing from the preparation of arsphenamin.
* A preliminary note on this subject was published in the Proceedings of the Society for Experimental Biology and Medicine **18**:210, 1921.

1. Schamberg, J. F.; Kolmer, J. A., and Raiziss, G. W.: Experimental and Clinical Studies of the Toxicity of Dioxydiamino-Arsenobenzol Dihydrochloride, J. Cutan. Dis. **35**:286, 1917. Schamberg, J. F.; Kolmer, J. A.; Raiziss, G. W., and Weiss, C.: Laboratory and Clinical Studies Bearing on the Causes of the Reactions Following Intravenous Injections of Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **1**:235, 1920. Weiss, C.: Phenol Elimination in the Dog After Intravenous Injection of Neo-Arsphenamin, Proc. Soc. Exper. Biol. & Med. **17**:103, 1920.

2. Marischler, J., and Schneider, N.: The Effect of Subcutaneous Injections of Salvarsan on Metabolism, Lwowski Tygodnik Lekarski (Lemberg Medical Weekly [Polish]) **7**:63, 81, 1912.

ing decrease in the nitrogen output. These authors probably used acid solutions of arsphenamin (although no data as to this are given in the original article). They concluded that arsphenamin acts like an acid, combining with the alkali of the body, especially with the calcium of the bone cells.

Rowntree, Marshall and Chesney [3] reported a case of "tabes dorsalis with acute and chronic nephritis" in which death resulted from arsphenamin poisoning. The total nonprotein and amino-nitrogen of the blood were distinctly above normal, being 150 and 12.4 mg. per hundred c.c., respectively.

Rappleye [4] studied the effects of intravenous injections of arsphenamin on the blood urea and the phenolsulphonephthalein elimination in paretic patients. In one series of cases, with normal urea values just before injection (from 7.8 to 15.4 mg. urea nitrogen per hundred c.c. of blood), only three out of the nine patients who were examined one hour after the injection, showed very small increases of from 2.5 to 3.1 mg. urea nitrogen in 100 c.c. of blood. In two other series of cases tested three and twenty-four hours after injection, respectively, no changes were detected.

Rappleye also tested the blood urea and kidney function in another series of cases which had been under treatment for a long time, and had received a total of from 11 to 32 gm. of diarsenol (the Canadian brand of arsphenamin). Only two of the four patients who had received more than 19 gm. of diarsenol showed low dye elimination (10 and 20 per cent., respectively). Although these patients "were in bed and suffering from considerable edema and were in poor general condition, showing occasional hyalin and granular casts in the urine," their blood urea nitrogen values were normal. Of the remaining six patients who had received less than 19 gm. of diarsenol, all had normal blood urea nitrogen values, although five of them eliminated low percentages of phenolsulphonephthalein (from 20 to 50 per cent.), and three of the latter showed albumin and casts in the urine. In only three of the entire series of ten cases, were the phenolsulphonephthalein and urea-nitrogen values comparable. These three gave normal figures. In all others, the phenolsulphonephthalein elimination was much lower than normal, but there was no increase in the urea nitrogen of the blood. Rappleye concludes that diarsenol has no deleterious effect on the kidneys when their function is good at the outset.

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3. Rowntree, L. B.; Marshall, E. K., and Chesney, A. M.: Studies in Liver Function, Tr. Assn. Am. Phys. **29**:586, 1914.

4. Rappleye, W. C.: Notes on the Effect of Intravenous Diarsenol, J. Lab & Clin. M. **4**:630, 1919.

Elliott and Todd[5] made similar studies on syphilitic young men who were receiving weekly intravenous injections of arsphenamin. They report as follows: Of twenty patients on whom phenolsulphonephthalein determinations were made both before and after a course of six arsphenamin injections with a total dosage of 2.7 gm., five showed a reduction of from 10 to 17 per cent. each, while the other fifteen remained practically unchanged. The urea-nitrogen content of the blood in these twenty cases showed an average of 14.3 mg. per hundred c.c. before and 16.0 mg. after treatment, or practically no change. One case showed an increase of 9 mg. No details are given of these analyses.

In another series of nine cases, receiving injections twice a week with the same total dosage (2.7 gm.), the results were as follows: Before injection, the urea nitrogen of the blood was normal, varying from 12.6 to 20 mg. per hundred c.c. of blood. After injection, it increased slightly (2 mg. per hundred c.c.) in four of the patients, but none of them had more than 20 mg. urea-nitrogen per hundred c.c. (the upper normal limit). The phenolsulphonephthalein elimination, on the other hand, was low to begin with—from 41 to 58 per cent. before injection—and was decreased somewhat, being from 40 to 51 per cent. after injection. In three of these cases there were reductions of from 11 to 17 per cent., while in two others there was 5 per cent. reduction, without corresponding retention of nitrogen.

In one case of acute syphilitic nephritis, Elliott and Todd observed high blood urea figures which declined rapidly under the arsphenamin treatment. Albumin also disappeared from the urine. The phenolsulphonephthalein excretion, on the other hand, which was rather high to begin with, declined somewhat during the treatment, in spite of the obvious renal improvement. The authors concluded that "these findings suggest that the admitted inadequacy of the phenolsulphonephthalein test to detect acute nephritis applies also to syphilitic nephritis."

Bailey and MacKay,[6] in an extensive chemical study of the blood and urine of twenty-five cases of syphilis in which toxic jaundice had developed under combined mercury and novarsenobillon (French brand of neo-arsphenamin) treatment, observed:

(1) In eleven of the cases, bile pigments were found in the plasma, and, as a rule, also bile salts.

(2) The greatest excretion of urobilinogen and urobilin was in the jaundiced cases. In the absence of jaundice, the output of these pigments was less than half.

5. Elliott, J. A., and Todd, L. C.: Effects of Arsphenamin on Renal Function in Syphilitic Patients, Arch. Dermat. & Syph. **2**:699, 1920.

6. Bailey, C. V., and MacKay, A.: Toxic Jaundice in Patients Under Antisyphilitic Treatment, Arch. Int. Med. **25**:628 (May) 1920.

(3) In the voided urine, the relative excretion of urobilinogen to urobilin was greatest in the well patients and least in the severe liver cases, indicating a decreased excretion of oxidase in the latter.

(4) In twelve of the patients with no disorder of the liver, the percentage of cholesterol varied from 0.117 to 0.210, with an average of 0.155, or within a fairly normal range. In all of the twenty-five cases of toxic jaundice, the cholesterol value was strikingly high, varying from 0.165 to 0.292 per cent., with an average of 0.235 per cent. In twenty-one of the twenty-five cases the values were over 0.2 per cent. Bailey and MacKay consider hypercholesteremia as being an early and marked sign of toxic jaundice and a valuable indication of a precarious state of the liver in this disease.

(5) The blood sugar and rate of excretion of sugar in the urine were normal in all of these patients.

(6) As for the nitrogenous constituents of the blood of these patients (who were on a high protein diet), the urea-nitrogen was normal (from 8 to 20 mg. per hundred c.c. of blood) in eight, but above normal (22 mg. and above) in the majority; one was as high as 49 mg. per hundred c.c. of blood. These abnormal values were ascribed, in part, to the high protein diet and the various physic restrictions placed on the patients (soldiers), and, in part, to impaired kidney elimination, since they were accompanied by slight increases in the creatinin and marked increases in the uric acid of the blood as well as a decreased elimination of uric acid in the urine. The high blood uric acid was attributed to an increased production of this substance resulting from a destruction of liver nuclear substance. It is of interest to note that casts and protein were found only occasionally in the urines of a few of those patients who showed retention of nitrogen in the blood.

While this manuscript was being prepared, Anderson's paper on the effect of arsphenamin on kidney function appeared.[7] This author reports chemical analyses of the blood in thirty-eight cases of syphilis in which the total dosage of arsphenamin ranged from 8 to 21 gm. with an average of about 14 gm. The treatment extended over a period of two years and included inunctions or injections of various mercurials in addition to arsphenamin injections. Of the thirty-eight patients (we omit here the case which he characterized as nephropathic), twenty-four had total nonprotein nitrogen values higher than 30 mg. (the upper normal limit), four of these ranging from 40 to 46 mg. per c.c. of blood. The urea-nitrogen and creatinin values were normal in all, although one case showed albumin and globulin in the urine

7. Anderson, H. B.: Some Observations on the Use of Arsphenamin, Am. J. M. Sc. **162**:80, 1921.

(no casts). The phenolsulphonephthalein test gave the following results. Of five patients with somewhat subnormal dye elimination (from 45 to 50 per cent. in two hours) only one patient had a non-protein nitrogen value of 46, the others being normal. Case 25 of Anderson, diagnosticated as "tabes and nephritis" had a phenolsulphonephthalein elimination of 40 per cent. in two hours, total non-protein nitrogen 37 mg. per hundred c.c. of blood, and urea and creatinin normal. The urine showed a distinct trace of albumin but no globulin and a few granular casts. Anderson draws the conclusion that there is no evidence of kidney injury.

In this connection, some of the recent histopathologic studies of Kolmer and Lucke [8] must be referred to briefly. These authors found the following changes in normal rabbits and rats injected intravenously with repeated small (therapeutic) doses of either neo-arsphenamin or alkaline arsphenamin:

> The liver showed small areas of focal necrosis and slight periportal fibrosis. The latter was confined to the tissue about the bile ducts and blood vessels. The kidneys revealed vascular and tubular changes characterized as "nephrosis." More or less marked chronic passive congestion was found with moderate hemosiderosis in the spleen; inconspicuous amounts of hemosiderin occurred in the lung. Occasional vessels contained thrombi composed of partly or entirely conglutinated or hyalinized erythrocytes. The lipoids of the suprarenals were at first increased in quantity; later a slight exhaustion appeared. Parenchymatous changes of mild degree were seen in the various organs.

PLAN AND METHODS OF INVESTIGATION

As has been brought out in the review of the literature, previous writers have limited their work to a single chemical analysis of the blood and urine of the patient after a course of arsphenamin injections had been given, with the hope of detecting kidney injury. The present work was begun before any of the above publications had appeared. Our object being primarily to study the mechanism of early arsphenamin reactions, we deemed it necessary to hospitalize our cases, and to make frequent analyses of the blood and urine before injection and then for a sufficient interval after treatment. In this way we hoped to detect changes, which could, with some degree of certainty, be ascribed to the action of the drug.

Five cases of tertiary syphilis with varying degrees of optic atrophy were selected from the Skin Clinic of Dr. Jay F. Schamberg, Polyclinic Hospital, Graduate School of Medicine, University of Pennsylvania. They were kept in a ward at the Polyclinic Hospital and given the usual house diet, which was low in proteins and fats, rich in carbohydrates and fairly constant from day to day. Their water intake

8. Kolmer, J. A., and Lucke, B.: Experimental Studies on the Histopathologic Changes Produced by Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **2**:289, 1920; Ibid. **3**:483, 1921.

was also controlled. Blood specimens were taken in the first two cases, three hours after a constant prescribed breakfast and in the last three cases, before breakfast.

The following were investigated: (1) The urea and total nonprotein nitrogen, sugar and uric acid of the blood, by the methods of Folin and Wu.[9] The total nonprotein nitrogen was estimated by the digestion and direct nesslerization technic, and urea nitrogen by the acration and titration method of Van Slyke and Cullen.[10] (2) The carbon dioxid combining power of the plasma was determined by Van Slyke's method.[11] (3) Kidney function was determined by the phenolsulphonephthalein test of Rowntree and Geraghty,[12] the dye being injected intramuscularly. (4) The daily twenty-four hour specimens of urine were also analyzed routinely for sugar and albumin, and microscopic examinations were made of the sediment. (5) The hydrogen-ion concentration of the blood and urine was measured by the colorimetric method of Sörenson, as developed by Bayliss[13] and Clark,[14] respectively. (6) Total nitrogen in the daily twenty-four-hour urine was estimated by the gross Kjeldahl method in the usual way. (7) Arsenic elimination in the urine was determined by Green's microtitration method. These results are reported separately.[15]

Before beginning this investigation the various methods employed were carefully tested out by running "recovery" and "control" experiments. All determinations reported were done in duplicate, and only checking results were accepted.

REPORT OF CASES[16]

Case 1.—T. M., aged 38; optic atrophy of left eye. This patient was in good physical condition. He had been under continuous treatment for more than two years, and had always suffered reactions. During the "control periods" (before injection), normal values for urea, total nonprotein nitrogen and blood sugar were observed. Oct. 26, 1920, before breakfast, the patient was given an intravenous injection of 0.6 gm. of an alkaline solution of arsphenamin, dissolved in 120 c.c. distilled water. The patient had a very mild reaction—nausea and vomiting, which continued until the next morning. Three hours

9. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919; Ibid. **41**:367, 1920.

10. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211, 1914.

11. Van Slyke, D. D.: A Method for the Determination of Carbon Dioxid and Carbonates in Solution, J. Biol. Chem. **30**:347, 1917.

12. Rowntree, L. G., and Geraghty, T. J.: Described by Myers,[17] pp. 103-104.

13. Bayliss, W. M.: The Neutrality of the Blood, Brit. J. Physiol. **53**: 162, 1919.

14. Clark, W. M.: The Determination of Hydrogen Ions, Williams and Wilkins Co., Baltimore, 1920.

15. Weiss, C., and Raiziss, G. W.: The Elimination of Arsenic in the Urine of Syphilitic Patients After Intravenous Injection of Arsphenamin, Arch. Int. Med. (1922) to be published.

16. Additional data are given in the preceding paper.[15]

after the injection, the total nonprotein nitrogen rose to 32.9 mg., which is slightly above the upper normal limits given by Myers.[17] The urea remained unchanged. No food had been taken during this interval. The blood sugar increased from 100 to 123.8 mg. per hundred c.c. On the following morning, the figures for urea and total nonprotein nitrogen (blood specimen obtained three hours after a prescribed breakfast) continued to rise, the former reaching 6.8 mg. above the normal range.

TABLE 1.—Showing Chemical Changes in the Blood of Syphilitics During Arsphenamin Treatment

Date	Total Nonprotein Nitrogen *	Urea Nitrogen	Sugar	Remarks
Case 1: T. M.; male; aged 35; optic atrophy				
10/25/20	24.2	11.1	85.1	
10/26/20	30.0	13.2	100.0	†
10/26/20	32.9	13.2	123.8	V‡
10/27/20	36.8	20.6	130.2	V
10/29/20	31.4	17.2	133.8	
11/ 2/20	39.5	14.3	115.6	
11/ 4/20	33.4	14.9	105.9	
11/ 8/20	34.3	22.4	131.6	
11/ 9/20	23.2	8.1	133.3	†
11/ 9/20	28.4	9.4	129.9	D‡
11/10/20	44.3	14.8	121.2	
11/13/20	34.5	11.3	137.9	
11/16/20	32.6	12.6	137.9	
11/18/20	31.0	12.4	139.9	
11/22/20	32.4	18.1	121.6	
11/23/20	34.8	16.9	116.3	V†
11/24/20	38.2	18.3	117.6	
11/26/20	30.3	13.5	108.1	
Case 2: M. J. male; aged 28; optic atrophy				
1/19/21	33.5	11.4	93.5	
1/20/21	32.1	11.4	88.3	
1/21/21	32.6	11.7	111.4	
1/25/21	30.7	12.2	75.5	†
1/25/21	32.8	15.5	153.8	V‡
1/27/21	31.5	11.3	113.0	
1/28/21	31.5	12.6	89.9	
1/31/21	30.7	14.2	137.9	
2/ 2/21	38.8	18.6	96.4	G
2/ 4/21	35.8	17.5	119.0	
2/ 7/21	30.9	14.3	107.5	

* All figures are given in milligrams per hundred c.c. of blood.
† Injection immediately after sample was drawn.
‡ Patient received an intravenous injection of 0.6 gm. arsphenamin three hours before this sample of blood was drawn.
V = "reaction"—patient vomited.
D = severe reaction with vomiting, diarrhea and pain in the legs.
G = gastric crisis. C = slight reaction, chills.

During the succeeding days, the values fluctuated somewhat. One week after injection a total nonprotein nitrogen value of 39.5 mg. per hundred c.c. of blood was observed. The urea nitrogen of this specimen was normal (14.3 mg.). The highest urea value, observed thirteen days after injection, was 22.4 mg. with a corresponding nonprotein nitrogen figure of 34.28 mg., both indicative of a very mild nitrogen retention.

After the second injection, the reaction was much more severe. The patient became very sick; he had vomiting, diarrhea, pain in the legs and oliguria with bile tinged urine. The blood specimen taken three hours after this injection (no food having been consumed) showed increases similar to those seen after the first dose. On the next morning, however, the highest value

17. Myers, V. C.: Practical Chemical Analysis of Blood, St. Louis, C. V. Mosby Co., 1921, pp. 70-82, 103-104.

for total nonprotein nitrogen was obtained, 44.3 mg. per hundred c.c. blood. The urea-nitrogen remained normal, 14.8 mg. per hundred c.c. An increase of 2 gm. above the usual range was observed in the urinary nitrogen excretion of the succeeding day. The urea and sugar continued to remain normal during the next two weeks, but the total nonprotein nitrogen figures were slightly above normal.

The third injection, now given, was followed by a mild reaction, and the analytical figures were very much similar to those seen after the first dose. The blood sugar values never assumed pathologic significance.

Case 2.—J. M., male, aged 28; total optic atrophy. This patient was in good physical condition; he had been under continuous treatment for over two years. During the control period (one week) the values for urea and total nonprotein nitrogen were or gradually became normal. A mild reaction (vomiting) followed the first injection of 0.6 gm. of alkaline arsphenamin. The blood specimen taken three hours after this injection (the patient having taken no food) showed slight rises (from 2 to 3 mg.) in the urea and total nonprotein nitrogen. The blood sugar was more than doubled but never assumed pathologic significance. No other significant changes were observed until eight days later when the urea and total nonprotein nitrogen rose above their usual values, reaching 18.6 and 38.8 mg. per hundred c.c. of blood, respectively. Both gradually declined during the course of the next few days.

Case 3.—K. W., male, aged 39; locomotor ataxia; total optic atrophy. This patient was not in good nervous or physical condition. During the control period of observation (lasting twelve days) the values for urea-nitrogen, sugar and uric acid were normal. The total nonprotein nitrogen values, however,

TABLE 2.—Biochemical Data on Case 3

K. W.: male; aged 39; optic atrophy

Date	Total Nonprotein Nitrogen*	Urea Nitrogen	Sugar	Uric Acid	Remarks
2/23/21	32.2	9.9	126.6		
2/25/21	33.8	11.0	124.6		
2/28/21	35.1	12.5	132.5	2.4	
3/2/21	35.2	12.3	158.2	2.4	
3/4/21	33.0	13.7	144.4	2.4	
3/7/21	28.0	9.1	173.2	1.3	†
3/7/21	30.9	14.5	160.6	1.4	C‡
3/8/21	31.4	11.7	173.5		
3/10/21	28.9	8.6	160.6	2.4	
3/14/21	29.1	6.0	95.5	2.4	
3/16/21	27.9	9.6	96.4	2.4	
3/18/21	24.0	7.3	93.0		
3/21/21	26.5	12.2	86.4	2.4	†
3/21/21	29.0	14.0	149.3	2.4	V‡
3/22/21	35.2	14.9	147.6	2.0	
3/24/21	24.6	8.9	107.0	...	†
3/24/21	26.4	10.3	109.5	...	C‡
3/25/21	26.5	13.1	102.6		
3/29/21	22.9	7.3	97.3	2.2	
3/31/21	24.9	10.0	98.2	2.4	
4/5/21	34.7	11.2	95.2	2.6	
4/7/21	26.1	14.9	91.3	2.2	

* All figures are given in milligrams per hundred c.c. of blood.

† Injection immediately after sample was drawn.

‡ Patient received an intravenous injection of 0.6 gm. arsphenamin three hours before this sample of blood was drawn.

V = "reaction"—patient had severe chills.

C = slight reaction—chills.

were often somewhat above normal, ranging from 28 to 35.2 mg. per hundred c.c. of blood. The first injection of 0.6 gm. arsphenamin was not followed by any untoward symptoms, except slight chills. The usual small increases in the urea and nonprotein nitrogen (and uric acid) of the blood were observed three hours after the injection. No other significant changes were detected.

The second injection of 0.6 gm., given a fortnight after the first, was followed by somewhat more severe chills. The blood findings were similar, except that the blood sugar rose appreciably three hours after the injection.

Three days later a third injection was given and was followed by similar results. The urea nitrogen content of the blood in this patient never rose above 15 mg. per hundred c.c.

Case 4.—G. R., male, aged 48; partial optic atrophy; diminished hearing; tremor; Rhomberg positive. Loss of tactile sensation. General physical condition fair. In this case and in Case 5 an effort was made to determine whether or not the alkali used to neutralize arsphenamin produced any appreciable change in the carbon dioxid combining power of the plasma or in the hydrogen-ion concentration (p_H) of the blood or urine. In addition to chemical analyses of the blood,[18] we made phenolsulphonephthalein elimination tests and careful examination of the urine for albumin and casts.

During the control period of observation (one week) this patient showed abnormal values for urea and total nonprotein nitrogen of the blood, from 24 to 30 and from 36 to 41 mg. per hundred c.c., respectively. The carbon dioxid and sugar values were, however, normal. The phenolsulphonephthalein elimination was not comparable with the nitrogen figures, being within the normal range. The urine frequently showed a few granular and hyalin casts, renal cells and leukocytes and an occasional red blood cell. There was no proteinuria or glycosuria. The p_H of the urine was within normal range.

After the first injection of 0.6 gm. alkaline arsphenamin no untoward symptoms were observed. There were the usual small increases in the total nonprotein nitrogen and sugar of the blood three hours after the injection. The urea, carbon dioxid combining power and the p_H of the blood remained unchanged. The urine taken immediately after the injection was completed, showed a very small increase in alkalinity. Forty-four hours after the injection an appreciable increase in the urea and total nonprotein nitrogen of the blood was observed. The former rose to 32.3 mg. and the latter to 44.1 mg. per hundred c.c. blood. One week later a second injection of 0.6 gm. was given. There was no clinical reaction. The increase in total nonprotein nitrogen observed three hours after the injection was 4 mg. per hundred c.c.; the small increases in urea nitrogen and sugar of the blood were similar to those usually noted. There was no increase in the p_H of the blood. A specimen of urine, taken immediately after the injection was completed, showed a very small increase in alkalinity similar to that noted in the first injection. Two days after the injection the urea dropped to normal although the total non-protein nitrogen remained unchanged. At no time was any decrease in the phenolsulphonephthalein elimination observed.

Case 5.—C. J., male, aged 53; partial optic atrophy. General physical condition very good; patient complained of headche and occasional pain in lumbar region.

This patient showed abnormal total nonprotein nitrogen content of the blood, although the urea and carbon dioxid combining power were normal. He never showed any reaction (except very mild diarrhea) nor any subnormal phenolsulphonephthalein elimination, although he regularly eliminated a few hyalin and granular casts, leukocytes and red cells in the urine. The second injection of 0.6 gm. alkaline arsphenamin (which we were able to follow more carefully than the first) resulted in no appreciable change, other than the usual marked rise in blood sugar (observed three hours after the injection). The carbon dioxid combining power of the plasma remained unaltered.

The third injection showed a more appreciable rise in the total nonprotein (but not in urea) nitrogen, and a similar increase in blood sugar three hours after the injection.

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18. Specimens of blood were taken before breakfast.

TABLE 3.—Biochemical Data on Cases 4 and 5

Case 4: G. R.; male; aged 48; optic atrophy

Date	Blood Analyses				Kidney Function Tests				Remarks
	Total Non-protein Nitrogen*	Urea Nitrogen	Sugar	Plasma† CO_2	Phenolsulphonephthalein Elimination, per Cent.		Albumin	Sediment	
					First Hour	Total 2 Hrs.			
6/15/21	41.1	24.0	88.9	58	55	70	Negative	One of two granular casts, slight amount of sediment	
6/17/21	41.1	30.0	109.8	58	50	65	Negative	Many granular casts, few hyalin casts, occasional red blood cells, many white blood cells	
6/20/21	36.5	23.9	101.8	58	45	60-65	Negative	Many granular and hyalin casts, few renal cells and white blood cells	
6/22/21	36.1	29.6	105.3	63	..	..	Negative	Few casts and white blood cells	‡
6/22/21	38.1	28.3	122.7	63	..	..	.....	.....	§
6/24/21	44.1	32.3	96.5	58	..	..	Negative	Few casts, many white blood cells	
6/28/21	35.5	21.4	102.0	60	50	±60	Negative	Few casts and white blood cells	‡
6/28/21	39.5	23.3	115.3	60	..	..	.....	.....	§
6/30/21	39.2	19.4	92.0	55	50	65-70	Negative	Increase in amount of sediment, many casts, white blood cells, few epithelial cells	

Case 5: S. J.; male; aged 53; optic atrophy

7/ 7/21	36.7	20.3	.....	58	..	..	.....	.....	‡
7 7/21	.....	.....	.....	53	..	..	.....	.....	§
7/12/21	33.1	15.4	117.3	57	45	65	Negative	Slight amount of sediment, occasional casts, red blood cells, white blood cells	
7/14/21	34.9	19.2	137.9	57	50	60	Negative	Few granular casts, white blood cells, renal cells, and spermatozoa	‡
7/18/21	34.2	12.3	91.3	55	..	..	.....	.....	D§
7/18/21	35.1	12.3	137.9	58	..	..	.....	.....	
7/21/21	32.0	15.9	97.1	56	50	60-65	Negative	Occasional hyalin cast and white blood cells	
7/25/21	33.3	12.8	94.8	61	..	..	Negative	Occasional granular cast and white blood cells	‡
7/25/21	38.2	12.9	120.9	..	..	..	.....	.....	§
7/28/21	30.6	17.4	103.1	53	40-45	65	Negative	Occasional white blood cells and a few spermatozoa	

* All figures for total nonprotein nitrogen, urea nitrogen and sugar are given in milligrams per hundred c.c. of blood.

† Cubic centimeters of carbon dioxid reduced to oxygen, 760 mm. bound as bicarbonate by 100 c.c. of plasma.

‡ Injected immediately after sample of blood was drawn.

§ Patient received an intravenous injection of 0.6 gm. arsphenamin three hours before this sample of blood was drawn.

‖ Blood drawn during injection after three fourths of dose had been administered.

± This phenolsulphonephthalein test was made the afternoon prior to injection.

D = very mild diarrhea.

THE MECHANISM OF EARLY ARSPHENAMIN REACTIONS

Evidence has been brought forth in the review of the literature as well as from our own data, that: (a) arsphenamin does not exert any selective injurious action on the kidneys; (b) patients with injured kidneys do not necessarily manifest arsphenamin reactions; and (c) patients with good kidney function may suffer from severe reactions.

What, then, is the mechanism of arsphenamin reactions?

Numerous theories have already been suggested and these have been reviewed by one of us (C.W.[1]) as well as by Hirano.[19] The latter suggested the hypothesis that arsphenamin causes a diminution in the epinephrin content of the suprarenals and, therefore, of the circulating blood thus producing shock to the organism. Work done in this Institute by Drs. Lucké, McCouch and Kolmer (*Journal Pharmacol. Exp. Therapeutics*, 1922 [in press] casts very grave doubt on Hirano's findings and interpretation. That arsphenamin reactions bear no relation to true anaphylactic shock has been shown by the pharmacologic studies of Hanzlik and Karsner.[20]

These authors, as well as Jackson and Smith,[21] have shown that in experimental animals, even therapeutic doses of arsphenamin raise the pulmonary arterial pressure and dilate the right heart. Hanzlik and Karsner maintain that the symptoms observed after arsphenamin or neo-arsphenamin injections are due primarily to injury to the circulatory apparatus caused by the arsenic. (No distinction is to be drawn between inorganic and organic arsenicals in their opinion.) "Amelioration or partial protection afforded by adrenalin or atropin is due entirely to improvement in the circulation."

Injury to the circulatory apparatus (and, perhaps, also destruction of erythrocytes due to the hemolytic action of arsphenamin) probably accounts for the small but constant increases in total nonprotein nitrogen of the blood observed by us within three hours after injection.

The recent toxicological data of Willcox and Webster [22] showing the wide-spread distribution of arsenic in the organs of fatal cases of

19. Hirano, N.: Experimental Studies on the Nature of Anaphylactoid Reactions Caused by the Repeated Intravenous Injection of Salvarsan, Kitasato Arch. Exper. M. **3**:1, 1919.

20. Hanzlik, P. J., and Karsner, H. T.: A Comparison of the Prophylactic Effects of Atropin and Epinephrin in Anaphylactic Shock and Anaphylactoid Phenomena from Various Colloids and Arepsenamin, J. Pharmacol. & Exper. Therap. **14**:425, 1920. Effects of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Bronchi of Perfused Lungs, loc. cit. **14**: 449, 1920.

21. Jackson, D. E., and Smith, M. I.: An Experimental Investigation of the Cause of Early Death from Arsphenamin, J. Pharmacol. & Exper. Therap. **12**:221, 1918.

22. Willcox, W. H., and Webster, J.: The Toxicology of Salvarsan, Brit. M. J. **1**:473, 1916; The Analyst **41**:231, 1916.

arsphenamin intoxication, as well as the histopathological studies of Kolmer and Lucké [8] already alluded to (showing that practically very organ is to a mild degree deleteriously affected during a course of arsphenamin injections in experimental animals), lead us to suggest that early arsphenamin reactions may not be due primarily to injury to any specific organ alone but to a general tissue injury which may be ascribed to the toxic action exerted by the drug or the products of its oxidation or reduction in the tissues of certain hypersensitive cases. That the liver also suffers injury is suggested by comparing our observation of increases in total nonprotein nitrogen, without corresponding increases in urea-nitrogen of the blood, with similar data published by Losee and Van Slyke [23] and Killian [24] on eclampsia, and of Rowntree, Marshall and Chesney [3] in various other diseases in which the liver is known to be involved.

SUMMARY

Five cases of tertiary syphilis with varying degrees of optic atrophy were studied. The details of the chemical analyses of the blood and urine and the history of the cases will be found in Tables 1, 2 and 3 and in the text. Herewith are presented a brief summary of the essential points noted.

1. *Urea and Total Nonprotein Nitrogen of the Blood.*—(a) Small but definite increases in the nonprotein nitrogen of the blood (from 2 to 5 mg. per hundred c.c.) were observed three hours after practically every intravenous injection of 0.6 gm. doses of arsphenamin (ten out of twelve injections). These increases cannot be accounted for by the nitrogen content of arsphenamin (which is 5 per cent.). The maximum rise accompanied the severest reaction (Case 1). The increases in urea nitrogen were not always parallel to those in the nonprotein nitrogen and often were absent or exceeded them.

(b) Blood specimens examined at intervals after every injection of arsphenamin showed significant increases above the original limits, only in those cases (Cases 1 and 2), in which the reactions were most pronounced. The nonprotein nitrogen in Case 1, which was from 24 to 30 mg. before injection, rose twenty-four hours after the injection to 44 mg. per hundred c.c. of blood. Case 2, with a less severe reaction, showed a milder increase (from 33.5 before, to 38.8 mg. eight days after injection). The urea nitrogen figures, however, remained normal.

(c) In no case was the final total nonprotein nitrogen or urea-nitrogen of the patient, when discharged (after one, two or three 0.6

23. Losee, J. R., and Van Slyke, D. D.: The Toxemias of Pregnancy, Am. J. M. Sc. **153**:94, 1917.
24. Killian, H.: Proc. New York Path. Soc., February, 1921.

gm. doses of arsphenamin) any higher than when admitted. On the contrary, many reductions were noted. All of the patients benefited greatly by the low protein diet and hospital care, as well as by the injections.

(d) Of the five cases studied(one (Case 4) had urea and total nonprotein nitrogen values distinctly above normal before treatment was begun. Yet this patient never showed untoward symptoms. On the other hand, Case 1, with normal blood figures, reacted severely. We cannot, therefore, in every case, ascribe arsphenamin reactions to impaired kidney function alone, as suggested by Wechselmann.[25]

2. *Blood Sugar.*—Marked but not pathologic increases in blood sugar occurred fairly constantly three hours after injection. Two or three times (Cases 2 and 3) we noted that the blood sugars were doubled, although no food had been taken during this interval. As a rule, these increased values gradually subsided in the course of a few days. Whether these sudden increases were due to stimulation of the suprarenals, resulting from the action of the drug or from mere fright, is a matter to be investigated.

Marked variations in blood sugar were also noted from day to day in specimens taken at the same hour before breakfast. The nervous state of the patient and the weather conditions seemed to be controlling factors.

3. *Uric Acid.*—The uric acid of the blood was studied in Case 3 and it was found to be constantly normal during the investigation.

4. *Carbon Dioxid Combining Power of Plasma.*—In cases 4 and 5 normal values were observed both before and during treatment. The amount of alkali added to acid arsphenamin to produce the disodium salt was insufficient to change either the bicarbonate reserve or the hydrogen ion concentration of the plasma or of the urine. Ferannini [26] draws similar conclusions from his pharmacologic studies of the respiratory rate in dogs.

5. *Phenolsulphonephthalein Elimination.*—The elimination of this dye was normal in each of the two patients studied (Cases 4 and 5) although the former showed distinct signs of nephritis. There were no changes after arsphenamin treatment.

The writers wish to thank Dr. Jay F. Schamberg, Dr. John A. Kolmer and Dr. George W. Raiziss of this Institute for their kind cooperation throughout the work.

25. Wechselmann, W.: Ueber die Pathogenese der Salvarsantodesfälle, Berlin, Urban and Schwarzenberg, 1913.

26. Ferrannini, L.: Richerche Sperimentali sull' azione farmacologia del Salvarsan, Riforma med. **27**:1065-1068, 1101-1106, 1126-1128, 1911.

STUDIES IN THE VARIATION OF THE LENGTH OF THE Q-R-S-T INTERVAL *

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I

RELATION TO HEART RATE AND TO CLINICAL CONDITIONS ASSOCIATED WITH CHRONIC HYPERTENSION

Variations in the length of the different phases of the human electrocardiogram have long been observed, and satisfactory explanations have been offered for many of them by various writers. The length of the entire ventricular complex is known to vary in different individuals and in the same individual at different times but the explanation of this phenomenon has received comparatively scant attention at the hands of cardiologists.

The normal ventricular complex, the Q-R-S-T group, is usually divided into subgroups, the Q-R-S interval and the S-T interval. Prolongation of the Q-R-S interval is due to defects in certain portions of the conducting tissues. This fact has been established by animal experiment and by carefully controlled clinical observation. There are, however, certain cases in which the Q-R-S interval is normal but the Q-R-S-T interval exceeds the accepted time limit. It is with such cases that these studies have to deal.

Because of the great number of angles from which the subject must be approached, it was considered advisable to report separately on each investigation or group of investigations.

This report considers only those hearts in which the rhythm is regular and the rate approximately constant and under 120 per minute. The clinical conditions considered in this report may be termed chronic as they have existed in each individual over a long period of time. The measurements reported here were all made from Lead II of the electrocardiogram.

The results of the work in other fields of this investigation will follow.

Lewis [1] has defined the time relation of the Q-R-S group. He states that this group must have a duration of no more than 0.1 second, and that it usually constitutes less than one third of the entire ventricular complex. A critical review of the literature fails to reveal any carefully controlled work that places a definite time limit on the S-T

* From the Medical Service, St. Luke's Hospital, Chicago.

1. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1920.

interval without taking into consideration other features of the heart's activity. It is, therefore, safe to assume that the ventricular complex may normally vary in its length, and while the Q-R-S group is rather restricted in its variations, the S-T interval has much more latitude. This assumption is borne out in the study of electrocardiograms taken from normal individuals.

Garrod,[2] Thurston,[3] Chapman,[4] Eyster,[5] Einthoven [6] and others have pointed out the relation of the duration of the systole to the heart rate. Lombard and Cope [7] have devised a formula by which the systolic length may be predicted from the heart rate. Katz,[8] in carefully controlled animal experiments, has shown that the formula of Lombard and Cope may be used to predict the systolic length in animals whose heart rate is under 150.

In this work the prediction of the systolic length has been undertaken using a modification of the Lombard and Cope formula. The Q-R-S-T group is taken to represent ventricular systole. Wiggers and Clough [9] have shown that systole of the ventricle may be divided into two periods, the isometric period and the ejection period. The isometric period varies between 0.04 and 0.06 second, regardless of the heart rate or systolic length and is comparable to the Q-R-S group in that its limits of variation are narrow. Lewis [1] states that while the Q-R-S group begins before the actual contraction of the ventricle, the ventricular contraction has its inception sometime during the recording of the Q-R-S and ends within 0.03 second of the completion of the T. As the initial phase of ventricular activity is recorded 0.2 second or less before the contraction, the Q-R-S-T may be taken to represent the period of ventricular activity with a probable error of less than 0.05 second.

Lombard and Cope [7] devised the formula $S = \frac{60}{K\sqrt{R}}$ to determine the relation of systole to heart rate. In this formula S represents the systolic length in seconds, R the heart rate per minute and K a constant which they found varied with different positions of the body.

In studying the electrocardiogram it was found that the substitution of cycle length in seconds for heart rate per minute greatly facilitated matters. The heart rate is reciprocal of cycle length and may be expressed by the formula $R = \frac{60}{C}$, R being the heart rate per minute

2. Garrod, A. H.: J. Anat. & Physiol. **5**:17, 1871.
3. Thurston, Edgar: J. Anat. & Physiol. **10**:494, 1876.
4. Chapman, P. M.: Brit. M. J. **1**:511, 1894.
5. Eyster, J. A. E.: J. Exper. M. **14**:594, 1911.
6. Einthoven, W.: Arch. f. d. ges. Physiol. **122**:532, 1908.
7. Lombard, W. P., and Cope, O. M.: Am. J. Physiol. **49**:140, 1919.
8. Katz, L. N.: J. Lab. & Clin. M. **6**:291, 1921.
9. Wiggers, C. J., and Clough, H. D.: J. Lab. & Clin. M. **4**:624, 1919.

and C the cycle length in seconds. The original formula now becomes $S = \frac{60}{K\frac{\sqrt{60}}{C}}$. To simplify the equation both sides are squared resulting in $S^2 = \frac{60^2}{K^2\frac{60}{C}}$ or $\frac{60C}{K^2}$. Extraction of the square root results in $S = \frac{\sqrt{60C}}{K}$. Up to this point the method followed was that suggested by Katz [8] in the plotting of his curves.

It now becomes necessary to determine the value of K for the electrocardiogram. This was done by measuring the systolic and cycle lengths of a number of electrocardiograms from normal individuals. The values of S and C being known, the equation becomes $KS = \sqrt{60C}$ and it appears that 20 is the proper valuation of K. The manner of arriving at this conclusion is shown in Table 1.

TABLE 1.—Manner of Determining Value of K in Formula $KS = \sqrt{60C}$

E. C. G. No.	Cycle Length C	Q-R-S-T Interval S	$KS = \sqrt{60\,C}$	K
9	0.59	0.30	$0.30\ K = \sqrt{3.54}$	19.7
12	0.78	0.33	$0.33\ K = \sqrt{46.8}$	20.8
17	0.68	0.32	$0.32\ K = \sqrt{40.8}$	20.0
41	0.88	0.35	$0.35\ K = \sqrt{52.8}$	20.7
47	0.70	0.32	$0.32\ K = \sqrt{42.0}$	20.3
56	0.80	0.34	$0.34\ K = \sqrt{48.0}$	20.2
81	0.80	0.36	$0.36\ K = \sqrt{48.0}$	19.2
138	0.84	0.36	$0.36\ K = \sqrt{50.4}$	19.8
143	0.68	0.32	$0.32\ K = \sqrt{40.8}$	20.0
166	0.68	0.33	$0.33\ K = \sqrt{40.8}$	19.5

These were cardiograms of known normal individuals.
Average value of K is 20.02.

Since $S = \frac{\sqrt{60C}}{K}$ and the value of K has been determined it is now possible to predict the normal duration of systole for any heart rate considered in this paper. The equation may now be further simplified and becomes $S = \frac{7.8\sqrt{C}}{20}$ or $S = .39\sqrt{C}$. The last formula is the one which is used in this study for the prediction of the Q-R-S-T interval.

Bazett,[10] in analyzing the relation of systole to cycle length, projected images of his electrocardiograms on a large sheet of millimeter

10. Bazett, H. C.: Heart **7**:353, 1920.

ruled paper. In this way very accurate measurements were made possible. He evolved the formula $S = K\sqrt{C}$. He found that the value of K was 0.37 for men and 0.40 for women. After the publication of Bazett's results, the cardiograms used in this series were reexamined and it was found that approximately one third were taken from women and two thirds from men.

Considering the fact that this work was done independently and by a different method from that of Bazett the results correspond exceedingly well.

It is apparent, then, that ventricular systole bears a definite relation to heart rate or cycle length, and it is evident that this fact must be considered before speculating on the significance of prolonged Q-R-S-T intervals. Evidence is here presented to show that unusually long Q-R-S-T intervals may be well within the calculated limits and the prolongation only a relative one. Table 2 shows a number of tracings in which the Q-R-S-T group measures 0.40 second or more and yet the calculated systole corresponds very closely with the measured one.

A further study of this series of tracings reveals that quite another condition may be present. The Q-R-S.T interval may have all the appearance of being normal in its duration but the application of the formula will show that it is prolonged beyond its predicted length. It may be within the accepted normal limits yet absolutely prolonged. Table 3 records a series of cardiograms in which the Q-R-S-T interval falls well within the usual normal limits. None of these intervals is prolonged beyond 0.40 second yet each of them is prolonged 0.05 second or more beyond the predicted length.

In selecting from the studied material those cardiograms in which the Q-R-S-T interval was definitely prolonged, none were chosen which did not show a prolongation of 0.05 second or more. The clinical conditions that seem to stand out preeminently as a cause for the increase in systolic length are those conditions associated with high blood pressure. Table 4 shows a number of tracings exhibiting this prolongation and in all of these cases the blood pressure is well above the normal.

Meakins [11] has published a series of cases in which the Q-R-S-T interval is prolonged and he calls attention to the frequent occurrence of high blood pressure. In Meakins' work, however, the relation of the systolic length to heart rate has not been sufficiently emphasized and it will be found that many of the apparently long systolic intervals correspond closely to the predicted lengths.

11. Meakins, J.: Arch. Int. Med. **24**:489 (Oct.) 1919.

TABLE 2.—Long Q-R-S-T Intervals Which Correspond Closely to Their Predicted Lengths

Patient	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
Mrs. N.	54	1.12	0.42	0.41	0.01+	Normal individual
G. G.	50	1.20	0.41	0.43	0.02—	Normal individual
G. Z.	50	1.20	0.44	0.43	0.01+	Diabetes mellitus
C. B.	30	2.00	0.55	0.55	0	Complete heart block
T. L.	49	1.23	0.44	0.43	0.01+	Chronic arthritis

TABLE 3.—Q-R-S-T Intervals Within the Accepted Normal Limit Which Are Prolonged 0.05 Second or More Beyond Their Predicted Length

E. C. G. No.	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
34	83	0.72	0.40	0.33	0.07+	Addison's disease
53	86	0.70	0.39	0.32	0.07+	Mitral disease
55	77	0.78	0.40	0.34	0.06+	Hypertension; arteriosclerosis
90	94	0.64	0.38	0.31	0.07+	Hypertension; cardiac hypertrophy
123	90	0.66	0.38	0.32	0.06+	Chronic cholecystitis
133	107	0.56	0.36	0.29	0.07+	Hypertension; uterine fibroids
154	100	0.60	0.37	0.30	0.07+	Diabetes mellitus
159	77	0.78	0.39	0.34	0.05+	Carcinoma of stomach
190	100	0.60	0.36	0.30	0.06+	Lung abscess
27W	83	0.72	0.39	0.33	0.06+	Pernicious anemia

TABLE 4.—Q-R-S-T Intervals from Patients With High Blood Pressure Showing Prolonged Systole

E. C. G. No.	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
28	80	0.75	0.40	0.34	0.06+	Hypertension; mitral stenosis; S. 220, D. 104
40	107	0.56	0.34	0.29	0.05+	Hypertension; chronic nephritis; S. 210, D. 148
45	88	0.68	0.38	0.32	0.06+	Hypertension; mitral stenosis; S. 160, D. 102
55	77	0.78	0.40	0.34	0.06+	Hypertension; senile arteriosclerosis; S. 190, D. 110
90	94	0.64	0.38	0.31	0.07+	Hypertension; arteriosclerosis; S. 182, D. 102
133	108	0.56	0.36	0.29	0.07+	Hypertension; uterine fibroids; S. 200, D. 128
163	72	0.84	0.41	0.36	0.05+	Hypertension; chronic nephritis; S. 202, D. 120
191	73	0.82	0.40	0.35	0.05+	Hypertension; diabetes; S. 260, D. 150
195	83	0.72	0.40	0.33	0.07+	Hypertension; S. 180, D. 100
251	82	0.73	0.40	0.33	0.07+	Hypertension; S. 220, D. 100

In this table S. represents systolic pressure and D. diastolic pressure.

Bowen [12] was the first to call attention to the augmented systolic length in the heart working against increased pressure. In his observations on normal individuals doing measured amounts of muscular work he found that as cycle length shortened with increased heart rate, the systolic length tended to become longer. As this observation was at variance with any previously reported, he carefully checked his apparatus to be sure that his results were real rather than apparent. After assuring himself of the correctness of his observations, he explained this phenomenon by comparing the heart to a simple pumping engine which slows when it meets an increased resistance. The rise in blood pressure which accompanies the beginning of muscular work furnished the increased resistance against which the heart must work.

More recently Patterson, Piper and Starling,[13] working with heart and lung preparations, have shown that heart volume, intracardiac pressure, and systolic length all increase to meet an increased arterial resistance. In their work it was possible to control all features so that the diastolic inflow could be kept at a constant level and by increasing the arterial resistance it was shown that the heart dilates and, in this process, the individual muscle fibers become lengthened. If the law of the heart muscle corresponds to that of skeletal muscle, that the energy set free on contraction depends on the initial length of the muscle fibers, then greater contractile stress and prolonged systole should result. This was found to occur in the work of Patterson, Piper and Starling.

These experiments serve very well to explan the prolonged Q-R-S-T interval in the patients in this study exhibiting high blood pressure. They also serve to show that ventricular systole measured by the electrocardiogram may be favorably compared to that measured by mechanical means.

It was observed, however, in this study, that many of the patients whose Q-R-S-T interval is not prolonged exhibit greatly increased blood pressures. Table 5 records a series of cases in which the blood pressure is high and yet the measured and predicted systolic lengths closely correspond.

A consideration of Tables 4 and 5 demonstrates clearly that factors other than a simple increase in the arterial resistance must operate to produce a prolongation of the Q-R-S-T interval.

In attempting to explain the lack of similarity in the behavior of different individuals, consideration must be given to the work of Wiggers [14] dealing with the relation of systolic length to heart rate, diastolic inflow and arterial resistance. He states that the duration of

12. Bowen, W. P.: Am. J. Physiol. **11**:59, 1904.
13. Patterson, S. W.; Piper, H., and Starling, E. H.: J. Physiol. **48**:465, 1914.
14. Wiggers, C. J.: Am. J. Physiol. **56**:439, 1921.

systole is prolonged by increased venous inflow, whether or not this increase is accompanied by a rise in arterial resistance. He found also that increase in the arterial resistance caused prolongation of systole only when the pressure causing the resistance was applied on the aorta near the semilunar valves. When the resistance was met with in the peripheral circulation or even in the abdominal aorta no lengthening of systole took place; indeed, the systolic length tended to become shorter. He concluded, further, that the duration of systole at a constant heart rate was dependent on the initial pressure in the ventricle rather than on the initial length of its fibers.

TABLE 5.—Q-R-S-T Intervals from Patients With High Blood Pressure Showing no Prolongation of Systole

F. C. G. No.	Heart Rate	Cycle Length	Q-R-S-T Interval			Diagnosis
			Measured	Calculated	Deviation of Measured from Calculated	
1	77	0.78	0.34	0.34	0	Mitral and aortic disease; S. 202, D. 120
17	88	0.68	0.32	0.32	0	Mitral and aortic disease; S. 182, D. 76
38	70	0.88	0.37	0.36	0.01+	Myocarditis; renal disease; S. 240, D. 140
80	84	0.72	0.34	0.33	0.01+	Hypertension; S. 202, D. 110
85	111	0.54	0.28	0.28	0	Acute alcoholism; hypertension; S. 166, D. 88
103	117	0.52	0.28	0.28	0	Abscess of nose; S. 188, D. 112
126	96	0.62	0.31	0.31	0	Aortic aneurysm; S. 160, D. 70
151	63	0.96	0.38	0.38	0	Hypertension; S. 250, D. 120
152	81	0.74	0.34	0.34	0	Hypertension; chronic nephritis; S. 238, D. 110
208	73	0.82	0.36	0.35	0.01+	Aortic disease; S. 182, D. 110

In this table S. represents systolic pressure and D. diastolic pressure.

In striving to apply these conclusions to the results obtained in the human electrocardiogram one must enter largely into the fields of speculation. It is obviously impossible to measure venous inflow and, while increased venous pressure may be estimated easily enough, an increase in the venous pressure does not necessarily carry with it an increased venous inflow into the ventricle. It would also be very difficult to determine the location of the etiologic factor in the production of an increased arterial resistance.

In spite of these difficulties it does not appear that increased initial tension in the ventricle will account for the prolongation of the Q-R-S-T interval in these patients. All of the patients, whose records appear in this report, had been carrying their vascular overload for a considerable period of time and they were subjected to no unusual stress at the time their cardiograms were made. Most of them, in fact, had been at rest for some time. Under these conditions it is improbable that there should be any increase in the initial tension in the ventricle for that particular heart.

Wiggers does not state whether the heart volume failed to increase when the pressure causing increased arterial resistance was applied at some distance from the aortic valves, but it is possible that heart volume would not increase if the pressure were applied for a comparatively short time.

In such an event the intervening arterial system would take care of the increased resistance so that there would be no increase in initial tension in the ventricle, as Wiggers states, and neither would there be increase in initial length of its fibers.

If, however, the factor, producing the increased resistance, continued to act over a long period of time, such as it must in the cases of chronic hypertension reported here, sooner or later the increased tension must make itself felt in the ventricle and with the increase in intraventricular pressure comes an augmented initial length of its fibers.

The conclusion is forced, therefore, that the duration of systole in hypertension is a measure of the initial length of the ventricular fibers and, to such an extent, a measure of its muscular dilatation.

It is possible to determine the effect on the Q-R-S-T interval of rapidly rising or falling blood pressures. Such a series of cases is under observation at the present time and will be reported on later.

It is probable that the variation in the behavior of different individuals is of prognostic value but these cases have not been under observation a sufficiently long time to venture a definite opinion on the prognostic significance of the Q-R-S-T interval. This will be reported on later.

SUMMARY AND CONCLUSIONS

1. It is possible to predict with a reasonable degree of accuracy the duration of systole in normal individuals.

2. Clinical conditions accompanied by high blood pressure are often associated with prolongation of the Q-R-S-T interval.

3. It is probable that this prolongation is of prognostic value, but from the data at hand at present a definite statement may not be made.

POSTOPERATIVE PULMONARY COMPLICATIONS *

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INTRODUCTION

It is with some hesitation that we again present this subject.[1] That there remains, however, considerable divergence in the minds of both surgeons and anesthetists as to the etiologic factors, and therefore, the prevention and treatment of pulmonary complications there is no doubt. The retiring president of the American Association of Anesthetists stated this Spring that only 3 per cent. of anesthetists considered such complications as embolic in origin and in the most recent textbook of medicine [2] aspiration is put forward as the chief cause of postoperative pneumonia. Previous studies had led us to believe that the majority of these lesions are infarcts and an analysis of the cases subjected to operation in this clinic during the past year brings additional evidence to support this view. The recent literature contains many excellent papers in agreement with this opinion, and we feel that it is unfortunate that anesthetists and anesthesia should bear the blame for such complications when the facts would seem to exonerate both, in the majority of cases.

The cases subjected to operation in this hospital during 1920 will form the basis for this report. Statistical reports are unquestionably open to criticism, the use of hospital records possibly more so than in other fields. For no matter how meticulously kept, when studied from the viewpoint of a researcher, much will be found missing. Moreover, let alone the fact that many of the observations are made by another worker, they are often inexact. This is an example of the practical impossibility of cooperative research. It may be said, however, that our previous interest in this subject [1] has made it possible to obviate some of the inaccuracies that can occur. In this clinic all patients are constantly watched for the appearance of such complications and the roentgen ray is generously used as a control. Moreover, when such a lesion does occur an additional diagnosis card is filed away for future reference so that all proven cases are easily available for study when desired.

As might be expected, this arrangement has enabled us to assemble a steadily increasing percentage of cases. Whereas in 1916 of 3,490 cases we [1] were able to identify only sixty-five with pulmonary compli-

* From the Surgical Clinic, Peter Bent Brigham Hospital.

1. *a.* Culter, E. C., and Morton, J. J.: Postoperative Pulmonary Complications, Surg., Gynec. & Obst. **25**:621, 1917. *b.* Cutler, E. C., and Hunt, A. M.: Postoperative Pulmonary Complications, Arch. Surg. **1**:114 (Jan.) 1920.

2. Lord, F. T.: Postoperative Pneumonia, Nelson's Loose Leaf System Med. **1**:296, 1920.

cations, during 1920 we found sixty-three cases among 1,604 cases, a difference in respective morbidity of from 1.86 to 3.92 per cent. This increasing morbidity is comparative to contemporary studies. McKesson [3] reported 3.03 per cent. morbidity among 39,438 collected cases in 1918. That the increasing morbidity figure is due to better records is further emphasized by the comparative drop in the mortality percentage.[4] In 1916 our cases showed a mortality percentage of morbidity of 50.7 as opposed to our present figures of 7.9. The cases studied in this report give an approximate morbidity of 1 in every 25 cases and an approximate mortality of 1 death in every 320 cases. Although this indicates a great decrease, these figures should still cause concern.

As in previous reports, patients with bulbar palsy or a terminal pneumonia, in association with definitely serious or fatal primary lesions, are excluded. Otherwise, all patients submitted to some form of operative procedure under anesthesia are included. The entire field of pulmonary complications is again studied since it appears that such studies are of greater value in that the etiology is often the same in the many varied clinical lesions and the clinical classification is difficult owing to a confusion in the signs and symptoms presented. Any attempted comparative study of statistical reports is open to the further criticism that in no two clinics are the conditions the same. That is particularly true of this very subject, and the report of a clinic such as this, in which the majority of patients are from the poorer classes of a large city, is not suitable for accurate comparison with a clinic such as that at Rochester, Minn.[5] Again, no comparison should be made with special clinics, as those given over to gynecology.[6] In a search, however, for the underlying pathology, all the material can be used since it is probable that no matter what the type of case or operation the mechanism resulting in pulmonary complications is the same.

The result of the present study appears to corroborate a previous report of ours[1] in which embolism from the operative field seemed to be the chief cause of pulmonary complications. In the present report each case was carefully scrutinized with a view to determining the

3. McKesson, E. I.: Some Observations on Postoperative Lung Complications, Am. J. Surg. **32**:16, 1918 (Quart. suppl. Anesth.).

4. The comparative studies at the Presbyterian Hospital with figures for 1898 (75), 1916 (81) and 1917 (82) show the same tendency to an increased morbidity and decreased mortality due to more accurate records. In 1898 Schultze reported 0.38 per cent. postoperative pneumonias, whereas in 1916 Whipple reported 2.6 per cent. of this complication.

5. *a.* Beckman, E. H.: Pulmonary and Circulatory Complications Following Surgical Operations, Mayo Clinic Papers, Philadelphia and London, W. B. Saunders Co., 1910, p. 594. *b.* Complications Following Surgical Operations, 1912, p. 738. *c.* 1913, p. 776.

6. Pfannenstiel, J.: Ueber die Vorzuge der Athernarkose, Zentralbl. f. Gynäk. **27**:8, 1903.

etiology of the lesion at the time of its occurence. Roentgen ray studies confirm the type and extent of the majority of these lesions.

REVIEW OF LITERATURE

Except for recent reports the literature pertaining to this field was fully covered in previous studies.[1] At that time reports covering the whole field of pulmonary complications were few although there were many excellent studies concerning the complications following laparotomy and the incidence of postoperative pneumonia alone. Table 1 includes the comparative figures for total pulmonary complications in the various clinics up to the present time.

TABLE 1.—TOTAL PULMONARY COMPLICATIONS

Clinic	Author and Year	No. of Cases	Pulmonary Morbidity		Pulmonary Mortality		Mortality per Cent. of Morbidity
			No.	Per Cent.	No.	Per Cent.	
Montreal General Hospital	Armstrong,[7] 1906	2,500	55	2.2	32	1.28	58.1
Von Eiselberg, Vienna	Ranzi,[8] 1909	6,871	203	3.8			
Combined statistics	Von Lichtenberg,[9] 1908	23,673	440	1.9			
Mayo Clinic	Beckman,[5a] 1910	3,657	41	1.12	9	0.24	21.0
Mayo Clinic*	Beckman,[5b] 1912	5,835	92	1.57	6	0.10	6.5
Mayo Clinic*	Beckman,[5c] 1913	6,825	87	1.27	0	0.00	0.0
Massachusetts General Hospital	Cutler and Morton,[1a] 1917	3,490	65	1.86	33	0.94	50.7
Combined statistics	McKesson,[3] 1918	39,438	..	3.03	..	1.06	
Peter Bent Brigham Hospital	Cutler and Hunt,[1b] 1920	1,562	55	3.52	11	0.7	20.0
Pittsburgh	Decker,[10] 1921	5,976	69	1.2	29	0.5	42.0
Peter Bent Brigham Hospital	Cutler and Hunt, 1921	1,604	63	3.92	5	0.31	7.93

* Amended to include pulmonary embolism.

The chronologic order of the data in this table demonstrates graphically the increasing morbidity with its concomitant decrease in mortality. The figures of Decker alone disagree. The reason for this appears to be a failure to include minor complications. It is indeed almost impossible to arrive at accurate data unless each case is studied from this viewpoint and checked, at the time of occurrence, for future reference.

The discussion of the etiology of these complications has brought to light two opposing views,—one, that the anesthetic and the other that embolism plays the chief rôle. That inhalation anesthesia produces some irritation, and that the aspiration of mouth contents occurs there

7. Armstrong, G. E.: Remarks on Lung Complications After Operations with Anesthesia, Brit. M. J. **1**:1141. 1906.

8. Ranzi, E.: Ueber postoperative Lungenkomplikationen embolisher Natur, Arch. f. klin. Chir. **87**:380, 1908.

9. Lichtenberg, A.: Die postoperativen Lungenkomplikationen, Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **11**:129, 1908.

10. Decker, H. R.: Postoperative Complications and Sequels of the Respiratory Tract, Penn. M. J. **24**:391, 1921.

can be no doubt (Hoelscher [11] and Kelly [12]). That a perfectly smooth inhalation anesthesia reduces such undesirable sequels is vigorously upheld (Poppert,[13] Offergeld,[14] von Lichtenberg,[15] Ladd and Osgood,[16] Magaw,[17] Bevan,[18] Kroenlein,[19] Keen,[20] Herb,[21] Henderson [22]). This, however, fails to explain why, with local anesthesia, the proportion of such complications is equally high (Gottstein,[23] Mikulicz,[24] Henle [25] and Sauerbruch [26]). It also fails to explain why with anesthesia in expert hands these complications continue to occur.[27]

The statement [2] that aspiration is the chief cause of postoperative pneumonia is not proven by the facts. There is an increasing mass of evidence demonstrating the frequency of postoperative embolism and its relation to pulmonary complications. W. J. Mayo [28] states that

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11. Hoelscher, R.: Experimentelle Untersuchungen über die Entstehung der Erkrankungen der Luftwege nach Aethernarkose, Arch. f. klin. Chir. **57**:175. 1898.

12. Kelly, R. E.: Anesthesia by the Intratracheal Insufflation of Ether, Brit. M. J. **2**:112, 617. 1912.

13. Poppert: Experimentelle und klinische Beiträge zur Aethernarkose und zur Aetherchloroform Mischnarkose, Deutsch. Ztschr. f. Chir. **67**:505, 1902.

14. Offergeld: Lungenkomplikationen nach Aethernarkosen, Arch. f. klin. Chir. **83**:505, 1907.

15. Lichtenberg, A.: Experimenteller Beitrag zur Frage der Entstehung der Pneumonie nach Narkosen, München. med. Wchnschr. **53**:2286, 1906.

16. Ladd, W. E., and Osgood, G.: Ganze-Ether, or a Modified Drop Method, with Its Effects on Acetonuria, Ann. Surg. **46**:460, 1907.

17. Magaw, A.: A Review of Over Fourteen Thousand Surgical Anesthesias, Surg., Gynec. & Obst. **3**:795, 1906.

18. Bevan, A. D.: The Choice and Technic of the Anesthetic, Tr. Am. Surg Assn. **33**:21, 1915; **29**:177, 1911.

19. Kroenlein, R. V.: Discussion, Verhandl. d. deutsch. Gesellsch. f. Chir. **34**:131. 1905.

20. Keen, W. W.: The Dangers of Ether as an Anesthetic, Boston M. & S. J. **173**:831, 1915.

21. Herb, I.: Ether: Simplicity in Its Administration, J. A. M. A. **66**:1376 (April 29) 1916.

22. Henderson, F.: Ether Anesthesia, Collected Papers Mayo Clinic, Philadelphia and London, W. B. Saunders Co., 1913, p. 701.

23. Gottstein, G.: Erfahrungen über lokale Anästhesie in der Breslauer Chirurgischen Klinik, Arch. f. klin. Chir. **57**:409, 1898.

24. Mikulicz, J.: Die Methoden der Schmerzbetäubung und ihre gegenseitige Abgrenzung, Verhandl. d. deutsch. Gesellsch. f. Chir. **30**:560, 1901.

25. Henle: Die Methoden der Schmerzbetäubung und ihre gegenseitige Abgrenzung, Verhandl. d. deutsch. Gesellsch. f. Chir. **30**:240, 1901.

26. Sauerbruch, F.: Der Stand der Klinischen und Operativen Chirurgie, Beitr. z. klin. Chir. **122**:234, 1921.

27. This statement will be objected to by many. Only let these consider that in most large institutions and especially in those from which reports come, anesthesia is in really expert hands now. Yet these complications continue. Also let them take into consideration that a betterment of operative technic has also taken place and consider that a reduction in such complications may be due to this factor quite as well as to the improvements in the administration of anesthesia.

28. Mayo, W. J.: Mortality and End Results in Surgery, Surg., Gynec. & Obst. **32**:97, 1921.

minute septic emboli from the operative field are a common cause of secondary pulmonary complications. He laments that these complications are too frequently attributed to the anesthetic, and says that they are quite as frequently found in cases in which local anesthesia is employed. The recent illuminating papers of Ochsner and Schneider,[29] Hampton and Wharton,[30] Capelle,[31] McCann [32] and Rupp [33] demonstrate both the mechanism of thrombosis and embolism subsequent to operation and the great frequency of this condition as a source of pulmonary complications. These ideas are by no means of recent origin, and a study of the papers by Zahn,[34], Miller,[35] Gebele,[36] Otte,[37] Zurhelle,[38] Homans,[39] Michaelis,[40] Henderson,[41] Grant [42] and Eisenreich [43] reveals statistics and studies in support of this view. Zahn's paper, written in 1897, discusses the part passive congestion in the lung during operation may have as increasing the liability to infarction. In addition to such direct contributions are the many excellent reports both clinical [44] and experimental on fatal pulmonary embolism and pulmonary infarction. The experimental and pathologic studies of pul-

29. Ochsner, A. J., and Schneider, C. C.: Fatal Postoperative Pulmonary Thrombosis, Ann. Surg. **72**:91, 1920.

30. Hampton, H., and Wharton, L. R.: Venous Thrombosis, Pulmonary Infarction and Embolism Following Gynecological Operations, Bull. Johns Hopkins Hosp. **31**:95, 1920.

31. Capelle: Einiges zur Frage der Postoperativen Thromboembolie, Beitr. z. klin. Chir. **119**:485. 1920.

32. McCann, F.: Suggestions for the Prevention of Postoperative Thrombosis and Embolism, Brit. M. J. **1**:277, 1918.

33. Rupp, A.: Postoperative Thrombose und Lungenembolie, Arch. f. klin. Chir. **115**:672 (March) 1921.

34. Zahn, F. W.: Ueber die Folgen des Verschlüssens der Lungenarterien und Pfortaderaste durch Embolie, Verhandl. d. Gesellsch. deutsch. Naturforsch. u. Aerzte **19**:9. 1897.

35. Miller, R. B.: The Significance of Postoperative Pleurisy: Its Relation to Pulmonary Embolism, Am. Med. **4**:173, 1902.

36. Gebele: Ueber Embolische Lungen Affektionen nach Bauchoperationen; Eine klinisch-experimentelle Studie, Beitr. z. klin. Chir. **43**:251, 1904.

37. Otte, A.: Ueber die postoperativen Lungenkomplikationen und Thrombosen nach Aethernarkosen, München. med. Wchnschr. **54**:2473, 1907.

38. Zurhelle, E.: Thrombose und Embolie nach Gynäkologischen Operationen, Arch. f. Gynak. **84**:443, 1908.

39. Homans, J.: Postoperative Pulmonary Complications, Bull. Johns Hopkins Hosp. **20**:128. 1909.

40. Michaelis: Zur Frage des Praemonitorischen Symptoms von Thrombose und Embolie, Ztschr. f. Geburtsh. u. Gynäk. **70**:285, 1912.

41. Henderson, F.: St. Paul M. J. **16**:74, 1914.

42. Grant, H. H.: Thrombophlebitis and Pulmonary Embolism, Mississippi Valley M. J. **30**:217. 1918.

43. Eisenreich, O.: Embolism After Gynecologic Operations, Monatschr. f Geburtsh. u. Gynäk. **53**:190, 1920.

44. Wilson, L. B.: Fatal Postoperative Embolism, Collected Papers Mayo Clinic, Philadelphia, W. B. Saunders & Co., 1912, p. 727.

monary infarction are well covered by Welch,[45] McCallum,[46] Karsner and Ash [47] and Karsner and Austin.[48] That these postoperative lesions are usually situated in the lower lobes, more frequently on the right side than on the left, and thus comparable to pathologic studies on embolism and infarction may be carried as an additional argument for this mechanism. Indeed, to one familiar with the literature it is difficult to accept aspiration as the chief factor in such complications unless infarction can be disproved. The papers referred to present excellent discussions of the clinical signs and suggest prophylactic measures. With these ideas both our studies of 1919 and 1920 seem to agree and bring additional proof.

Etiologic factors other than the two cited may be considered of secondary importance. A focus of pulmonary disease existing at the time of operation unquestionably is the cause, at times, of a subsequent complication. The flare-up of a quiescent tubercular lesion or of an old bronchitis under inhalation anesthesia is unquestioned. Such lesions, however, do not always light up, and the fact that equally following operations under local anesthesia activity may be stirred up suggests the possibility of embolism as the direct cause even in such cases. The fact that the embolus reaches an already injured field makes its influence the more marked.

The importance of sepsis as a secondary factor cannot be denied, and there are cases with septic abdominal lesions in which, following operation, the lung is involved by direct extension. That a lymphatic avenue is open for such extension has been shown by the anatomic studies of Sabin,[49] Cunningham [50] and Miller.[51] The importance of sepsis both in the initiation of and the setting free of thrombi is an old story. The danger which it adds to embolism is manifest. Many cases of lung abscess following tonsillectomy usually have been thought to be due to the inhalation of mouth infectious material owing to position.

45. Welch, W. H.: An Area of Coagulative Necrosis Resulting from Shutting Off of the Blood Supply in an Infarct, Papers and Addresses, Baltimore, The Johns Hopkins Press **1**:110, 1920.

46. McCallum, W. P.: Infarction, A Textbook of Pathology, Ed. 2, Philadelphia and London, W. B. Saunders & Co., 1920, p. 33.

47. Karsner and Ash: Studies in Infarction, Experimental Bland Infarction of the Lung, J. M. Research **22**:1912-1913.

48. Karsner and Austin: Studies in Infarction, J. A. M. A. **57**:951 (Oct. 10) 1911.

49. Sabin, F. R.: The Method of Growth of the Lymphatic System, Science, New York **44**:145, 1916.

50. Cunningham, R. S.: On the Development of the Lymphatics in the Lungs of the Pig, Proc. Am. Assn. Anat., Anat. Rec. **9**:69, 1915.

51. Miller, W. S.: Some Essential Points in the Anatomy of the Lung, Am. J. Roentgenol. **4**:269, 1917. The Vascular Supply of the Pleura Pulmonalis, Am. J. Anat. **7**:389, 1908.

The recent report of W. B. Porter [52] concerning such lesions following local anesthesia, and his suggestion of the logical embolic route is of interest in this relation. And Burnham's [53] paper on pleurisy and empyema evidences the importance of a septic focus. In all his cases in which empyema developed the original operation was for a septic abdominal lesion.

Acidosis has been considered as having an influence in the production of these lesions. There has been, however, no satisfactory explanation of the mechanism by which this produces its effect, and some investigators [54] have denied its existence. It is possible that where asphyxia is produced there is some acidosis, and thereby the natural resistance to infection is lowered. Whether this is due to the anesthetic [55] or to the effects of the operation [56] is unknown.

Chilling and cold possibly produce some effect in a similarly remote manner. The work of Miller and Noble,[57] Hill [58] and Mudd and Grant [59] would appear to show that there is some lowered resistance to infection with chilling. Moreover, such clinical investigators as Boothby,[60] Homans,[39] Keen,[20] Armstrong,[7] Gerulanos,[61] and Decker [10] have felt that either external exposure or chilling by cold wet packs during operation played a part in the subsequent pulmonary complications.

These factors, by the production of a lowered immunity, may open the body to attack by organisms commonly present. That Group IV pneumococcus is commonly found in these cases (Whipple [62] and Cleve-

52. Porter, W. B.: Pulmonary Abscess Following Tonsillectomy Under Local Anesthesia, Virginia M. Month. **47**:606 (March) 1921.

53. Burnham, A. C.: Postoperative Pleurisy with Effusion and Empyema, Surg., Gynec. & Obst. **19**:468, 1914.

54. Caldwell, G. A., and Cleveland, M.: Observations on the Relation of Acidosis to Anesthesia, Surg., Gynec. & Obst. **25**:22, 1917.

55. Carter, W. S.: Effect of Ether on the Alkali Reserve, Arch. Int. Med. **26**:319 (Sept.) 1920. Collip, J. B.: Effect of Surgical Anesthesia on the Reaction of the Blood, Brit. J. Exper. Path. **1**:282, 1920. Jeanbrau, E., Cristol, P., and Bonnet, V.: Anesthesia and Acidosis, J. d'urol. méd. et. chir. **11**:505 (May-June) 1921.

56. Farrar, L. K. P.: Acidosis in Operative Surgery; Occurrence During Operation and Its Treatment by Glucose and Gum Acacia Given Intravenously, Surg., Gynec. & Obst. **32**:328, 1921.

57. Miller, J. A., and Noble, W. C.: The Effects of Exposure to Cold on Experimental Infection of the Respiratory Tract. J. Exper. M. **24**:223, 1916.

58. Hill: The Influence of the Atmospheric Environment on the Respiratory Membrane, Brit. M. Research Committee, Ser. 32, p. 141, 1919.

59. Mudd, S., and Grant, S. B.: Reactions to Chilling of the Body Surface, J. M. Research **40**:53, 1919.

60. Boothby, W. M.: Postoperative Pneumonia (Discussion) J. A. M. A. **67**:539 (Aug. 12) 1916.

61. Gerulanos, M.: Lungen Komplikationen nach Operativen Eingriffen, Deutsch. Ztschr. f. Chir. **57**:371, 1898.

62. Whipple, A. O.: A Study of postoperative Pneumonia in the Presbyterian Hospital During 1915, Med. Rec. **89**:581, 1916. A Study of Postoperative Pneumonitis, Surg., Gynec. & Obst. **26**:29, 1918.

land [63]), might seem to be additional evidence that this mechanism existed. It should, however, be recognized that Group IV pneumococcus is commonly found in normal mouths (Stillman,[64] Dochez and Cole [65]). Provided, that a focus of pulmonary disease already existed, this lowered resistance might enable organisms present to get a start and thus a more virulent mixed type of infection might occur.[66]

It is difficult, however, to appreciate the importance of such secondary factors, and also that aspiration is the chief factor, when it is so well known that the experimental production of pneumonia by the bronchial route is extremely difficult. Blake and Cecil's [67] studies alone seem to be successful by this method, except when enormous dosage has been used.

The foregoing facts may be taken as a defense of inhalation anesthesia and anesthetists. It is astonishing that so few of the latter have attempted their own defense when the general concensus of opinion now definitely favors embolism as the chief factor in the production of these lesions. The earlier reports on "ether pneumonia" cast a most unjust opprobrium on the anesthetic. That venous thrombosis, fatal pulmonary embolism and pulmonary infarction are common there can be no doubt. McCallum [46] and Welch [45] have given admirable descriptions of the underlying pathology. The right lower lobe is most frequently the site of both these clinical lesions and the pathologic types recorded. Moreover, infarction can be the only explanation in cases in which local anesthesia is used. Why search for additional factors when the pathologic and clinical studies emphasize the importance and frequency of embolism, and when the clinical picture is far more frequently of the type ascribable to this factor?

As is shown in the cited reports, and as the cases presented later show, the onset in the majority of these cases is abrupt, dissimilar to the onset of infection elsewhere, and the subsidence, except when the embolus has arisen in a septic field or landed in a focus of pre-existing pulmonary disease, is almost equally rapid. Moreover, the symptom of pain, the small areas involved and the typical lobular distribution of

63. Cleveland, M.: Further Study in Postoperative Pneumonitis, Surg., Gynec. & Obst. **28**:282, 1919.

64. Stillman, E. G.: A Contribution to the Epidemiology of Lobar Pneumonia, J. Exper. M. **24**:651, 1916.

65. Dochez, A. R., and Cole, R. I.: Pneumococcus Infection, Forchheimer's Therapeusis of Internal Diseases, New York and London, D. Appleton & Co., **5**:472, 1914.

66. Wadsworth, A. B.: Experimental Studies on the Etiology of Acute Pneumonitis, Am. J. M. Sc. **127**:851, 1904. A Study of Experimental Organizing Pneumonia, J. M. Research **34**:147, 1918.

67. Blake, F. G., and Cecil, R. L.: Production of Pneumococcus Pneumonia in Monkeys, J. Exper. M. **31**:403, 1920. Pathology and Pathogenesis of Pneumococcus Lobar Pneumonia in Monkeys, J. Exper. M. **31**:445, 1920.

the lesion, with often cone-shaped roentgen-ray shadows, is so striking as to leave little doubt as to the kind of lesion present.

PRESENTATION OF MATERIAL

From Jan. 1, 1920, to Jan. 1, 1921, 1,604 cases [68] in this clinic were submitted to some form of operative procedure under anesthesia. Sixty-three of these patients developed a pulmonary complication that might be attributable to the operative intervention or to the anesthetic. There were five deaths among these sixty-three cases. In addition five other patients died with pulmonary lesions following operation, but three of these suffered from bulbar paralysis due to intracranial lesions and two were old men, admitted "in extremis," with septic genito-urinary lesions, who, after some simple emergency intervention developed septicemia with its concomitant terminal pneumonia. It appears only fair to remove such cases from this discussion. Thus in 3.93 per cent. of the cases (one in twenty-six) a complication developed and 0.3 per cent. (1 in 321) patients died from one of the complications.

The conception that small emboli from the operative field are the chief etiologic factors makes the classification simpler. All cases in which this mode of occurrence was obvious can be placed in a distinct class. We have elected to term these, cases of pulmonary infarction. The further divisions are, lobar and bronchopneumonia, bronchitis, pleurisy, pulmonary embolism, empyema, lung abscess and cases in which there has been exacerbation of a tuberculous lesion.

We found that unless a separate division was made for the embolic cases the greatest difficulty in classification arose. Thus many lesions, in which this mechanism was obvious, simulated partly pleurisy, there being pain and a friction rub, and partly pneumonia, since a small patch of consolidation was demonstrable both on physical examination and by the roentgen ray. In this report, therefore, we have placed in the class termed infarction all those cases in which the mechanism of embolism was undoubted (excepting the typical fatal pulmonary embolism cases). Ranzi [9] called these small embolic lesions embolic pneumonia, a somewhat confusing pathologic term. In the other classes we feel there must be also some cases in which embolism was present, but either the presence of sepsis in the wound or a preexisting pulmonary lesion so confused the picture that classification as infarction was not justifiable.

Pathologists regard as pulmonary infarction only those lesions that go on to coagulative necrosis. Thus they may object to this nomenclature. The mechanism of these minor infarctions, however, is the

68. This does not include cystoscopies, dressings and the applications of plaster cast unless anesthesia was employed.

same as with larger coagulative necrotic lesions and certainly both in etiology and pathology the lesions are more nearly infarction than true pneumonia. Observers in the past, including ourselves, by classifying such lesions as pneumonia have certainly not clarified the issue. It is our hope that the submitted evidence in regards to such lesions will lead others to adopt the same classification. If this is followed it would appear that a better understanding of pulmonary complications as a whole must result.

TABLE 2.—Morbidity and Mortality of Various Complications

Complications	No. of Cases	Morbidity Percentage	No. of Deaths	Mortality Percentage of Morbidity	Approximate Morbidity per 100 Cases	Approximate Mortality per 100 Cases
Lobar pneumonia	1	0.06	1	100	1:1604	1:1604
Bronchopneumonia	7	0.43	1	14.2	1:229	1:1604
Bronchitis	16	0.99	0	0	1:100	0
Exacerbation of tuberculosis	2	0.12	0	0	1:804	0
Pleurisy	2	0.12	0	0	1:804	0
Empyema	1	0.06	1	100	1:1604	1:1604
Pulmonary infarction	32	1.99	0	0	1:50	0
Pulmonary embolism	2	0.12	2	100	1:804	1:804
Totals	63	3.92	5	7.93	1:25	1:320

Table 2 depicts the great preponderance of infarction cases. The freedom of this group from fatalities will be discussed later. It is clear, however, that in these cases death is due either to a large pulmonary embolism (a separate class) or to septic lesions. Here the confusion in the picture may place the case in the pneumonia or bronchitis class.

The infrequency of true lobar pneumonia is striking and further emphasizes the general tendency in the more accurate recent studies wherein lobar pneumonia is shown gradually to be disappearing as a postoperative lesion. This is especially true when the clinical findings have been verified by roentgen-ray studies. The reason for this lies in the mechanism of its production, i. e., embolism rather than infection.

Lobar Pneumonia.—There was only one case this year in which the complication was of the lobar pneumonia type. It is only fair to state that without the roentgen-ray studies we should have misplaced even this one case among the bronchopneumonias.

History.— Patient, 50 years of age, was operated on for an indirect left inguinal hernia under procain. Local anesthesia was used since the past history and physical examination indicated an already damaged lung. Three years previously the patient had suffered from a severe attack of pneumonia and ever since had been much troubled with asthma and frequent attacks of pleurisy. Moreover, physical examination of the lungs demonstrated relative dulness in the right upper lobe and many sonorous and musical râles throughout the entire right chest. Within two days following operation there was evident difficulty in breathing and some productive coughing. This increased and the

temperature and respiratory rate began to climb. By the fourth day postoperative there was a demonstrable area of consolidation in the right lower chest. Roentgen-ray studies on the eleventh day showed that all three lobes were uniformly involved, another roentgen-ray examination made on the eighteenth day showed beginning resolution in the upper and lower lobes but no change in the middle lobe. Shortly following this the urinary output diminished and the patient's general condition rapidly deteriorated. He died on the thirtieth day after operation.

This case is presented in some detail because it is both typical and atypical; typical in that a pre-existing focus of pulmonary disease flared up into a serious and fatal complication; atypical in that the lesion was lobar rather than lobular. Indeed, were it not for the excellent roentgen-ray studies, we had sufficient other clinical evidence to designate it a bronchopneumonia. The explanation of the fatality must lie in some connection with the previous attack of pneumonia, the patient's individual susceptibility and the possibility that he still harbored a malignant organism. One may suppose, however, that in the absence of inhalation irritants, emboli from the field of operation may have been the means of stirring into activity an already prepared focus of disease.

Bronchopneumonia.—We have placed seven cases in this group. All cases showed multiple areas of consolidation at some period following operation. There was one fatality. The anesthesia was gas-oxygen in four cases and ether in three. In two of the gas-oxygen cases, a little ether was given for added relaxation while opening the abdomen. In the straight ether cases, the open mask method was used twice and the Connell machine with an intranasal pharyngeal tube once. The operations were: laparotomy, six times, three times for appendicitis and once each for gastric ulcer, salpingitis and hydronephrosis, and craniotomy for extracerebellar acoustic neuroma once. The latter case ended fatally. The well known relative predominance of such complications with abdominal operations is thus exemplified.

The cranial case was of unusual interest to us in that we have rarely observed pulmonary complications in such cases, except when there has been ninth nerve involvement, which apparently was not present in this case. However, following a long, tedious, suboccipital operation this nerve may, to some extent, have been injured. The patient was 47, a good risk and did well following operation until the seventh day when without previous intimation there was a sudden rise in pulse, temperature and respiration. Bilateral basal bronchopneumonia progressed steadily until death on the twenty-fourth day postoperative. The sudden onset, although without pain, suggests the possibility of embolic origin of the complication. The large vessels encountered in such explorations are an obvious source of such thrombi.

The other six cases have both sepsis and abdominal section in common, a well recognized dangerous combination.[69] The three appendix cases were all acute either with abscess or perforation, the case of salpingitis was equally acute, a large pyosalpinx having ruptured and given the signs of a general peritonitis, and the gastric ulcer case with a sleeve resection for a pyloric lesion certainly holds infectious possibilities. The lungs were clear before operation in all but one case. The complications were confined to the bases in all cases, bilateral in one case, left side twice and at the right base three times. The time of onset varied from immediately following operation to the end of the first week. It should be said, however, that in all septic cases the recognition of a concomitant complication is always delayed and difficult because of the already existent picture of disease. In two cases only was the onset of the complication striking from a study of the chart. One of these began on the second and one on the eighth day after operation. The majority of these patients had a productive cough due, apparently, to a mild associated bronchitis. The presence of sepsis makes it difficult to explain the underlying etiology. It does not seem reasonable, however, to suppose that aspiration has produced this untoward effect only in such septic cases and the lobular rather than lobar distribution of the lesions gives us encouragement to believe that minute septic emboli may be at the bottom of the trouble in these cases. Or the infection may have progressed by direct extension.

Bronchitis.—In this group are sixteen cases, and, as a whole, they form a very distinctive picture. The whole field of surgery is covered, both septic and aseptic; six patients were operated on for hernia; the other operations, except for one each on the breast and thigh, were for varying abdominal conditions. Septic lesions were present in more than half the cases, and the patients were of all ages and both sexes. Ether was given in eleven cases and gas-oxygen in five.

In eleven cases there was evidence of previously existent pulmonary disease either in the past history or in the physical examination. This usually was a chronic, intermittent, troublesome bronchitis. And this appears to be of the greatest importance. There are undoubtedly many cases among all pulmonary complications, like those in this group, in which the development of complications can justly be charged to the

69. See the excellent papers of Bibergeil,[70] Läwen[71] and Robb and Dittrick[72] in which the high percentage of such complications following laparotomy is demonstrated and discussed.

70. Bibergeil, E.: Ueber Lungen Komplicationen nach Bauch Operationen, Arch. f. klin. Chir. **78**:339, 1905.

71. Läwen, A.: Ueber Lungenkomplikationen nach Bauchoperationen, Beitr. z. klin. Chir. **50**:501, 1906.

72. Robb and Dittrick: Pulmonary Complications Following Abdominal Operations, Surg., Gynec. & Obst. **3**:51, 1906.

anesthetic. In such cases the irritation of a pulmonary anesthesia is sufficient to flare up a quiescent lesion. However, it must be understood thoroughly that the existence of such a focus does not always entail postoperative disease. By making roentgenograms in a large series of cases before and after operation, irrespective of signs and symptoms, we have been able to prove to ourselves that many times such foci are present before operation and yet undergo no demonstrable change after inhalation anesthesia. Just what the criteria are that determine whether a case shall become active is not clear, but the fact that in three of these sixteen cases the sudden and late onset of the disease pictured the symptomatology of small emboli may mean that in a certain proportion of these lesions, clinically recognized as bronchitis, the flare-up is due to minute emboli from the operative field that land in an already prepared area. In one of the cases classified here as bronchitis an uneventful convalescence occurred until the eighth day when a careful physical examination, done to explain a rise in temperature, revealed a few râles at the base of the right lung. Such a case might possibly have been better classified under pulmonary infarction.

The majority of cases in this group are typical of postoperative bronchitis, showing an immediate respiratory distress with a good deal of cyanosis, frothy sputum and widespread râles. The upright position and warm vapor inhalation proves of much benefit. In cases in which any cardiac damage is suspected digitalis may be of assistance.

Exacerbation of Tuberculosis.—There are two cases in this year's complications in which, subsequent to operation, an acute pulmonary tuberculosis developed. One patient had acute appendicitis, the other had tuberculous lymphadenitis. In the appendix case ether was given as the examination had revealed no pulmonary disease; in the second case, both the physical signs and a chest roentgenogram gave warning and gas-oxygen was used. Both patients developed almost immediately following operation the signs of bronchopneumonia which were corroborated by roentgen-ray studies which also confirmed the presence of chronic lesions in the apices. Such a flare-up must be expected in a certain percentage of patients with this condition. These cases are presented here to emphasize the importance of pre-existent nontuberculous pulmonary disease as exemplified in the bronchitis group of cases just discussed. Thus, a warning is sounded concerning casual pre-operative pulmonary examination. In all such cases the anesthetic of choice is local; next choice, gas-oxygen.

Pleurisy.—Because of our adoption of infarction as a class of pulmonary complication we find that the simple pleurisy class is very small. However, it seemed wisest that the embolic lesions resulting in symp-

toms that chiefly resemble pleurisy should be grouped with those larger lesions that sometimes resemble pneumonia. We have, therefore, only classified two cases this year as pleurisy. These are both of the serous type and due to direct extension of infection from intra-abdominal disease.[50] One case occurred in a case of splenic abscess and one in a case of high retrocecal appendix. At a late period during convalescence respiratory pain led to a chest examination with the subsequent finding of a straw colored fluid in both cases. In one organisms (streptococcus) were present and the chest was repeatedly aspirated. Both patients made good recoveries and were discharged well.

The etiology of such cases is manifestly direct extension through the diaphragm. The work of Sabin [49] and Miller [51] demonstrates the avenues along which such extension may occur.

Empyema.—One case of postoperative empyema occurred. The case was one of cholelithiasis (common-duct stone) in a man, aged 72. Apparently because of insufficient local resistance an abscess developed in the field of operation, gravitated down to the kidney and then spread upward until a large subphrenic abscess formed. This finally ruptured into the pleural cavity. The mechanism of the etiology in this case is exactly that causing serous pleurisy, only more obvious and direct. It needs no explanation.

Pulmonary Infarction.—We have placed thirty-two of the total sixty-three complications in this group. The great relative size of this group needs explanation for it is somewhat of a diversion from the accepted classification of postoperative pulmonary disease. To all, however, who are familiar with the difficulties of such classifications, this group will be well understood.

In the past there have been many excellent papers on the embolic origin of these complications. In most of such these lesions of embolic origin, unless fatal, have been termed pneumonia. There have remained, however, certain minor lesions, quite evidently of the same origin, which have been designated pleurisy, and further, certain of the other classes of complication, as empyema and lung abscess, have been known to be embolic in origin. We have long felt that the present method of classification was unsatisfactory. Evidently, such lesions are not a true pneumonia, and, furthermore, there were many borderline cases which we found the greatest difficulty in classifying as either pneumonia or pleurisy. Morever, as will be shown later, these cases form a group with a rather typical clinical picture. The onset is usually abrupt, the physical signs are characteristic, and the subsidence is sudden, except when the emboli have arisen in a septic field. As discussed above under pneumonia, sepsis in the wound obscures the onset, the typical picture and the subsidence of such lesions. When septic emboli

are present, the clinical picture may simulate pneumonia or lung abscess may result, but when the clot is sterile, the resultant changes are characteristic of minor pulmonary infarction.

There are no fatalities in these thirty-two cases. All ages and both sexes are included. All but seven cases were laparotomies. The other operations were one each for varicose veins, cancer of the tongue, cancer of the breast, urethral stricture, tonsillectomy and two cranial explorations. Anesthetic: procain, once; gas-oxygen, seven times; ether, twenty-four times.

The clinical picture of all cases bears a close relationship. The onset may occur from the second day to the third week, usually with sudden pain on respiration, followed by expectoration in about one-half the cases. The sputum is often blood tinged. Preceding the onset of symptoms there is usually a rise in pulse, temperature and respirations, and with the pain these may increase. Immediate auscultation of the chest reveals one or more small areas filled with fine râles over which there is some impairment of breath sounds and, if the focus is sufficiently large, some change in fremitus. When pain is present a friction rub may be the most distinct sign. However, it must be remembered that although this is a characteristic sign when present it is so only because it creates pain and thereby directs attention to that part. A friction rub results only when the area of the infarct reaches the periphery of a lobe, and it must be understood if we are to recognize all these lesions, that some of the smaller thrombi do not cause sufficiently large infarcts to do this.

We have long felt that infarction can occur early or even immediately on recovery from operation. Cases have been observed in which characteristic signs were present on recovery from ether with chest pain, friction rub, bloody sputum and a demonstrable area of consolidation both by physical signs and the roentgen ray. In this year's series the onset in twenty-one of the thirty-two cases was within the first four days and in six cases it was within twenty-four hours.

Roentgen-ray studies should always be made and are often of the greatest value. Invariably they will demonstrate small areas of consolidation which from time to time will take the form of a cone-shaped shadow with its base out. Roentgen-ray studies, morever, should be made immediately, since these lesions chiefly represent merely a change in blood distribution and soon clear up. The adjustment to normal is complete, as a rule, within six or seven days.

In order to demonstrate more completely our conception of these lesions, the following cases with their charts and roentgen-ray studies are presented.

REPORT OF CASES

Case 1 (P. B. B. H. Surg. No. 13020).—J. B., aged 25, single.

Diagnosis.—Right indirect inguinal hernia.

Operation.—Aug. 25, 1920, procain, 1 per cent.; Dr. Cutler. On the first day after operation the patient complained of severe pain in his back; his temperature kept rising and there was evident respiratory difficulty. Morphin and digitalis were administered to control pain and coughing. Examination of the

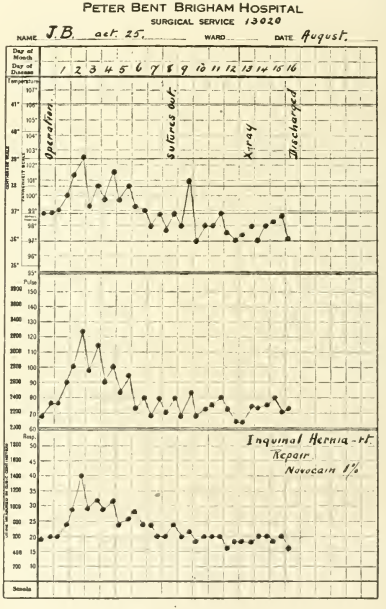


Fig. 1.—Case 1. Clinical chart.

chest showed small areas in both lungs in which there was slight dulness, increased voice sounds and a few râles with some increase in tactile fremitus. Within ten days these signs had all disappeared. Unfortunately no roentgen-ray studies were made until the twelfth day postoperative but even as late as that a subsiding bronchopneumonic process in the right lower lobe was demonstrable. Discharged well (Figs. 1 and 2).

This case was unusually severe. It is presented because of its immediate occurrence following operation. That emboli can actually take place during operation we feel satisfied and have known a patient to come out of the anesthetic with chest pain, a demonstrable friction rub and spitting up blood tinged sputum. The rough use of retractors surely could endanger a patient to this extent.

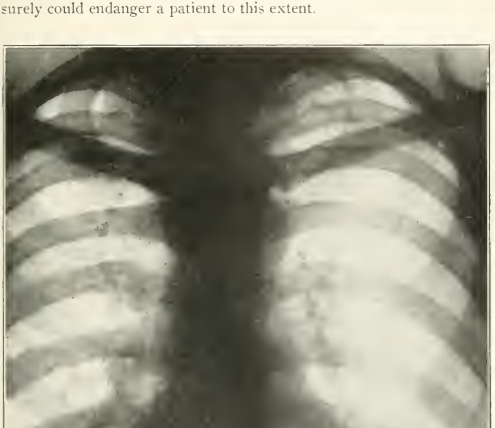


Fig. 2.—Case 1. Chest plate.

Case 2 (P. B. B. H. Surg. No. 13387).—A. H. McM., aged 33, married.

Diagnosis.—Varix femoral vein.

Operation.—Exploration, Oct. 16, 1920; ether; Dr. Homans. Convalescence normal until the eighth day after operation when the patient complained of a slight cough, and there was a beginning rise in pulse, temperature and respirations. Examination of the chest revealed a small patch of impaired resonance, bronchovesicular breathing and râles in the back on the left side below the angle of the scapula. Within ten days all these signs had subsided, but a roentgen-ray examination made on the seventeenth day after operation showed a spotty consolidation in the left upper and lower lobes. Discharged well (Figs. 3 and 4).

In this case, a sudden lesion appeared in a healthy young man eight days after a simple incision over the left femoral vein.

Case 3 (P. B. B. H. Surg. No. 13544).—D. D. B., aged 43, married. *Diagnosis.*—Duodenal ulcer.

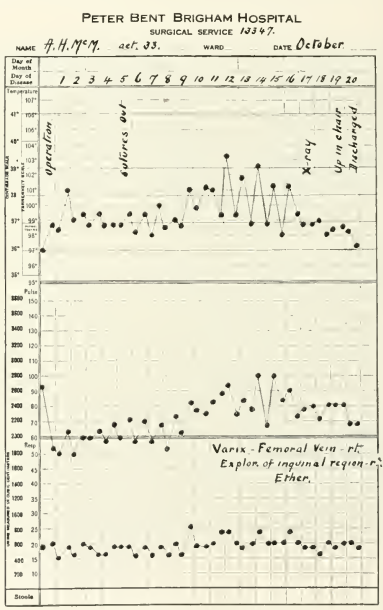


Fig. 3.—Case 2. Clinical chart.

Operation.—Cauterization of ulcer; posterior gastro-enterostomy, Nov. 22, 1920; gas-oxygen-ether; Dr. Cheever. Convalescence undisturbed until the eighth day after operation when the patient complained of pain in the right chest on breathing. Examination showed a friction rub, increased breath sounds and a few râles at the level of the angle of the right scapula. The temperature, respiration and pulse rate began to climb and all physical signs became more marked. There was no sputum. The leukocyte count rose to

15,000. On the eleventh day after operation a roentgen-ray examination showed a definite pneumonic process involving the middle and upper lobes on the right side. The entire picture cleared up in ten days (Figs. 5 and 6).

Case 4 (P. B. B. H. Surg. No. 12932).—E. A. H., aged 48, married.

Diagnosis.—Pyonephrosis in right kidney.

Operation.—Right nephrectomy, Aug. 13, 1920; gas-oxygen; Dr. Quinby. Convalescence uninterrupted until the fifth day postoperative when the patient complained of pain in the right lower chest. Examination of the lungs was

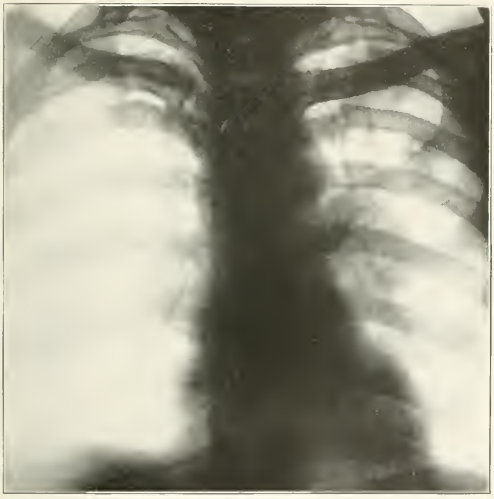


Fig. 4.—Case 2. Chest plate.

negative although there was a slight rise in pulse rate, temperature and respirations. Two days later auscultation revealed rather distant breath sounds and a questionable rub. There also was some limitation in the diaphragmatic excursion and diminished resonance. A roentgen-ray examination on the seventeenth day after operation revealed a resolving pneumonic patch involving the lower right lobe. From this time on improvement was rapid and the patient was free from symptoms and signs when discharged thirty days after operation (Figs. 7 and 8).

The explanation of why kidney operations sometimes result in pulmonary complications on the same side is not clear, except when there is direct extension of an infectious lesion, as when empyema occurs. Is

it possible that the manipulations on that side damage the lung somewhat so as to render it more susceptible to infarction? Or is it merely because pulmonary lesions usually involve the lower lobes? We have seen such complications in the opposite lung from the site of operation.

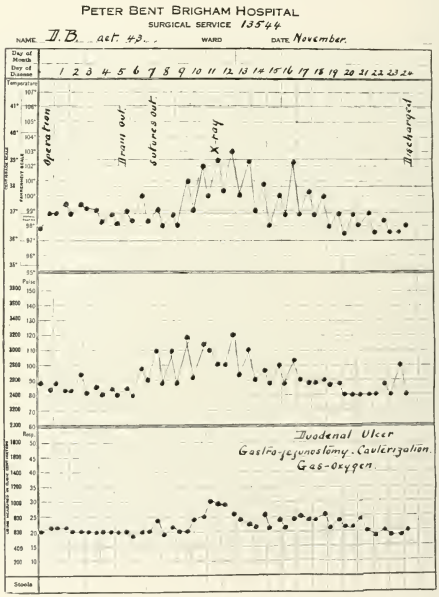


Fig. 5.—Case 3. Clinical chart.

Case 5 (P. B. B. H. Surg. No. 13363).—A. T. S., aged 28, single.

Diagnosis.—Acute appendicitis.

Operation.—Appendicectomy; no drainage, Oct. 18, 1920, ether, Dr. Jameson. Convalescence uninterrupted and unusually clear until the seventh day after operation when the patient complained of sudden severe pain in the right side of the chest and within a few hours he expectorated some bright blood-stained sputum. The temperature rose somewhat and respirations climbed markedly. Examination of the chest revealed a small patch behind the angle

of the scapula in which there were medium moist râles. No other signs were demonstrable and the whole picture subsided in three days. A roentgenogram made on the eleventh day after operation showed an increase in the shadow at the hilum on the right side and a little fluid at the base of the right lung. The patient was discharged well on the fifteenth day (Figs. 9 and 10).

This case presents a more ideal picture of this group as a whole than the preceding ones. All the cases, however, present different aspects, and include operations under the chief anesthetics.

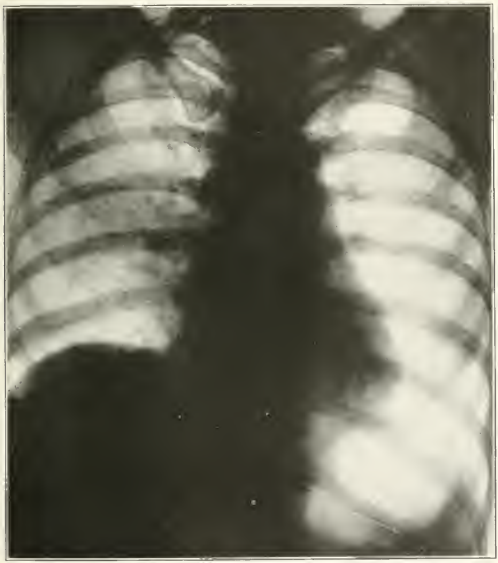


Fig. 6.—Case 3. Chest plate.

Pulmonary Embolism.—There are two fatal cases of pulmonary embolism in this year's series. A man, aged 67, operated on for prostatic hypertrophy, died on the third day after operation; a woman, aged 55, operated on for ulcer of the stomach, died on the twenty-third day, three days after getting out of bed. A necropsy was held in both

cases, and the emboli were demonstrable in the pulmonary arteries. There is no need for any discussion concerning this frightful complication. We would, however, like to call to mind that granted that such large emboli occur, the mechanism for the manufacture of smaller ones must be the same and probably they occur with far greater frequency than in the large ones.

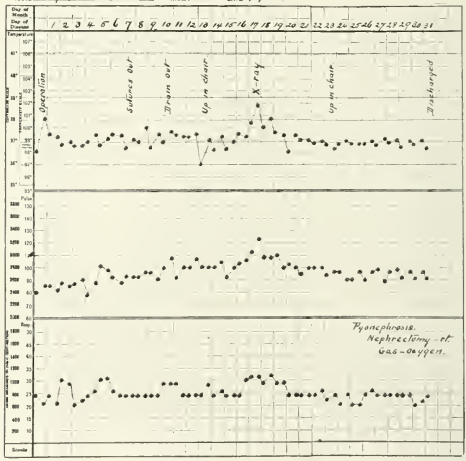


Fig. 7.—Case 4. Clinical chart.

DISCUSSION

The material presented would appear to indicate that a large proportion of postoperative pulmonary complications are caused by embolism from the operative field. This opinion, which we have previously attempted to substantiate [1b] is in agreement with a large proportion of the studies in this field.[7a] It is, however, by no means generally accepted and curiously enough not by the anesthetists whom it attempts to defend! Preexistent pulmonary disease appears to be the

77. Consult introduction and review of the literature cited.

next most important factor. Such lesions are usually brought to activity through the irritation of an inhalation anesthetic and result in bronchitis or pneumonia. It is only in this type of case that the anesthesia has been proven at fault. The presence of sepsis in the operative field and the location of the operation are often important secondary factors. They do not, however, offer an explanation as to the mechanism by

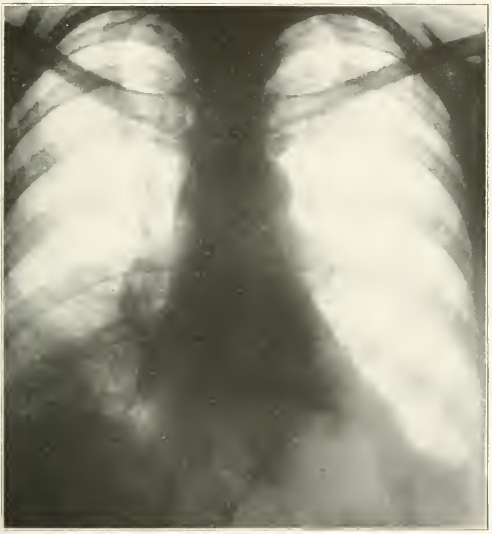


Fig. 8.—Case 4. Chest plate.

which the lung is injured. The further secondary factors of chilling, acidosis and seasonal incidence bear a varying relation in each case.

The arguments favoring embolism are: (1) the typical clinical picture, with sudden onset, focal signs, and, unless sepsis is present, rapid subsidence; (2) the fact that these complications occur frequently with local anesthesia; and (3) that they occur in a definite proportion according to anatomic divisions, these divisions being those kept in

greatest mobility and giving easy access by blood and lymphatic channels to the lung.[74] In favor of inhalation irritation is (1) the evidence that aspiration into the lung of the mouth contents does occur during anesthesia; (2) that Group IV pneumococcus, a common mouth inhab-

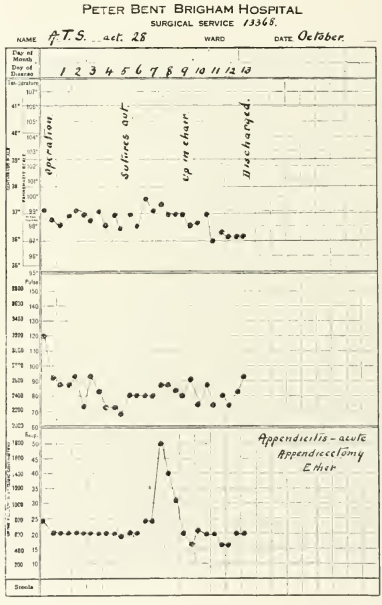


Fig. 9.—Case 5. Clinical chart.

itant, is most frequently found in these cases and (3) the many reports, including our own, that in certain cases with a pre-existing pulmonary disease inhalation anesthesia seems to have caused a flare-up of such a lesion.

74. Mandl, F.: Postoperative Lung Complications, Wien. klin. Wchnschr. **34**:214 (April 28) 1921.

Although under anesthesia the aspiration to the lung of mouth content undoubtedly occurs, there is no great proof that it effects any great pathology. All surgeons will recall execrable anesthesias with blue, coughing, vomiting patients. And yet, in how many such cases did pulmonary complication develop? If this were the chief factor, why is it that with the increasing perfection of the technic of anesthesia such complications continue to be found? And what is the explanation

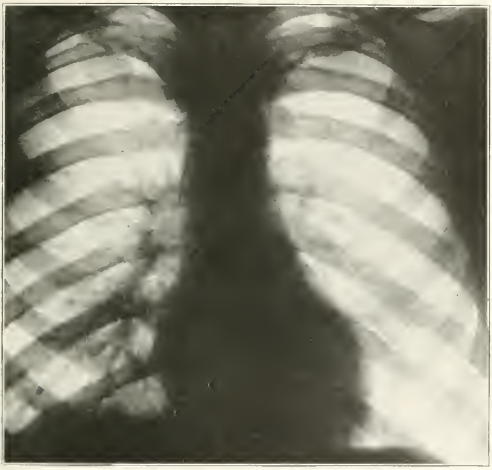


Fig. 10.—Case 5. Chest plate.

for those cases occurring with local anesthesia? That Group IV pneumococcus is found in the sputum in such cases is no proof that a true pneumonia has occurred for it has been shown that many normal mouths harbor this organism. Morever, the enormous volume of experimental pneumonia work does not reveal much success with inhalation infection except with doses so large that the conditions are not comparable to what might actually occur. Blake and Cecil's work on monkeys stands out almost alone, for the successful production of

pneumonia with small doses. Those who would blame inhalation anesthesia must bring more evidence to substantiate their hypothesis.

Of the sixty-three cases with complications reported in this series, only thirteen gave evidence of a pre-existing pulmonary lesion. Moreover, control roentgen-ray studies demonstrated that many persons with such lesions take inhalation anesthesia without any bad effects, whereas in more than 50 per cent. of the reported cases a typical picture of mild pulmonary infarction is presented.

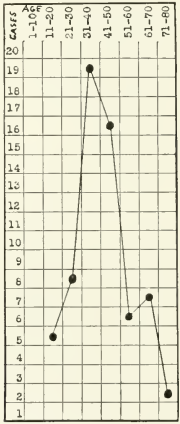


Fig. 11.—Incidence of postoperative pulmonary complications by decades.

Against the influence inhalation anesthesia may have in the production of these lesions are the facts, (1) that they occur equally when the anesthesia is in the most skillful hands; (2) that they occur with local anesthesia and, (3) that they occur in a greater relation to the mobility of the part than can be explained on any irritation hypothesis. With irritation, the presence of Group IV pneumococcus and a pre-existing pulmonary lesion one might expect a lobar distribution were this the true mechanism of these complications whereas lobar pneumonia proved to be a rare lesion in this study.

The part that the predisposing, accessory and secondary factors play is not clear. Chilling can be ruled out in a well ordered clinic.[75] The production of a real acidosis is still under dispute. If it does exist we might expect some lowering of the resistance to infection.[76] That the majority of the complications have occurred during the middle decade when individual resistance is at its best is not in keeping with this theory.

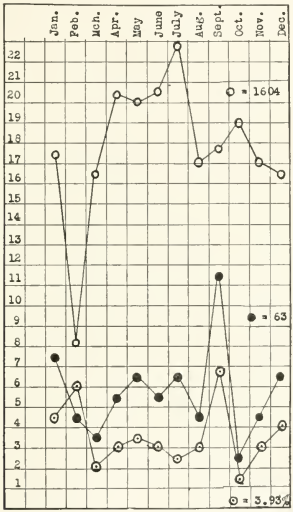


Fig. 12.—Seasonal variations in postoperative pulmonary complications: open circle, number of operations per month (the number at the side should be multiplied by 10); solid circle, number of pulmonary complications per month; circle and dot, percentage of pulmonary complications per month.

In a previous study [1b] the material presented demonstrated the great frequency of such complications with abdominal operations and the

75. Mandl [74] reports that during the winter 1919-1920 in Hochenegg's clinic in Vienna no coal was available and that the percentage of postoperative complications increased markedly. Such complications, however, do occur in the most luxuriously appointed clinics.

76. Hamburger, H. J.: Researches on Phagocytosis, Brit. M. J. **1**:37, 1916.

cases this year bear out the general comparison. The incidence in this restricted field has been so striking that there have been many excellent studies concerning it. Table 3 demonstrates the number of complications in relation to the field of operation.

TABLE 3.—Complications in Relation to Field of Operation

Operative Field	Lobar Pneumonia	Broncho-Pneumonia	Pulmonary infarction	Bronchitis	Pleurisy	Empyema	Pulmonary Embolism	Exacerbation of tuberculosis	Totals
Cranium	..	1	2	..	..	..	..	..	3
Breast	..	..	1	1	..	..	..	..	2
Kidney	..	1	2	2	..	..	..	..	5
Upper abdomen	..	1	4	5	1	1	1	..	13
Lower abdomen:									
1. General	..	3	3	..	..	1	.	1	8
2. Inguinal hernia	1	..	6	4	..	..	..	..	11
3. Pelvis	..	1	7	2	..	..	..	..	10
4. Bladder (prostate)	..	..	1	..	..	..	1	..	2
Perineum	..	..	1	..	..	..	..	..	1
Scrotum	..	..	..	1	..	..	..	..	1
Lower extremity	..	..	..	1	..	..	..	..	1
Varicose veins	..	..	3	..	..	..	..	..	3
Mouth	..	..	2	..	..	..	..	..	2
Neck	..	..	..	..	..	..	..	1	1
Total									63

This table demonstrates again that the preponderance of such complications follow abdominal operations. In this series forty-three of the sixty-three cases followed celiotomy (68 per cent.). Casually, it might not appear that infarction would be more common with abdominal operations and yet there are certainly several reasons favoring this. The anatomic studies of Sabin have demonstrated the free lymphatic drainage. But what of the blood supply? A large part of the intra-abdominal vascular tree drains to the portal system and must be excluded. The generally accepted higher incidence of such complications with epigastric lesions led us to believe that it was the incision in the abdominal wall itself which was most important, and the fact that this year two patients on whom an exploratory laparotomy was performed developed typical infarcts would seem to uphold this. The greater mobility of the parts due to respiratory movements is the direct cause for setting free the emboli, and the use of retractors, often used with great force in laparotomies, is an added danger. Furthermore, it has appeared that when great gentleness in traction was exerted and where perfect hemostasis and accurate closure was practised the incidence has been lessened. It is, however, quite possible, as we have previously indicated, that by the transfer of particles through the larger lymphatics pulmonary changes resulting in the signs of infarction occur. Mandl [74] reports that pulmonary complications in 1,379 laparotomies reached 14.5 per cent., whereas 1,585 operations elsewhere yielded 8.5 per cent. complications. These figures are higher than our own but are relatively the same.

PETER BENT BRIGHAM HOSPITAL
ANAESTHESIA CHART

A

Name ..... Ward ..... Age ..... Date of Operation .....

Lungs ..... Heart .....

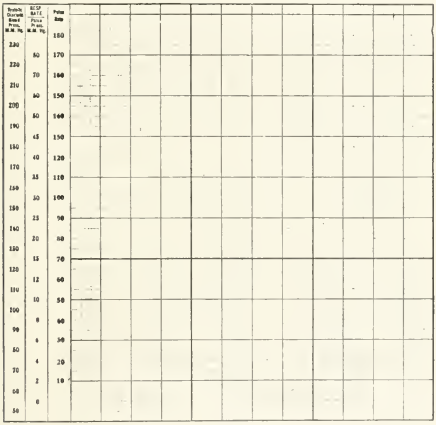
Urine ..... Blood Pressure ..... Rectal Temperature .....

Operator ..... 1st Assist ..... Preliminary Drugs .....

Operation ..... Anaesthetic ..... Amount .....

..... Method of Administration .....

Time of starting anaesth., beginning of op., removal of anaesth., and close of op. to be recorded on chart.



CODE:—● PULSE RATE; ○ RESPIRATION RATE; V SYSTOLIC AND DIASTOLIC BLOOD PRESS; X PULSE PRESS.

Induction:—.....

Subsequent anaesthesia:—.....

.....

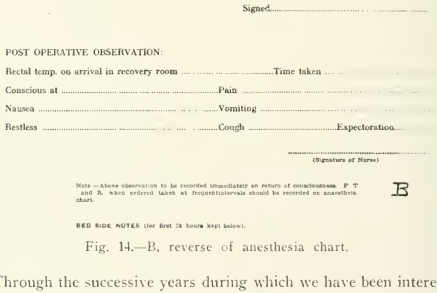
Condition on leaving operating room:—.....

.....

Drains ..... Anaesthetist .....

Fig. 13.—A, front of chart used to record progress of anesthesia.

In the material presented this year there are no cases in which we feel that aspiration or irritation due to the anesthetic was the chief causal element, except in those cases in which a pre-existing pulmonary lesion had been demonstrated. Thus, in the bronchitis and tuberculosis group there is no doubt that the inhalation anesthetic is to be blamed in many of the cases, but certainly not in all, for these complications also occurred with local anesthesia. And, moreover, a routine series of pre-operative and postoperative chest plates demonstrated the roentgen-ray evidence of pre-existing disease in which sometimes no change occurred after operation under inhalation anesthesia.



Post Operative Orders: .....

Signed.....

POST OPERATIVE OBSERVATION:

Rectal temp. on arrival in recovery room .....Time taken .....

Conscious at .....Pain .....

Nausea .....Vomiting .....

Restless .....Cough .....Expectoration.....

(Signature of Nurse)

Note.—Above observation to be recorded immediately on return of consciousness. P. T. and R. when ordered taken at frequent intervals should be recorded on anaesthesia chart.

B

BED SIDE NOTES (for first 24 hours kept below).

Fig. 14.—B, reverse of anesthesia chart.

Through the successive years during which we have been interested in this subject the roentgen ray has steadily proved an increasingly valuable and reliable adjunct to accurate diagnosis. The opportunities to put it to more extensive use during 1920 have not only enabled us to make more accurate diagnoses and to pick up doubtful cases but have given us a greater insight into pulmonary conditions and, in particular, the frequency, type and reaction to inhalation anesthesia of such pre-existing foci of pulmonary disease. These studies have proved to our satisfaction that without such controls the classification and study of these complications is difficult and incomplete.

A study of the distribution of the complications resulting from infarction, embolism and pneumonia, shows twenty-five situated in the base of the right lung, eleven in the base of the left lung and six bilateral. If the lesions were irritative and infectious, it is unusual

that involvement of the upper lobes never occurred. Welch states that pulmonary infarction is most common in the lower lobes, more frequently right than left.

Figure 11 demonstrates the incidence of pulmonary complications by decades. Figure 12 shows the seasonal variations and Table 4 shows the types of complications in relation to the various anesthetics. There is little to be said about any of these findings. Obviously the majority of complications occur in the fourth decade as the majority of patients are that age. It should be remembered that pneumonias of either type are more frequent in the first two decades and the fifth decade (Osler and Macrae[77]). The seasonal chart shows no striking segregation in relation to climatic conditions. Table 4 shows that about one half as many cases received gas-oxygen as ether. This alone, however, is not convincing since obviously those with pre-existing pul-

TABLE 4.—Anesthetics Used in Various Complications

Complications	Ether	Gas-Oxygen and Ether	Gas-Oxygen	Procain	Totals
Lobar pneumonia	0	0	0	1	1
Bronchopneumonia	4	1	2	0	7
Bronchitis	11	0	5	0	16
Exacerbation of tuberculosis	1	0	1	0	2
Pleurisy	0	0	2	0	2
Empyema	1	0	0	0	1
Infarction	24	0	7	1	32
Pulmonary embolism	0	0	2	0	2
Totals	41	1	19	2	63

monary signs were usually given gas-oxygen. That only two complications occurred with procain is exceptional although not far from proportionate to the total use of this anesthetic in this clinic and the fact that local anesthesia is rarely used in abdominal operations excludes this added predisposing factor in the local anesthesia cases reported. Of the total 1,604 operations, 875 were performed under ether, 546 under gas-oxygen, 179 under procain, 2 under chloroform and in two cases no anesthesia was used. The morbidity percentage is 4.6 per cent. for ether, 3.5 per cent. for gas-oxygen and 1.1 per cent. for procain.

The difficulties of assembling accurate data have been somewhat mitigated by the use of the chart shown in Figures 13 and 14 which is reproduced in the hope that the few clinics which have not as yet adopted some such form may be led to use one. We have found the data contained on this chart of the greatest value—(1) in ensuring a careful anesthesia, and (2) for all kinds of follow-up work and case studies. It has the great value of providing the anesthetists with sufficient work so that their attention is never side-tracked to the operation or to other activities in their proximity.

77. Osler, W., and Macrae, T.: Lobar Pneumonia, Mod. Med. **1**:202, 1913.

As a further postoperative protection all patients are kept on the operating room floor, in separate recovery rooms and under constant observation until fully conscious. This does away with the possible danger which may come from transporting unconscious patients through draughty corridors and from the more active risk of reaching a short-handed ward where they cannot be under constant observation during the period of recovery.

The condition known as massive collapse of the lung first described by Sir John Bradford [78] has recently through the papers of Scrimger [79] been brought into the category of postoperative pulmonary complications. In Scrimger's last paper he reports seven such cases in 540 operations. The routine anesthetic of chloroform-ether is used. His patients soon after operation developed sudden respiratory distress, pain and cough. Roentgen-ray studies revealed marked displacement of the heart to the affected side. Recovery usually occurred within twenty-four hours. The etiology of this condition is not known, possibly it is due to inhibition of the diaphragm or to vagal influences causing contraction of the muscular elements of the lung. Mortimer [80] places great stress on respiratory movements and states that the lower lobes may collapse when movements of the diaphragm are restricted either by pain or bandages. This condition deserves greater study and necessitates control roentgenograms. It has not been observed in this clinic.[81]

SUMMARY AND CONCLUSIONS

Postoperative pulmonary complications are due in the majority of cases to embolism from the operative field. The result is pulmonary infarction or fatal pulmonary embolism. The latter is a rapidly fatal, well recognized clinical picture. The former is caused by the transmission to the lung of a small thrombus or many thrombi with resultant characteristic clinical picture. This consists of sudden pain, expectoration, often blood tinged, the elevation of respiration and pulse rates and temperature, and the signs of a focal consolidation often overlaid by a friction rub. These patches are demonstrable by the roentgen ray, provided such studies are made at once. There usually follows rapid defervescence and the subsidence of all symptoms within a week.

78. Bradford, Sir J. R.: Massive Collapse of the Lung, Oxford Medicine, New York, and Oxford University Press **2**:127, 1920.

79. Scrimger, F. A. C.: Postoperative Massive Collapse of the Lung, Surg., Gynec. & Obst. **32**:486, 1921.

80. Mortimer, J. D.: Med. Press & Circ. **108**:505, 1919.

81. Schultze, E. C.: A Report of Twenty-Seven Cases of Pneumonia Following the Inhalation of Ether and Chloroform, Med. & Surg. Rep. Presbyterian Hospital, N. Y. (Jan.) 1898, p. 311.

The causes of infarction are (1) trauma; (2) the mobility of the part; (3) sepsis. The prognosis in this group is excellent.

Irritation and aspiration due to inhalation anesthesia may be the cause of a small percentage of postoperative pulmonary complications. These usually fall into the bronchitis or pneumonia groups. Inhalation anesthesia rarely results in such lesions unless there is present a pre-existing pulmonary disease such as a chronic bronchitis, incipient tuberculosis or a definite tendency towards pulmonary disease.

The fact that these complications occur with local anesthesia, with inhalation anesthesia in the most expert hands and in a definite relation to the mobility of the operative field is taken as evidence against the importance of the irritation of inhalation anesthesia in the production of these lesions.

Anesthetists and anesthesia should not bear the blame for these complications.

There is as yet no proof or evidence that chilling or acidosis plays any appreciable rôle in this field.

A reduction in the number of cases that result in these complications can be had by (1) a reduction in trauma at operation; (2) accurate hemostasis; (3) the careful control of sepsis and (4) the use of great caution in operating upon patients who have demonstrable pulmonary disease. A high fluid intake and all general precautions giving assistance to the circulatory apparatus will be of definite value once such complications are established.

We are greatly indebted to Dr. Lawrence Reynolds, roentgenologist of the Peter Bent Brigham Hospital, for his excellent plates, fluoroscopic studies and cooperation.

THE PATHOLOGY OF CIRRHOSIS OF THE LIVER

AN HISTORIC-PATHOLOGIC STUDY

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Cirrhosis of the liver is a chronic, recurring, probably focal, possibly diffuse degeneration or necrosis of the parenchymatous cells of the liver, modified by concurrent and intercurrent periods of regenerative proliferation of the parenchyma, with connective tissue replacement of destroyed areas. Acceptance of this definition and any concept that cirrhosis of the liver is a disease entity are incompatible. The granular liver, with its associated splenic tumor and portal stasis, is as surely a consequence of some preceding disease as the cyanotic induration of the liver and lungs and edema are the consequences of chronic valvular heart disease. That disease is the degeneration or necrosis of the liver cells, a process, the clinical manifestations of which are as yet unknown.

The question arises: Are we concerned with a single disease resulting in this picture, or are there many entirely different processes which eventuate in the same ultimate anatomic picture? Further, and perhaps more important, is the question whether the primary disease has its seat in the liver, or whether that organ is involved only secondarily or in association with some other organ, as for example, the spleen. The varying clinical pictures under which cirrhosis may manifest itself, particularly with reference to its onset, and still more, its etiology, makes it seem reasonable to assume that the end-result called cirrhosis of the liver can be produced by a variety of primary clinical processes. Accepting its association with other diseases, the second question may be reasonably assumed to be correctly answered when it is stated that it may be primary in the liver or may be secondary to (or associated with) disease in some other organ. Of course, this statement might, with equal accuracy, be made the other way around, namely, that this pathologic picture may exist alone or it may produce lesions in other organs. Perhaps, both are true. For example, it might be secondary to changes in the spleen in Banti's disease, while the brain lesion in Wilson's disease might be dependent on the liver pathology.

ETIOLOGY

The intimate relationship of the etiology and pathogenesis of cirrhosis is sufficient reason for a brief resumé of the usual etiologic factors concerned in Laennec's cirrhosis, especially since this relationship is here particularly interesting and apparently insoluble.

The term "alcoholic cirrhosis" applied so universally to the hobnail liver characteristic of Laennec's cirrhosis is not altogether justifiable. Alcohol is undoubtedly closely associated etiologically with the great majority of cases; and that alcohol alone can produce the disease has apparently been proved experimentally by many workers. Grover [1] published the most recent work on experimental alcoholic cirrhosis, and has made an admirable collection of the literature. He concludes that alcohol given to experimental animals over a long period of time can produce a degeneration of liver cells followed by connective tissue proliferation. He concedes that other processes may be associated, but, if so, their nature is so obscure that their modus operandi is not known. Saltykow [2] produced cirrhosis of the liver by injecting alcohol into the ear vein of rabbits. Fahr [3] and Schäfer [4] were successful in similar experiments. Kyrle and Schopper [5] produced parenchymatous changes and fatty degeneration in all cases of repeated introduction of alcohol by intravenous, subcutaneous and gastric routes. In seven cases there was necrosis of portions of the lobule and replacement fibrosis; in fourteen cases there was round-cell infiltration in the portal fields, and in seven others, there was connective tissue proliferation with bile duct formation. The livers of three rabbits showed typical Laennec's cirrhosis.

Not all workers, however, were able to produce cirrhosis in experimental animals. Pogenpohl,[6] Klopstock,[7] von Baumgarten [8] and Bischoff [9] were notably unsuccessful. All agreed, however, that alcohol was productive of extensive fatty degeneration.

Lancereaux,[10] who studied the etiology of cirrhosis of the liver for many years, concluded that cirrhosis could be produced by substances used as preservatives and to give certain wines an especially "dry" flavor. He had particular reference to potassium bisulphate with which salt he was able to produce Laennec's cirrhosis by feeding it to animals.

MacCallum, in his last textbook (1916), is very emphatic that it has not been demonstrated experimentally that alcohol produces cirrhosis. If a large number of chronic alcohol addicts be studied, only a very few will be found to suffer from cirrhosis. He states that all sorts of degenerations may take place, both in experimental alcoholism

1. Grover: Arch. Int. Med. **17**:193 (Feb.) 1916.
2. Saltykow: Verhandl. d. deutsch. patholog. Gesellsch. **15**:228, 1910; Zentralbl. f. allg. Path. u. path. Anat. **22**: 1910.
3. Fahr: Virchows Arch. f. path. Anat. **217**:397, 1911.
4. Schäfer: Virchows Arch. f. path. Anat. **215**: 1913.
5. Kyrle and Schopper: Virchows Arch. f. path. Anat. **215**:359, 1913.
6. Pogenpohl: Virchows Arch. f. path. Anat. **116**:466, 1909.
7. Klopstock: Berl. klin. Wchnschr. **47**:1532, 1910.
8. Von Baumgarten: Verhandl. d. Deutsch. path. Gesell., 1907.
9. Bischoff: Ztschr. f. Exper. Path. u. Therap. **11**:445, 1912.
10. Lancereaux: Bull. de l'Acad. de méd. Par. **74**:15, 1910.

in animals and overindulgence in man. Since MacCallum has been one of the particularly deep students of cirrhosis, his statements are of especial value. He calls attention to the work of Longcope, who has produced changes very closely resembling cirrhosis of the liver by the injection of proteins and by other experiments suggesting some form of protein sensitization or intoxication as the best explanation. MacCallum's ultimate conclusions are, that what we see as cirrhosis at the necropsy table is scar tissue and efforts at regeneration and that there are many processes which can lead to them.

These observations greatly accentuate the difficulty of establishing a clear-cut pathogenesis, particularly if one tries to accept the theory that cirrhosis of the liver is essentially secondary to some toxic process in the portal zone.

There are, however, so many etiologic factors other than alcoholism operative that this is only the beginning of confusion. Warthin recently, before the Portland Academy of Medicine, expressed the belief that some day it would or might be proved that cirrhosis was the result of the joint action of syphilis and alcohol. At that time he stated that he had demonstrated *Spirochaetae pallidae* in two such livers examined. Syphilis as an etiologic factor was the subject of a recent paper by Symmers.[11]

Malaria is immediately suspected in malarial districts. This may be a relic of the days of pure empiric medicine; the enlarged spleen of both diseases furnishing the empiric resemblance. However, malaria has not yet been entirely swept from the paragraphs on etiology, even in relatively recent articles.

The outstanding objection to alcoholism as the only etiologic factor is that we see so many cases in which there is not the slightest suspicion of alcoholic abuse. Indeed, the patient from whom the liver presented was taken, was a total abstainer, and so it is in many other case histories. It will be interesting to note whether the present prohibition law will cause this disease to diminish, or whether, in the perversity of things, the illicit brews and distillations, at present so frequently heard of, will actually continue to be a factor. Perhaps, their vicious nature and impurities will lead to a greater morbidity with reference to cirrhosis among drinkers than ever before.

Recently Miller,[12] in discussing this question, published figures which show a definite decrease in the admission of cases of cirrhosis of the liver to Cook County Hospital since prohibition went into effect July 1, 1919. He feels, however, that some of the reduction in the number of cases admitted to the hospital may have been due to the influenza epidemic raging at that time, during which the hospital was

11. Symmers: Internat. Clin. **1**:58, 1917.
12. Miller: J. A. M. A. **76**:1646 (June 19) 1921.

closed to all but acute cases. More time must elapse and illicit vending be better controlled before the effect of prohibition can be estimated accurately.

It is possible that a particular type or degree of gastro-enteritis must be produced by alcoholism before cirrhosis can develop. On this basis we can also explain those cases in which alcohol was not indulged in, on the assumption that an identical or very similar gastro-enteritis is produced by other etiologic factors, for example, the custom of pepper and curry eating in India. Cirrhosis then follows as it does after that of alcoholism. It does not, however, explain those cases of experimental cirrhosis in which alcohol was administered subcutaneously and intravenously.

As in all chronic degenerative diseases, infection is being spoken of more and more in recent literature as a possible etiologic factor in cirrhosis, and there is much to commend this hypothesis. In searching the literature we found this etiology mentioned by Raoul Gaston [13] as early as 1893. He believed that he had established an infections origin for some cases which followed prolonged infectious diseases. His interpretation was that an inflammatory infiltration had occurred about the radicals of the portal vein, and thus precipitated the disease. It is to be noted that at that time the disease was believed to be primary in the connective tissue.

The etiology of no chronic degenerative disease would be complete unless some mention be made of chronic metabolic or digestive toxicoses. They are visionary, indeed, and yet possess an alluring appeal in so many diseases, and especially in connection with cirrhosis, that they cannot be dismissed entirely, theoretical though they be at present. Particularly appealing is the assumption that the poison responsible for this disease may be produced in the spleen.

Tabulate the clinical types of Laennec's cirrhosis and the all-comprising single etiologic factor at once disappears.

1. *Laennec's Cirrhosis in Topers.*—These are so predominant in numbers that alcohol becomes overwhelmingly the greatest single factor.

2. *Laennec's Cirrhosis, Where Alcoholism Clearly Was Not a Factor.*—The etiology of these cases is entirely unknown. They are not so rare as is generally assumed, and are most common in women and children.

3. *Banti's Disease.*—By definition Banti described this as a certain type of anaemia, plus Laennec's cirrhosis and splenomegaly in which the etiology must be unknown. If the victim of this disease is a chronic alcoholic Banti's disease may not be used as a designation.

13. Gaston, Raoul: Thésé de Par., Du Foie Infectieux, Paris, 1893.

4. *Diabéte Bronzé; Cirrhose Pigmentaire.*—Clearly this is a definite clinical entity. It is perhaps an event in the course of some other disease, but for that matter the same may be said of Banti's disease.

5. *Progressive Lenticular Degeneration* (commonly called Wilson's disease [14]). Here we have a rare familial nervous disease occurring during the years of adolescence in individuals who are not addicted to alcoholic excess, frequently not even to occasional indulgence. The etiology is entirely unknown.

Cirrhosis is occasionally found by surgeons unrelated to the condition which called for the operation and apparently of no immediate clinical importance.[15] So, too, it is often accidentally found at necropsy, apparently not the cause of death nor even contributory. However, some caution should be exercised in brushing aside a cirrhosis of the liver as an "accidental finding" at necropsy. This is exactly what occurred in the first case of progressive lenticular degeneration found at necropsy at the National Hospital for the Paralyzed and Epileptic in London, only to be resurrected from the archives years later by Wilson, who then properly classified it and placed it in his series reported in Brain in 1912. Howard and Royce [16] narrowly missed making the same mistake in their case. It is just this association with other apparently more important anatomic findings that makes such "accidentally" found cirrhoses interesting and at the same time extremely puzzling.

PATHOGENESIS

The older theories located the origin of the disease in the connective tissue stroma, a chronic interstitial hepatitis. Assuming that the disease was more or less acute in its earlier stages, and that all acute inflammatory processes are associated with edema and hyperemia, the swollen liver of early cases was thus readily explained. As the disease progressed it became more chronic, hence more productive and the cellular elements of the connective tissue proliferated, sooner or later insinuating themselves between the liver cells in the lobule, gradually snaring them off. As the new tissue acquired age it began to contract, reducing the size of the liver simultaneously by contraction and by pinching the liver cells to death, lessened parenchyma meaning lesser volume. In younger individuals the snaring process was likely to take larger bites of tissue, while in older individuals small areas would be surrounded, so the theory stated. Hence we had multilobular and unilobular cirrhoses, both terms now very little used, the former being reserved by some writers for the end-result of syphilitic hepatitis in children.

14. Wilson: Brain **34**:295, 1912.
15. Mayo: J. A. M. A. **70**:136 (May 11) 1918.
16. Howard and Royce: Arch. Int. Med. **24**:497 (Nov. 15) 1919.

This theory of the pathogenesis of the disease did not take into consideration the incongruity of assuming a special connective tissue vulnerability in the liver as compared with that of other parenchymatous organs. No other organ was known to suffer an inflammatory disease in its supporting structures with secondary destruction of the parenchyma. Indeed, it is a well known law that a tissue is vulnerable in direct proportion to its specialization.

Furthermore, pathologists of that day did not understand the regenerative powers of parenchymatous organs and particularly those of the liver. Ponfick [17] was the first pathologist to experiment on the regenerative power of the liver. He found that as much as four-fifths of the liver of dogs could be removed with subsequent regeneration to normal size. Considering that the liver normally has an enormous surplus of tissue as a margin of safety, its regenerative power after experimental extirpations is but another manifestation of its marvelously large margin of safety.

In 1894, Marchand [18] reported a case of acute yellow atrophy terminating in "multiple nodular hyperplasia." The patient, a woman, aged 28, was brought to the hospital moribund, therefore an accurate history was not available. It was ascertained, however, that she had had "catarrhal jaundice" for several months, during part of which time she had a swollen abdomen and legs, and that in the last few days she had become suddenly and seriously ill. The skin was yellowish and there were some small ecchymoses in the conjunctiva.

At the necropsy the liver was found greatly reduced in size, with a hobnail surface, the eminences ranging in size from that of a pea to a cherry. The elevated areas were pale reddish yellow in color, the depressions dark red. On cut section areas of yellowish liver tissue were seen with a reddish structure intervening and predominating, the former elevated, the latter depressed. Acinus markings were not to be seen in the nodules. Marchand gives a critical analysis of the pathologic anatomy and histology of this liver, reaching the conclusion that the process could not be a cirrhosis, because of the nature of the dark red structure between the nodules of liver cells, a technical study that must be read in the original to be appreciated. His conclusion was that he had before him "a liver presenting changes which can leave no doubt that we are dealing with the residua or results of a so-called acute yellow atrophy." He mentions a similar case published by Klebs, which "showed anatomically in extenso the picture of a typical red atrophy of the liver whereas the clinical course of the disease had been that of a chronic, possibly recurrent type of the disease."

17. Ponfick, quoted by Kretz: Verhandl. d. Deutsch. path. Gesellsch. **8**
18. Marchand: Beitr. z. path. Anat. u. z. allg. Path. **17**: 1894.

Marchand's concluding paragraph freely translated, states that we have

> the very unusual example of a yellow atrophic liver which has reached an unusually high degree of regeneration, or better still, reproduction. It is not unlikely that under more favorable circumstances a greater development of regenerative changes could have occurred; never, however, could complete regeneration of structure be attained. If we could imagine the regeneration I have described still further advanced, we would then have the picture of a large lobule cirrhosis of the liver such as we see in childhood.

Meder,[19] his assistant, published six or seven cases very closely resembling Marchand's. MacCallum[20] reports similar changes of a reproductive nature occurring after acute yellow atrophy.[20a]

Kretz[21] was the first to coordinate these facts, namely, the regenerative changes in the liver, as ascertained by Ponfick experimentally and by Marchand pathologically, and the close resemblance of Marchand's and similar cases of the end stages of acute yellow atrophy, on the one hand, with fully developed cirrhosis of the liver on the other. He enunciated the present day conception of the pathogenesis of cirrhosis of the liver, for which MacCallum,[22] the greatest American student of cirrhosis, gives him full credit. Yet Ackerman[23] was the first to express the belief that the disease was primarily a parenchymatous process.

The primary process in cirrhosis of the liver is a parenchymatous change as in actue yellow atrophy, but not so rapid; slowly the parenchyma is destroyed—a little today, a little more tomorrow—inumerable minimal attacks, continuing from onset to termination, with periods of quiescence intervening. While the degeneration and necrosis of cells is progressing, regenerative mitoses are occurring concurrently, at first only among the liver cells, but later the biliary ducts, genetically closely related to liver cells, partake in the effort to replace destroyed liver cells by metaplasia, perhaps after the regenerative powers of the liver cells have become exhausted or cannot maintain the pace set by the advancing disease. Periods of complete quiescence may result in restitution to nearly normal liver sufficiency. Alternating periods of progress

19. Meder: Beitr. z. path. Anat. u. z. allg. Path. **17**: 1894.

20. MacCallum: Johns Hopkins Hosp. Rep. **10**: 1903.

20a. Since this paper was submitted for publication, I found a liver of this type at necropsy in the body of a young man, aged 22. Briefly, the clinical history was that he had had jaundice for five years, which was associated with ascites and edema, marked weakness and frequent bowel movements. The mode of onset could not be determined definitely but was more or less acute. The clinical diagnosis had been chronic pancreatitis. At necropsy a nodular, hyperplastic liver was found. The immediate cause of death was a terminal peritonitis. The case will be reported in full later.

21. Kretz: Wien. klin. Wchnschr. **13**: 1900; u. Ergb. d. allg. Path. **8**: 1904.

22. MacCallum: J. A. M. A. **43**:480 (Sept. 3) 1904.

23. Ackerman: Virchows Arch. f. path. Anat. **115.**

and quiescence may continue for years until finally the patient succumbs or, perhaps, in rare cases the disease may become permanently quiescent while the liver is still capable of meeting the metabolic needs of the individual.

So it is that the parenchyma dies and is replaced by connective tissue, new parenchyma replaces the old and is again destroyed to be replaced by other new parenchyma; constant repetition of destruction and regeneration resulting in a completely rebuilt liver. In advanced cases not the slightest vestige of the original tissue remains; even the circulatory system has been rebuilt.

If we are ever permitted to use comparisons and analogies, it seems justifiable here. So we may think of cirrhosis of the liver as the result of minute attacks of something closely resembling acute yellow atrophy, at least in the nature of its action. Acute yellow atrophy is no more a definite clinical entity than is Laennec's cirrhosis; both may be produced by a variety of causes. One should think of the two diseases as being analogous, one acute, the other chronic, differing only slightly in the nature of the pathologic process, but very markedly in degree. One is always acute and nearly always fatal; the other is chronic and likewise nearly always fatal. Occasionally the patient lives long enough after an attack of acute yellow atrophy to produce regenerative phenomena of sufficient degree to make the liver closely resemble that of the chronic process, in which the patient always lives long enough to excite regeneration.

The origin of the new or regenerated cells appearing in the nodules is manifestly from the surviving liver cells assisted by the bile ducts. The objection sometimes raised that it would be impossible for cells to regenerate in the presence of a circulating noxious agent capable of destroying mature cells is scarcely valid. There are many known instances of such occurrences. The further objection to this belief, that we do not see partially destroyed cells, is not true. We do see them, rarely it is true, but this is a very chronic disease; cellular death is hastened but not to a degree to be a predominating feature easily found in any given slide. The same may be said of another objection sometimes made, that we do not see mitoses. We do see them occasionally, especially early. MacCallum[22] answers this argument by referring to the differences in acute and chronic nephritis. Mitoses are seen in acute nephritis relatively frequently. Regenerative changes are perfectly evident macroscopically and are generally accepted in chronic nephritis but they are not sufficiently in evidence to be discovered microscopically. They are found only in acute cases or acute exacerbations.

This comparison of acute yellow atrophy and cirrhosis at once brings two diseases of obscure origin into close relationship clinically;

indeed, their behavior is often quite similar, except in the matter of time. It serves the further purpose of making the pathogenesis of the chronic form of the two diseases, cirrhosis, quite clear.

MINUTE ANATOMY OF LIVER

As a prerequisite for an understanding of the architecture of the cirrhotic liver, a clear conception of its normal architecture is essential.

Early in intra-uterine life the liver consists of two dense meshworks of capillaries derived from the portal vein and hepatic artery converging into the hepatic vein, within which are embedded the liver cells. Essentially the liver is a radiation of two sets of capillaries arising from a common point, the portal fissure, converging into a second common point, the hepatic vein. Since the liver is usually regarded embryologically as an epithelial bud arising from the primitive foregut, therefore essentially an epithelial structure, an adequate conception of its complicated vascular architecture cannot be obtained. Indeed, it is just this that leads to the usual misconception of the anatomy of the lobule or acinus, described as it is, as a rounded or polyhedral mass of radiating cells with a central vein, surrounded by a connective tissue capsule. There are actually no such glandular lobules in the liver each separate and distinct from its neighbor. The liver is essentially a vascular skeleton in the interstices of which is a mass of cells, just like the flesh on a skeleton. Hence, all parts of the liver tissue are not only in contiguity but in direct continuity with all other parts without complete connective tissue separation or segregation into lobules.

The efferent blood flows into the ultimate hepatic vein through its various collaterals, these branches collecting the blood from different parts of the liver by a system of "continental divides" which makes the separation into lobules or acini as we must understand them. These "continental divides" between acini are theoretically hard and fast divisions but histologically and physiologically they are neither visible nor demonstrable, in fact, they may vary with physiologic necessities. At various points this parenchymatous mass or theoretical lobule is penetrated by branches of the portal vein and hepatic artery, clothed by a thin coat of connective tissue in which are also enclosed the bile ducts. It is the multitudinous, almost ubiquitous, ramifications of these vessels that give the appearance of well defined rounded lobules separated one from the other by connective tissue, since they tend to course along the "continental divides." It is an artefact pure and simple produced by the necessity of making thin cross sections for minute study. What is seen are cross sections of branches of the larger real acinus or lobule, which may or may not contain a branch of the central vein. These cross section lobules are not isolated anatomically one from the other, and still less so physiologically.

Physiologically, the passage across the "continental divide" from one lobule to the other is not marked by any boundary whatever. That which is often seen and usually interpreted as the boundary between lobules is really a "tunnel" or path within which the portal vein and hepatic artery traverse the lobule. Such paths are, however, sometimes really located between lobules because it is a vantage point for the distribution of blood or collection of bile.

In order to have a simple comparison so that the structure of the liver, as a whole, may clearly be visualized in a brief description, it may be regarded as consisting of a vascular skeleton, for the first half of which the lower half of a pine tree is used to represent the hepatic vein and its branches, the pine needles representing the ultimate or so-called central veins of the lobules. If the parenchyma of the liver can be imagined to have been poured into the lower half of the tree, like batter into a mold, filling out all spaces in the interstices between the branches, the best concept of the gross, and at the same time histologic, relationship of the parenchyma to the hepatic vein would be obtained. If one could imagine this artificial, half-finished liver to have been completed by introducing at some point on the upper surface another lower half pine tree so inserted into the original mass that its branches fit and dove-tail between the branches of the original tree, the second representing the portal vein, a reasonably understandable concept of the relations of the hepatic vein, parenchyma and portal vein will be gained. It would, at the same time, permit one to accept the usual concept of the liver lobule or acinus and at the same time shatter it by showing that no lobule is entirely independent and separate from its neighbor. If one could still further imagine these two trees fitted one into the other so accurately that not only the branches would fit between each other, but the needles on the branches of one fit between the needles on the branches of the other, one would have a conception of the intimate relationship of the ultimate branches of portal and hepatic veins.

In order to understand the relationship which the hepatic artery and biliary ducts bear to the whole, one needs to return to the moment when the second half tree was introduced into the half finished liver and imagine a dense net-work of vessels having been wound about the branches of the second half tree, one red to represent the hepatic artery, the other green to represent the biliary ducts.

Obviously a description of this sort is purely artificial and does not consider the embryologic facts, yet it is far more nearly correct than the description given in courses on histologic anatomy, which also clearly ignore the embryology. In fact, most slides for histologic study are derived from the liver of the pig, because it is peculiarly rich in

connective tissue. This makes the so-called lobule or acinus appear especially distinct, particularly for teaching purposes, and erroneous teachings at that.

The plan of building up an acinus about a single unbranched, central (efferent) vein in this manner and using it as an index of a typical lobule, surrounding it with columns of liver cells and then completing the lobule as it were, by pasting the afferent portal vein and hepatic artery on the finished lobule without showing its relationship to its neighbors is irrational and leads to false notions of simplicity. It would seem far better were we taught from the very outset how complicated the structure and relationship of the lobule really are. And yet the behavior of the liver in certain circulatory disturbances, particularly high grades of passive congestion, make it appear that these artificial structures or lobules functionate or behave more or less as structures of some independence.

Mall injected livers through the hepatic vein and after corrosion demonstrated that it branches very freely, that there is no such structure as a separate terminal central vein for each lobule, but rather that the peripheral or terminal branches anastomose freely. Reconstruction of the lobules about these veins produces an exceedingly complicated outline, not at all rounded or polyhedral as is usually taught. Such areas susceptible of apparent demonstration in slides are artefacts, as previously stated, produced by making cross sections of small branches of the lobule. The real lobule is a considerable mass of liver tissue enveloping a radical of the hepatic vein and its branches, penetrated and "tunnelled" by Glisson's capsule with contained vessels and ducts, so that afferent blood is introduced into it at many points. Such a lobule, if torn from its site, would be shaped roughly like an irregular pine tree, or, better still, a misshapen pine tree. It may have some branches or processes extending far afield, it may be bent on itself, or show marked twists or bends. Most important of all it would not "shell out" of a connective tissue capsule, because it has none. Its margins or outer surface would be ragged for there is no sharp demarcation between lobules, therefore, it would be torn from its surroundings. Moreover, its communications with neighboring lobules would be shown by the mouths of gaping veins which had, when in situ, communicated or inosculated with those of nearby lobules. The "water-sheds" between areas of the same lobule tributory to one or another branch of its central vein are imperceptible and unmarked, indeed they may shift depending on secretory and circulatory exigencies. Exactly the same may be said of the greater "continental divides" between distinct lobules.

While this, in its essence, is not fundamentally different from the usual idea, it is of value when the finer pathologic anatomy of the

liver is under consideration, especially when an attempt is made to explain the long strands of passive congestion in the cyanotic liver or the long connective tissue strands of cirrhose cardiaque.

PATHOLOGY

The cirrhotic liver as it is seen at the necropsy presents certain changes, usually a diminution, occasionally an increase, in size, hobnail surface, and increased consistency and stiffness.

Examining the cut surface, three types of tissue, in varying relative quantities are found: (a) normal liver tissue; (b) nodules of liver tissue, lighter in color, varying in size from that of a millet seed to that of a large bean or occasionally a walnut, and (c) connective tissue.

The entire surface has a tawny to brown color, varying with age and degree, which led Laennec to give it the name cirrhosis. This color is produced by a histologic finding of considerable importance to be described later. No particular naked eye changes can be noted in the smaller blood vessels, except that the small dark area in the center of the acinus is entirely absent in the nodules, that is to say, the usual index of the acinus, the central vein, is absent.

Closer study of these nodules shows that they vary in size, are of paler color than normal liver tissue, and that they are likely, on cut section, to be elevated slightly above the level of surrounding structures, be it normal liver or connective tissue. They are not always rounded or oval but may at times show several rounded eminences as though a cluster had been cross sectioned. Examination of these nodules for the position of the efferent lobular (central) vein shows a very wide variation from the normal. It is no longer central but eccentric, often peripheral and occasionally actually beside the nodule, gathering its blood from the body of the nodule by exceedingly fine capillaries, whose walls correspond to Kupfer's cells. This can have but one meaning, namely, asymmetric destructive processes and, as a corollary, asymmetric regenerative processes. The nodules of lighter colored liver tissue, now universally accepted as regenerated liver cells, show a total absence of the acinal markings. The smooth continuity of liver tissue has disappeared; the nodules are isolated one from the other by strands of connective tissue, although clusters are sometimes seen. These clusters are usually regarded as being produced by budding from a parent mass rather than by a confluence of several groups or masses. Sometimes the nodules take up most of the cut surface; at other times almost the whole organ is composed of connective tissue with very small occasional nodules of liver tissue, often stained a deep green (bile stasis).

Further study of the blood vessels in any cross section shows that the larger vessels are closer together than normal. This corresponds to the general reduction in the mass of the liver.

The color of the cut surface is variable depending on the age of the patient as well as of the disease. The older both are, the darker the brown color. If there is much fatty degeneration or infiltration, there is a distinct yellow color, especially is this true of the nodules. Extensive hemosiderosis is the cause of the rusty or tawny color that gave the disease its name. Occasionally in the presence of jaundice, the liver is green in color.

The connective tissue is tough, present in varying quantities, depending on the degree of the disease, and in color varying with that of the liver in general. Where the connective tissue has shrunken considerably, it may be very white and shiny, but when so shrunken it is particularly likely to be associated with jaundice and to be dark green. The capsule, in general, follows the connective tissue in appearance.

The areas of normal liver tissue, if any remain, differ very little from the tissue of a healthy liver. It shows the same brownish liver color, with soft texture, and if there be sufficient passive congestion, which is nearly always true, the acinus markings are clearly visible.

If attention be directed to the histologic picture, one finds an extremely varied type of cell as well as a very unfamiliar general structure. The liver cells may show the following variations (though not all in any given slide): (a) Normal cells in the familiar radial arrangement; (b) normally arranged cells in various stages of retrogressive changes chiefly fatty degeneration, also parenchymatous degeneration and possibly actual necroses. These are original liver cells in process of destruction; (c) among the above normally arranged cells may be found large, very pale cells with unusually clear protoplasm, occurring singly or in groups, sometimes among the degenerating cells, sometimes wholly surrounded by connective tissue. Since there is no evidence of circulatory obstruction such as engorgment of capillaries, these cells could not have been snared off by contracting strands of connective tissue. Their clear, pale protoplasm with larger cell bodies at once proclaims them as newly formed cells, regenerated cells, if you please; (d) very large groups of the same type of cell, arranged more or less in parallel columns but entirely without radial arrangement or central vein, with an eccentrically placed vein. These represent nodules of regenerated cells with a new type of vascularization; (e) greatly increased numbers of bile ducts in the connective tissue surrounding the nodules; (f) among the cells of (c) and (d) may be found cells in various stages of degeneration.

It was with a definite purpose in mind that I described the normal liver structure in terms of its circulatory elements. I will consider more carefully the circulation of the cirrhotic liver.

During injection experiments on cirrhotic livers carried out by Kretz,[24] or under his direction, the following observations were made. If the injection mass was introduced through the portal vein it would appear in the hepatic vein at a time when large areas of hepatic tissue were still uninjected. These uninjected areas proved to be the larger nodules of newly formed liver cells as well as the small groups of isolated liver cells previously mentioned. If the hepatic artery was injected by a celloidin mass of different color it would be discovered that it was exactly these areas that would be injected. It was also noted that the hepatic artery was hypertrophic in such cases.

But one conclusion can be drawn from these findings, the regenerative process is directly under the nutritional influence of the hypertrophic hepatic artery. The portal vein continues to supply the original liver tissue, which has escaped the destructive influences of the disease and possibly some of the newly formed or regenerated masses of cells slightly or indifferently. Since the new groups of cells are drained chiefly by newly formed eccentric "central veins," a new communication between the hepatic artery and the portal vein is established via branches of the hepatic vein. Under the normal circulatory relationship between hepatic artery and portal vein, the latter is not embarrassed by the greater pressure of the hepatic artery, but with the opening of new channels through the regenerated nodules the anastomosis is much more extensive and free. This, plus the hypertrophy of the hepatic artery, leads to definite embarrassment of the portal circulation. It is like making an anastomosis much greater in size than the usual capillary transition between an artery and a vein, at the same time that the artery in question has had an opportunity to hypertrophy. Venous stasis and edema must result. This is probably the real reason for portal stasis and ascites, certainly when they appear before connective tissue production has taken place in the liver. The fact that injections of the portal vein in cirrhotic livers fail to fill large areas of liver tissue, newly formed to be sure, but liver tissue nevertheless, demonstrates the presence of an internal collateral circulation that is never mentioned when the collaterals of cirrhosis of the liver are described.

It has been shown by Ponfick that large masses of liver tissue may be resected in dogs only to have a regeneration take place adequate for the physiologic needs of the animal, plus a large margin of safety. The question arises whether this internal collateral circulation or anastomosis of the portal vein around rather than through the newly formed nodules in cirrhosis of the liver, is not the leak which is responsible for the hepatic insufficiency in this disease. To put it another way, is it not because the portal blood is carried past the nodules of regenerated liver cells rather than through them that insuf-

24. Kretz: Verhandl. d. deutsch. path. Gesell. 8.

ficiency results? The liver is doubly insufficient, first by reason of its parenchymatous loss, but also because the portal blood fails to reach the parenchyma in adequate quantities by reason of both internal and external collateral circulation. In spite of the parenchyma loss had the circulation been rebuilt properly, relative hepatic sufficiency would have prevailed much longer than is usually the case.

HISTOPATHOLOGY

Liver.—The microscopic picture is essentially one of disorder and disarrangement. In a well marked case there will be seen extensive areas of connective tissue arranged in strands or streets irregularly disposed, crossing and recrossing each other. In the meshes will be seen masses of liver cells in most unusual and disorderly arrangements. The cells are disposed more or less in parallel columns, but there is no evidence of systematic, much less systematic radial, arrangement. Efferent veins will not be found in these masses, or, if so, they will be eccentrically placed or in still other cases be found beside the cells. The portal vein will not present the normal close approach, but will be distant in the connective tissue strands in which it probably passes to the side of the nodules, rather than to or through them. The hepatic artery is seen in the connective tissue strands in a loose relationship to the portal vein. That it supplies the nodules with their afferent blood, as maintained in Kretz, cannot be demonstrated histologically. It is an assumption based entirely on his injection experiments. The capillaries in the nodules lying as they must between the columns of cells, have become intricate networks or labyrinths from which the efferent blood has great difficulty in escaping.

Occasionally, quite normally arranged liver lobules, with radiating cell columns—central veins and portal vein in normal contact—may be found, residuums of the original liver structure. Degeneration or necrosis, if seen at all, is most likely to be found in these lobules, though lesser retrogressive changes, especially fatty degeneration, are often seen in the cells of the regenerated nodules.

In the connective tissue strands are seen inumerable freely branching ducts, lined with cuboidal cells with deeply staining nuclei. These are newly formed bile ducts. They probably possess a double function. They are making unusual efforts by proliferation and branching to search out and assume contact with the new nodules for purposes of bile drainage, and, in addition they are probably concerned in the formation, in small part at least, of new liver cells, for they are genetically closely related to them. MacCullum has demonstrated this transformation several times in histologic slides by showing their transition and union with the liver cells in nodules or groups of newly formed cells.

The connective tissue strands are irregular in size and vascularity. The variations in size are dependent on the amount of destroyed liver tissue represented, that is to say, a large thick strand represents the collapsed skeleton of a large area of destroyed liver, a small strand less. While the increase in the bile ducts is, in part, absolute, some of the increase is relative, the collapse bringing original ducts closer together. The same is true of the increase in blood vessels—some are newly formed, others have collapsed with the skeleton into closer proximity. Often one can see indications of the lobules (their number, size, etc.) that have been destroyed in an area of connective tissue; it is almost as though the parenchyma had dropped out and the skeleton collapsed. The connective tissue is increased relatively as well as absolutely. Many round cells and wandering cells of all types are found in these areas.

Hemosiderin deposits in cirrhotic livers are extremely frequent; when diligently searched for, are found in more than half the cases. In studying old slides in our possession, derived from cases of cirrhoses of varying degrees, it was present in all of the more advanced cases. It is true that in some cases special stains may be necessary, yet when searching carefully, minute deposits will be found either in the connective tissue or the liver cells themselves. It is because it is not so overwhelmingly present as to be immediately striking that this finding is not more often described. Just why this should be found in a degenerative disease of a parenchymatous organ has been the subject of much controversy. It was to be expected during the early days of the literature of cirrhosis that it would be associated with and regarded as dependent on hemorrhages in the gastro-intestinal tract, absorption being through the portal system with subsequent deposit in the liver. Kretz [25] was the first to set up the hypothesis that this pigment was liberated by destruction of red blood corpuscles in the liver, probably by the action of a circulatory toxin, possibly a known chemical such as alcohol. Bleichroeder [26] has written very extensively on this phase of the pathology of cirrhosis.

To forestall any misapprehension we are not, when making these statements, thinking of cases of so-called bronze diabetes but of portal cirrhosis.

Spleen.—The spleen is very much enlarged, often it is much larger than the liver. There has been much controversy over the cause of this enlargement. Most of us were taught, and it is still believed by some, that this enlargement is due to the passive congestion associated with cirrhosis of the liver. There is, however, much accumulated evidence that there is a distinct pathologic process in the spleen typical

25. Kretz: Beitr. z. klin. Med. u. Therap., 1896.
26. Bleichroeder: Virchows Arch. f. path. Anat. **177.**

of cirrhosis of the liver. There are, for example, many cases of cirrhosis in which the spleen is greatly enlarged long before there is ascites, that it to say, long before passive congestion has occurred. Leichtenstern [27] was the first to call attention to these cases, indeed, he regarded them as pre-cirrhotic and called them by the name "Pre-cirrhotic Splenic Tumor." However, he is scarcely justified in the conclusion implied by the name, that the spleen is diseased before the liver, for cirrhosis is an insidious disease, it is always quite advanced before a diagnosis is made; in fact, the clinical manifestations of its early stages are entirely unknown. The splenic enlargement is always considerable, it is much greater than that of cardiac decompensation. It is not nearly as hard, either to palpation of the intact organ or when its cut surface is examined. The spleen of passive congestion gives the impression of being stuffed full to bursting, yet on the cut surface the pulp does not pout, nor can it be scraped off, both evidences of great increase in connective tissue. The spleen of cirrhosis is slightly softer, more like that of a subacute infection, its pulp usually pouts on the cut surface and can be scraped off readily. Its color is lighter than either the normal or the cardiac spleen, often having a slightly grayish tinge as though milky water had been poured over it, or it may have a rusty, tawny tinge. Bleichroeder found a considerable difference in the specific gravity, the spleen of cirrhosis on an average having a specific gravity of 1.059 against 1.044 for passive congestion.

Histologically, the spleen of cirrhosis shows a slight congestion as compared with the normal; presumably this is passive, but it does not approach that of the spleen of chronic cardiac decompensation. Furthermore, there is a great increase in the various types of wandering cells and lymphocytes. Various writers have described circumvascular proliferations which at times penetrate the blood vessels, one of them (Bleichroeder [26]), attributes to these a special pathogenetic significance, believing that they may become dislocated and swept from the spleen to the liver, there producing either focal necroses or setting up the inflammatory process that eventuates in the destruction of normal liver tissue.

Finally, there is a great deposit of hemosiderin and various other iron pigments, chiefly in the connective tissue of the spleen but also in the pulp and in the various wandering cells. The source of this is not yet clearly understood, but the assumption that it arises from extensive destruction of red blood corpuscles is as justifiable here as it is for the origin of the same deposits in the liver. Often it gives the spleen a slightly rusty or tawny color.

27. Leichtenstern, quoted by Naunyn: Verhandl. d. Deutsch. path. Gesell. **8.**

ASSOCIATED PATHOLOGY

Embarrassment of the portal circulation leads to various disturbances. First among these is ascites. This is often of extreme degree.

Passive congestion leads to a catarrhal pseudo-inflammation of the gastro-intestinal mucosa. The mucosa of the stomach is intensely injected, edematous and at times shows submucous extravasates. In well marked cases these may be very great and lead to distressing hematemesis. The mucosa is covered by an exceedingly tenacious mucus, often containing exfoliated epithelium and red and white blood corpuscles. The mucosa and serosa of the stomach and sometimes of the bowel are often tinged a faint brown by hemosiderin deposits, a finding attributed by some to the results of passive congestion and extravasates, by others to processes identical with those causing similar deposits in the liver and spleen. These are never seen in the stomach in the passive congestion of cardiac decompensation.[28]

Collateral venous hypertrophies or varicosities reach extreme degrees and represent efforts of the portal blood to reach the right heart by routes other than the normal. They are most marked in the anastomosis of the portal circulation with the systemic veins at the lower end of the esophagus and between the portal and systemic veins in the lower rectum via the hemorrhoidal veins and via the veins of the abdomen, the so-called caput medusae. It might be well again to mention the collateral circulation around the nodules of regenerated cells within the liver itself.

Obscure Indefinite Findings.—There is always a very low grade of secondary anemia present, the nature of which is not well understood, whether it is dependent on the same noxious agent that produces cirrhosis itself or on associated digestive and consequent nutritional disturbances is not yet settled. Possibly, it may be regarded as an abortive anemia of one of the types often associated with cirrhosis.

The heart usually shows slight myocardial changes of a degenerative nature. Whether this is dependent on the toxins producing the disease or on the toxins produced by the disease is not clear.

Most cirrhotic patients are slightly jaundiced, not the clear-cut yellow color seen in biliary obstruction, but a pale, almost imperceptible color, which seems to give an undertone of yellow to all light colored surface tissues, particlarly the sclerae and the skin of the covered parts of the body. The color is very much like that of low grade sepsis. The urine contains large amounts of urobilin and urobilinogen. The conclusion that this color is due to urobilin seems justifiable. True jaundice occurs in some cases, especially when contraction of the connective tissue has embarrassed biliary circulation.

28. Wagner: Arch. f. klin. Med. **34.**

Occasionally peculiar hemorrhages or ecchymoses are seen in the conjunctiva, the retina and the skin, especially where the texture is soft. These and the clinically noted attacks of epistaxis are as yet not satisfactorily explained. They remind one of the dyscrasias of certain blood diseases.

There are several notations in the literature of transformation of the normal into red bone marrow, especially in the femur.[29] Bleichroeder [26] maintains that this is true in the majority of cases, he having found changes in the upper end of the femur in twelve or thirteen cases examined for this change.

In certain instances, particularly those in which there is a very large spleen, there are very marked sclerotic changes in the splenic artery and vein and also in the mesenteric veins. Just how this is brought about is not very clear. It is most often present in Banti's syndrome and could be used as a particular argument against Banti's contentions. If the toxin producing cirrhosis originates in the spleen alone, why does it produce sclerotic and hyalin degeneration of identical nature in the mesenteric veins? Just this finding is particularly suggestive of an enteric origin for the poison though of course it does not explain why the splenic artery and vein should be similarly involved.

Tuberculosis, or rather, isolated occasional tubercles in the peritoneum, and the cirrhotic liver itself are frequent, apparently accidental findings. They are usually explained as having developed by virtue of the generally lowered resistance of the patient, and are believed to be terminal or subterminal events. Others see in them a close relationship etiologically. This phase of the subject has been given much study but without definite conclusions. Some writers have made a separate classification of these and called them tuberculous cirrhoses, a step scarcely warranted at present.

RELATION TO OTHER DISEASES

Banti [30] described what he believed to be a syndrome with a definite pathologic complex, worthy of separate classification. He set up certain requirements that make his definition exceedingly complex, indeed it is often regarded as impossible. There must be no known etiology for the disease; there must be enlargement of the spleen preceding the cirrhosis and anemia, which must be of a secondary type with a low leukocyte count, but relatively a lymphocytosis; and the disease must be separable into three stages: (a) splenomegaly; (b) anemia; (c) cirrhosis of the liver with ascites.

Banti himself does not always write in the same vein. More recently [31] he maintains for the disease a characteristic pathology, par-

29. Zypkin: Virchows Arch. f. path. Anat. **174.**
30. Banti: Sperimentale. 1894, p. 407.
31. Folia Haemat. **1**:11, 1910.

ticularly in the spleen. He speaks of it as a "fibroadenie," which is essentially a fibrosis of the malpihgian follicles situated around the splenic artery which itself shows hyalin changes, and an extensive fibrosis of the splenic reticulum. All of this he believes to be of noninflammatory origin, because he has not found fibroblasts present. There is hyalin degeneration of the capsule of the spleen, and cirrhosis of the liver differing in no respect from the usual picture, except in the splenic changes mentioned. Blood pigments were not found in the spleen or liver in his cases, hence he assumes that there was no blood destruction. The red bone marrow of secondary anemia is uniformly found. He assumes that there is an infectious agent producing the splenic changes ("fibroadenie") which, in turn, cause the spleen to elaborate a poison producing the liver cirrhosis. There is no known analogy for this in all pathogenesis, it is manufactured to fit the case, a reasoning from effect to cause.

Banti admits that the diagnosis cannot be completed until the liver is seen by the pathologist (or surgeon) and that the pathologist cannot make the diagnosis without the clinical data, namely the history of three consecutive stages, splenomegaly, anemia and cirrhosis. This is merely another way of saying that the disease is essentially undiagnosticable.

In a general way, the literature may be divided into two classes with reference to the acceptance or rejection of Banti's disease as a clinical entity: (1) That of authors who accept it, usually clinicians, with the notable exception of Naunyn,[27] and (2) that of authors who reject it, generally speaking, pathologists, though they usually manifest a more scientific conservatism and may be said to assume an attitude of skepticism.

While I have never seen a case classifiable as Banti's disease, it seems to me that there is no definite reason why it should at present be accepted as a clinical entity. There is too much controversy concerning it, and Banti is neither definite nor sure enough of himself. Finally, if we accept Banti's classification, there is no such disease as splenic anemia, for he does not permit even this to escape him, maintaining that it is Banti's disease in the second stage before cirrhosis has had time to develop.

Banti's contention that a poison is developed in the spleen has been supported in a scientific manner but once, and never since confirmed. Umber[32] made metabolic studies on a case and found that there was disintegration of the blood albumins on a toxemic basis. After extirpation of the spleen this ceased. This is possibly analogous to some of the experiments of Longcope, interpreted by him as anaphylactic phenomena. This is not to be construed as an effort to state that toxins

32. Umber: Ztschr. f. klin. Med. **55**: 1905.

cannot originate in the spleen, it has not been proved in cirrhosis. On the other hand, it seems proved in both splenic anemia and in hemolytic jaundice by the results obtained by splenectomy.

Mayo [33] arguing on purely clinical grounds, experience, if you please, states that extirpation of the spleen in cirrhosis, when the spleen is very large, is beneficial by reducing the volume of portal blood so that the liver may again "carry on." He suggests, however, that it may prevent "those irritants" ordinarily filtered out in the spleen from reaching the liver as, for example, in splenic anemia. He offers no proof of their existence. Again the alluring theory, that abnormal splenic metabolic products are the cause, cannot be resisted by one usually so matter of fact that theories have no place in his articles.

Every patient with cirrhosis of the liver is anemic or shows periods of anemia, of the secondary type. Every case shows great variations in its course, not only as to symptomatology but as to duration of the disease. It would seem more rational then to regard Banti's syndrome as one of the various clinical pictures under which cirrhosis may present itself. Moschcowitz [34] assumes this attitude with great emphasis, probably because the two cases presented in his article showing Banti's syndrome clinically, failed to show any evidences whatsoever of cirrhosis at necropsy.

It strikes me that Banti has surrounded his definition with so many conditions and modifications, some reasonable and some—e. g. his contention that the etiology must be unknown—so unreasonable as to make the disease purely imaginary. Dropping it will still leave a diagnostic pigeon-hole for all cases. Chronic cirrhosis with high grade anemia and splenomegaly will describe Banti's typical cases. Splenic anemia will cover those cases claimed by him to be in the second stage before cirrhosis has had time to develop.

Diabète Bronzé.—Diabète bronzé, or cirrhosis pigmentaire, is a disease of obscure origin characterized by a cirrhosis of the liver like that of portal cirrhosis with extensive visceral and cutaneous hemosiderosis, and diabetes mellitus.

Various theories of its pathogenesis are offered, the chief of which, ascribe the primary rôle variously to the hepatic cirrhosis, to the diabetes and to the hemosiderosis. Another somewhat differing etiology is offered in the form of an hypothetical toxin the cause of all the other pathologic changes. Under this characterization it is spoken of as hemochromatosis.

It is an extremely rare disease, the literature offering only seventy-five cases for study. In a general way they may be divided into two

33. Mayo: Ann. Surg. **68**:183 (Aug.) 1918.
34. Moschcowitz: J. A. M. A. **69**:1045 (Sept. 29) 1917.

groups, one, those in which the cirrhosis and pigmentation represent the less severe form, the other—probably an advanced stage—in which diabetes mellitus has been added to the foregoing changes.

The pathology of the cirrhosis differs but little from that of ordinary portal cirrhosis; the liver is usually larger than normal, death occurring before atrophy can occur. Ascites is rare. There are no distinctive features in the associated diabetes; it develops in the great majority of cases and is the cause of most of the deaths. It may be due to extensive hemosiderotic fibrosis of the pancreas.

Usually a moderate degree of secondary anemia is present.

Wilson's Disease.—The association of cirrhosis of the liver with a definite disease of the nervous system described by Wilson in 1912 is a most remarkable combination, an incongruity pathologically. It is a progressive degenerative disease located in the lenticular nuclei occurring in young adults, familial in occurrence, yet not hereditary. Its chief manifestations are various motor phenomena of extra pyramidal origin with some mental symptoms. Atrophic cirrhosis of the liver is constantly found. Aside from its remarkable association with a nervous disease, it is noteworthy that it occurs in youth, is familial, that alcohol is not implicated in its etiology, that ascites and other evidences of portal stasis are absent, and that clinically the cirrhosis is not demonstrable, even the small size of the liver has only rarely been demonstrated clinically. Wilson characterizes the changes in the liver as a multilobular or mixed cirrhosis.

CLASSIFICATIONS OF CIRRHOSIS

So very much has been written in efforts to prove that all cirrhoses are essentially the same process that we will venture a few remarks on this subject.

Mayo [33] is the most arbitrary of all writers and brusquely divides them into portal and biliary cirrhoses. The former is what is generally known as Laennec's cirrhosis, but he also includes all forms of hypertrophic cirrhoses, whether of alcoholic or other origin. He does not accept the view that the enlarged livers of certain types of cirrhosis, often containing considerable fat, later become atrophic. He therefore speaks of atrophic portal cirrhosis which he regards as the characteristic response to concentrated spirits, such as gin, and to pepper excess, and to poisons carried to the liver from the spleen. On the other hand, he speaks of hypertrophic portal cirrhosis which is the characteristic response to excesses of beer, and is associated with fat deposits. Biliary cirrhosis is dependent on infection of the biliary ducts, and is characterized by a large liver and a very large spleen. Mayo's classification could be summarized thus: (*a*) Portal cirrhosis, (a) atrophic type (Laennec); (b) hypertrophic type, (*b*) biliary cirrhosis, with an enlarged liver.

In his opinion, there is no pathologic or clinical basis for a separate classification of Hanot's cirrhosis. He believes that the disease so designated is either an obstructive biliary cirrhosis or an hemolytic icterus, in which there is work hypertrophy of the liver. Since hemolytic icterus is very frequently associated with gallbladder pathology (more than 60 per cent. of the cases), he believes that there are combinations of the two, that is to say, a work hypertrophy due to hemolytic jaundice plus biliary cirrhosis of infectious origin.

Pathologists still adhere to a much more elaborate scheme: (1) Laennec's cirrhosis (atrophic), including multilobular cirrhosis, nature not clear, probably syphilitic. (2) Hanot's cirrhosis (primary biliary hypertrophic cirrhosis). (3) Obstructive biliary cirrhosis. (4) Hepar lobatum. (5) Cirrhose cardiaque.

A brief description of the nonportal cirrhoses and other diseases sometimes confused with Laennec's type of cirrhosis will serve to clarify some of the difficulties in classifying them.

Hanot's Cirrhosis.—In 1876 Hanot presented for clinical and pathologic study a type of disease, la cirrhose hypertrophique avec icteré chronique. He based his studies on four cases of his own and about a dozen cases collected from the literature. The disease is characterized by a chronic intermittently febrile course, with severe jaundice but without clay-colored stools or ascites, with a very large, smooth liver and a very large spleen. Histologically, there is a striking intra-acinous development of connective tissue. In later publications he broadens his views considerably, so that it becomes somewhat difficult to know just what he includes. Still later writings are even less clear, and his original ideal type becomes confused. Perhaps he was led afield by other French writers who described various "forms" of Hanot's cirrhosis, some accepting as a standard the presence of intra-acinous development of connective tissue, others described a capillary cholangitis as the essential pathologic standard. As will be seen later, they were doubtless describing what is now called obstructive biliary cirrhosis. In answering these writers in the course of a long series of polemical articles, he allowed himself to become confused until his articles lost much of their clearness, and, like Banti, he did not seem to know just what constituted a clear-cut type, an ideal of the disease known by his name.

Today a somewhat broadened or modified view is taken as to what constitutes Hanot's cirrhosis. There are two distinct types or forms: *First*, those cases of cirrhosis in which there is a degenerative process in the liver associated with a toxemic jaundice. This description is strikingly like that of Mayo, who uses it to deny Hanot's cirrhosis a separate place in pathology, but terms it hemolytic jaundice with

work hypertrophy. However, these cases are said by Kretz [35] to develop an ascites if they live long enough, because of changes in the texture of the liver with contraction or atrophy, therefore, they do not conform to Hanot's requirements of an absent ascites, and are not his ideal type. These show no inflammation of the finer bile ducts but there is a very fine intralobular almost intercellular distribution of connective tissue breaking up the lobules into very small groups of cells. *Second,* those cases of jaundiced hypertrophic cirrhosis in which there is an intense capillary cholangitis, a type brought forward by Heineke [36] as the ideal type of Hanot. The connective tissue about the biliary capillaries proliferates and secondarily enters the acini insinuating itself between the cells. It shows no tendency to contract and cause atrophy of the liver, the feature which differentiates it from obstructive biliary cirrhosis. Its etiology is clearly infectious. In both types the liver is large, hard and smooth, often weighing as much as 5,000 gm. The spleen is also large and hard, much greater in size than in atrophic cirrhosis. Doubtless many cases of Laennec's cirrhosis with enlarged liver are erroneously described as being of Hanot's type.

Obstructive Biliary Cirrhosis.—Obstructive biliary cirrhosis is an exceedingly rare type. The liver is small, very hard, like leather, and is very dark green in color because of its etiology, chronic obstructive jaundice. Probably, one reason this disease is so rare is because modern surgery does not permit an obstructive jaundice to exist long enough to produce the consequent changes unless it be due to an exceedingly slowly progressing carcinoma of the gallbladder. Histologically, there is still normal acinal structure with intense bile stasis and consequent destruction of liver cells. These are destroyed in part by the biliary stasis and back pressure, but, perhaps, still more by the consequent chronic infection which is always associated, either sooner or later. A thick connective tissue mantle is formed about the biliary ducts and capillaries, associated with the histologic phenomena of inflammation.

Hepar Lobatum.—While often classified with the cirrhoses, hepar lobatum does not properly belong here. It is essentially normal liver tissue traversed by long, deep scars communicating with each other and dividing the liver into adventitious lobes. They are the remains of gummatous processes, and are often characteristically localized in the left lobe of the liver. Sometimes it is a mere connective tissue or scar-like membrane.

Multilobular Cirrhosis.—Multilobular cirrhosis is not clearly classified. The term is reserved by some writers for the end-result of gummatous hepatitis in children. The liver is small, roughly resem-

35. Kretz: Verhandl. d. Deutsch. path. Gesell **9.**
36. Heineke: Beitr. z. path. Anat. u. z. allg. Path. **22.**

bling that of Laennec's cirrhosis but not quite so tough. There are relatively large pseudo-acini produced by connective tissue subdivision of normal liver tissue in which true acini are present. Histologically, the connective tissue strands are broad, but differ from those of Laennec's cirrhosis in that there are no evidences of inflammatory infiltration, it is clearly a quiescent scar tissue. Biliary ducts show no evidences of sprouting and there is little or no parenchymatous regeneration. Normal acini clearly differentiate it from atrophic cirrhosis.

Cirrhose Cardiaque.—Cirrhose cardiaque is not a cirrhosis at all; it is a high degree of passive congestion in which the parenchymatous cells destroyed by back pressure of the blood have been replaced by connective tissue. It has been credited with a specific infectious etiology because it is most typically found in cases in which the cardiac difficulty was acquired in early youth especially in concretio pericardii cum corde.

RÉSUMÉ OF CLASSIFICATION

The following would represent a comparison of the orthodox classification of pathologists with the abrupt of Mayo, indicating the equivalents.

Pathologists' Classification	Mayo's Classification
1. Laennec's cirrhosis.....	
2. Biliary cirrhosis	2. Hemolytic jaundice, with work
(a) Primary biliary Hanot	1. Portal cirrhosis.
I. Toxemic without biliary capillary infection	hypertrophy.
II. Biliary capillary cholangitis	3. Biliary Cirrhosis.
(b) Biliary obstructive....	

3. Multilobular cirrhosis, probably an end-result of syphilis in childhood.

4. Hepar lobatum—post syphilitic scars.

5. Cirrhose cardiaque.

In closing, I cannot resist the temptation to give expression to a thought, which is growing into a conviction, that when dealing with cirrhosis of the liver we must regard it as closely allied to the diseases of the blood, for the following reasons. Banti's disease is an accepted blood disease, associated with cirrhosis of the portal type. Splenic anemia if accepted as a clinical entity always suggests liver changes to the clinician, a suggestion born of an involuntary association of the two, based possibly on Banti's writings. Diabété bronzé is a typical

cirrhosis and diabetes plus a marked disturbance in the metabolism of iron and a moderate anemia. From this to the hemosiderosis of ordinary atrophic cirrhosis is not so far a cry as to be unheard, especially if the latter be associated with an anemia. The jaundice present in most cases of cirrhosis is urobilin jaundice, probably the same substance which causes the yellow color in pernicious anemia. Some writers who have made special search have found red bone marrow of the type seen in the high grades of anemias. While it is true that this has not been found by many clinicians, it is also equally true that very few have searched for it. Finally, when we begin studying hypertrophic cirrhosis we find such practical men as Mayo abandoning the term hypertrophic cirrhosis and visualizing it as a work hypertrophy in hemolytic jaundice, a disease which is unquestionably classifiable as a disease of the blood.

THE ANTIDIURETIC EFFECT OF PITUITARY EXTRACT APPLIED INTRANASALLY IN A CASE OF DIABETES INSIPIDUS *

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INTRODUCTION

The combination in diabetes insipidus of insatiable thirst and polyuria interfering with sleep and all the ordinary activities of life naturally has stimulated numerous workers in the past ten years to devise some method whereby the lives of the sufferers of this disease could be made more tolerable. In 1913, Von der Velden [1] and Farini [2] demonstrated that the subcutaneous injection of pituitary extract checked both the polyuria and the polydipsia. This observation has been abundantly confirmed. Two features of hypophyseal therapy render it still highly unsatisfactory. First, the effect is transitory, and, second, hypodermic injection has always been essential and is inconvenient and difficult for continued use of patients.

Even though the effect is transitory, however, if pituitary extract could be introduced into the body in more frequent doses and in a less inconvenient manner, great comfort would naturally result. Absorption by way of the gastro-intestinal tract has been tried by many observers. Failure has attended practically all attempts to diminish the urinary output by dried extract given by mouth. Motzfeld [3] controlled the diuresis in one case by feeding fresh posterior lobe of the ox. Christie and Stewart [4] were, however, unable to confirm this result in their case. Christian,[5] in a case studied by him, found that pituitary extract introduced in suppositories, by colonic irrigation, and in gumdrops which were allowed to dissolve slowly in the mouth, failed to exercise any antidiuretic effect.

In the case under observation only 0.005 c.c. of pituitrin "O" [6] subcutaneously was necessary to effect a marked diminution in the

* From the Medical Clinic of the Peter Bent Brigham Hospital

1. Von der Velden, R.: Berl. klin. Wchnschr. **50**:2083, 1913.

2. Farini, A., and Ceccaroni, B.: Gazz. d. osp., Milano, **34**:879, 1913; Clin. med. ital., Milano **52**:497, 1913.

3. Motzfeld: Endocrinology **2**:112, 1918.

4. Christie and Stewart: Arch. Int. Med. **20**:10 (July) 1917.

5. Christian: Med. Clin. N. America **3**:849 (Jan.) 1920.

6. Pituitrin "O" is the aqueous extract of the posterior lobe of the pituitary prepared by Parke, Davis & Company for obstetric use and is one-half the strength of pituitrin "S" prepared for surgical use.

urinary output. Since so small an amount was effective and since certain methods had not been attempted, it seemed worth while to undertake the following study.

REPORT OF CASE

G. C., (No. 31,569), a schoolboy, aged 16, entered the Peter Bent Brigham Hospital Nov. 28, 1921, complaining of thirst and frequency of urination.

Family History.—Father, mother, two brothers and five sisters are living and well.

Past History.—Negative, save for diphtheria at 3.

Present Illness.—Patient felt perfectly well until three months before admission when he noted the rather sudden onset of polydipsia and polyuria which gradually increased.

Physical Examination.—Patient was a poorly developed and poorly nourished boy, with slight diffuse brownish pigmentation of the skin over the entire body. Ophthalmoscopic examination was negative. A complete general and neurologic examination, including perimetry, showed no other abnormalities.

Clinicol Pathology.—Blood: Hemoglobin was 85 per cent. (Sahli); red blood cells, 4,832,000; white blood cells, 11,300. A stained smear showed definite achromia and slight anisocytosis. The blood Wassermann reaction on two occasions was strongly positive. Blood sugar: 7.1 mg. per hundred c.c. Blood urea nitrogen, 10 mg. per hundred c.c.

The blood Wassermann reaction of the patient's father was very weakly positive.

Urine: Clear, pale, acid, without sediment; specific gravity, from 1.000 to 1.003; no albumin or sugar. Daily urine output varied from 6 to 9 liters.

Spinal Fluid: Clear and colorless; pressure, 155 mm. water; contained six cells per c. mm. Globulin reaction was slightly positive. The Wassermann reaction was weakly positive in 2 c.c. and in 1 c.c.

Roentgen-Ray Examination: Stereoscopic plates of the skull showed no evidence of any abnormality.

METHOD

The procedure employed was as follows: The patient was given a diet containing a fixed amount of protein and salt. This precaution was taken because it has been shown conclusively that the chlorid and nitrogen intake influences the urinary output.[7] Between meals the patient was encouraged to take as much liquid as he desired. He was not allowed to eat between meals nor was he allowed lemonade, coffee or other beverages which might introduce confusing factors. The water content of the food, while not accurately determined, was kept approximately uniform. Under this regimen, the patient's fluid intake was 5,000 c.c. from 7 a. m. to 7 p. m. and about 3,000 c.c. during the night. In order to establish a standard curve of excretion, the 5,000 c.c. intake was distributed evenly throughout the day, 200 c.c. being given every half hour from 7 a. m. to 7 p. m. During the same period, the urine was collected every hour. Under these conditions the fluid intake and output were relatively uniform. Single doses of pituitary extract subcutaneously, intranasally, by rectum and by mouth, and of histamin

7. Oehme and Oehme: Deutsch. Arch. f. klin Med. **127**:261, 1914.

subcutaneously and intranasally were administered. The intake being constant, the effect sought was a delayed excretion rather than a diminution in the total urinary output. This procedure, in excluding subjective factors and ensuring a more uniform rate of excretion makes effects of lesser magnitude discernible.

The methods which gave any indication of influencing the urinary output were then tested by placing the patient on unlimited fluids and noting the effect over twenty-four hours.

OBSERVATIONS

Effect of Pituitary Extract and Histamin.—The patient was put on a fixed intake of 200 c.c. every half hour with instructions to void every hour. On this regimen it was found that no antidiuretic effect was

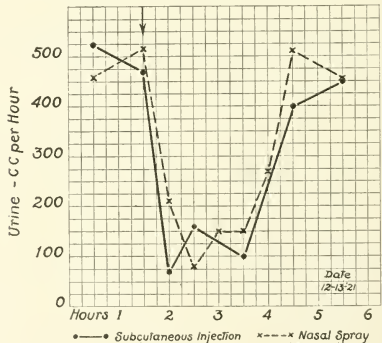

Chart 1.—The comparative antidiuretic effect of subcutaneous injection of pituitrin "O" and intranasal spray of pituitrin "O" with fluid intake of 200 c.c. every half hour. Solid line represents the effect of subcutaneous injection of 0.005 c.c. of pituitrin "O," dashes indicate the effect of 0.5 c.c. pituitrin "O" sprayed intranasally at time noted by arrow.

produced by: (1) 2 c.c. pituitrin "O" retained in the mouth for ten minutes and then swallowed; (2) from 4 to 8 c.c. pituitrin "O" with 20 c.c. tap water introduced by rectum; (3) histamin, 1 c.c. of 1:10,000 solution injected subcutaneously; (4) histamin, 0.1 c.c. sprayed intranasally; (5) tap water 1 c.c. sprayed intranasally. On the other hand, a marked antidiuretic effect was produced by: (1) from 0.005 c.c. to 0.5 c.c. pituitrin "O" injected subcutaneously; (2) from 0.5 to 5 c.c. pituitrin "O" sprayed intranasally (Chart 1; Table 1).

TABLE 1.—Effect of Administering Pituitary Extract and Histamin by Various Routes

Method	Urine per Hour				
	Before	After Administration			
	I	II	III	IV	V
No Antidiuretic Effect:					
2 c.c. pituitrin "O" by mouth	450	435	440	255	455
4 c.c. pituitrin "O" by rectum	425	510	225	395	530
1 c.c. histamin, 1:10,000, subcutaneously	540	560	436	400	427
Marked Antidiuretic Effect:					
0.25 c.c. pituitrin "O" subcutaneously	560	55	45	130	315
1.0 c.c. pituitrin "O" subcutaneously	550	95	50	150	325
0.8 c.c. oral pituitary extract, intranasally	410	45	360	510	570
5 c.c. oral pituitary extract, intranasally	335	75	95	140	485

In order to determine the efficacy of these measures in reducing the twenty-four hour intake and output, the patient was encouraged to drink all the water necessary for comfort. The fluid intake and output were carefully measured. The same diet was continued. One and five-tenths c.c. of oral pituitary extract was sprayed intranasally every three hours on one day (Column 2, Chart 2), and every four hours

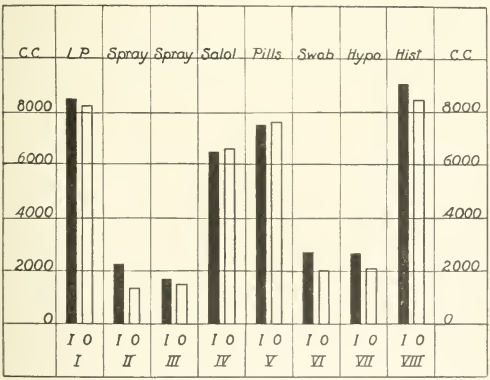

Chart 2.—Comparative effect of various measures on twenty-four hourly fluid intake and output. I. Indicates fluid intake; O, urinary output. I. Effect of lumbar puncture. II. Intranasal spray of 1.5 c.c. oral pituitary extract every three hours. III. Intranasal spray of 1.5 c.c. oral pituitary extract every four hours. IV. Phenyl salicylate coated tablets, 1.3 gm. V. Posterior lobe pituitary pills (Burroughs Wellcome Co.) 0.13 gm. every four hours. VI. Swab soaked in 1 c.c. pituitrin "O" inserted in one nostril and changed every four hours. VII. Subcutaneous injection of 0.5 c.c. pituitrin "O" every six hours. VIII. Histamin, 1 c.c. 1:10,000 solution (Parke, Davis & Company) injected subcutaneously every six hours.

on the next day (Column 3), with marked decrease in urinary output. A cotton plug soaked with 1 c.c. of pituitrin "O" was introduced into one nostril at four hour intervals with essentially the same result (Column 6). Pituitary extract was then withheld and after the patient had returned to his usual intake and output level, phenyl salicylate coated tablets (Column 4), and posterior lobe pituitary tablets (Burroughs Wellcome Co.), (Column 5), were administered by mouth.

The results are graphically represented in Chart 2.

Changes in Blood Concentration.—An attempt was made to determine what changes, if any, occurred in the concentration of the blood serum before and after intranasal administration of pituitary extract. The patient was allowed an unlimited intake of fluid. Two specimens of blood were taken at hourly intervals, after which 4 c.c. of pituitrin "O" was sprayed intranasally. Samples of blood were taken at the end of one-half hour, one hour, two hours and three hours. The protein concentration of the blood was determined by the refractometer. That this is both exceedingly sensitive and reliable as an index of blood concentration has been demonstrated by Reiss.[8]

TABLE 2.—CHANGES IN BLOOD CONCENTRATION BEFORE AND AFTER INTRANASAL ADMINISTRATION OF PITUITARY EXTRACT

Time	Percentage of Concentration	Urine (Water ad lib.)
9	9.25	420
10	9.25	95
10:30	9.25	0
11	8.96	18
12	...	46
1	8.0	33

Metabolism.—The possible effect of pituitrin on the metabolic rate was also investigated. The patient's basal metabolism was therefore determined on four occasions by the Tissot method, two determinations which checked within 4 per cent. being made each time. The normal standards of Aub and DuBois for calories per square meter of body surface (height-weight formula) per hour were used, and the results expressed in per cent. of normal. The determinations were made after a fourteen hours' fast, on two occasions after the administration of pituitary extract and on two other occasions without any medication.

The results were as follows: Dec. 15, 1921, —4; December 31, —26; Jan. 9, 1922, —20; January 13, —23. The relatively high result of the first determination was probably due to the patient's restlessness, associated with thirst and a desire to void. The second and third determinations were made immediately following pituitary extract

8. Reiss: Arch. f. exper. Path. u. Pharmakol. **51**:18, 1903.

sprays with the patient perfectly comfortable and quiet. The fourth determination was done two days after pituitary extract was discontinued, when his daily intake and output were 8,600 c.c. and 8,400 c.c., respectively. Prior to the first three determinations the patient had been deprived of water for approximately three hours, but on this fourth occasion he was permitted small amounts of warmed water at room temperature until one hour before the metabolic rate was determined. As a result, the patient was not restless and the metabolic rate was determined under more satisfactory conditions.

The foregoing results do not indicate any marked pituitary extract effect on the metabolic rate. Whether the lowered metabolism in this case bears any relation to the syndrome of diabetes insipidus, or whether it is due entirely to the malnutrition of the patient,[9] it is impossible to say.

DISCUSSION

Extract of the posterior lobe of the pituitary sprayed intranasally checked both the polyuria and polydipsia as effectively as hypodermic injections. All administrations of dried or aqueous extracts by mouth or rectum proved ineffectual, this being in accord with the results of practically all previous observers.

Histamin, whether sprayed, swallowed or injected subcutaneously, failed to modify the thirst or polyuria. One c.c. of a 1:10,000 solution injected subcutaneously did not cause any toxic symptoms. The preparation used was shown by Dale's method to be physiologically active in concentrations of $\frac{1}{2}$:10,000,000.

Lumbar puncture, performed on two different occasions, did not lower the water or urinary output as it did in the cases reported by Herrick [10] and Graham.[11]

The effect of pituitary extract intranasally and subcutaneously was a diminution of the water intake and urinary output with a corresponding alleviation of thirst, a rise in the specific gravity of the urine and a dilution of the blood. The dilution of the blood has also been noted by Konschegg and Shuster [12] and by Priestly.[13]

Whether intranasal sprays will be as successful in other cases, is, of course, impossible to state, for it is conceivable that the efficacy of the method in this instance was due to the small amount of pituitary extract that the patient required.

The exact mechanism underlying the nasopharyngeal absorption is not clear. Certain facts are, however, of considerable interest in this

9. Benedict, Francis G., Miles, Victor R., Rath, Pane, Smith, H., Monmouth: Publication No. 280, Carnegie Institution of Washington, 1919, p. 694.
10. Herrick: Arch. Int. Med. **10**:1 (July) 1912.
11. Graham: J. A. M. A. **69**:1498 (Nov. 3) 1917.
12. Konschegg and Shuster: Deutsch. Med. Wchnschr. **51**:1091, 1915.
13. Priestly, J. G.: J. Physiol. **55**:305, 1921.

connection. "That the lymphatics of the nasal mucosa are in almost direct communication with the subarachnoid space has been clearly demonstrated," [14] and clinically, in children, a surprisingly small patch of inflammation in the nasopharynx excites convulsions, stupor and other phenomena indicative of considerable cerebral irritation.[15] Flexner [16] has shown that after intraspinal inoculation of monkeys with the *Diplococcus Intracellularis,* the organisms can be detected both free and intracellularly in the nasopharynx; and similarly, the virus of poliomyelitis has been demonstrated in the nasal mucosa of monkeys inoculated intraspinally.[17] The successful inoculation of poliomyelitis virus into the nasopharynx of monkeys, clearly demonstrating that the nasopharynx may serve as a portal of entry, is also suggestive in this connection.[18]

The preceding evidence indicates that the nasopharynx constitutes an important factor in certain diseased states, but whether absorption in the present instance is accomplished by the blood stream, by the lymphatics, or by both channels, it is impossible to state.

CONCLUSIONS

1. In a case of diabetes insipidus under observation, extract of the posterior lobe of the pituitary applied intranasally checked both the polyuria and polydipsia as effectively as hypodermic injection.

2. Histamin, subcutaneously; lumbar puncture, and pituitary extract by mouth, by rectum, and by phenyl salicylate coated tablets, proved ineffectual.

NOTE.—After this paper had been written, three additional cases of diabetes insipidus were studied. In each instance intranasal application of pituitary extract was found to be fully as satisfactory as hypodermic injection in reducing the fluid intake and urinary output to an approximately normal level.

14. Peabody, Draper and Dochez: A Clinical Study of Acute Poliomyelitis, Monograph of the Rockefeller Institute for Medical Research, No. 4, June 1, 1912, p. 12.

15. Schloss, O.: Personal communication.

16. Flexner, S.: J. A. M. A. **55**:1105 (Sept. 24) 1910.

17. Flexner, S., and Lewis, P. A.: J. A. M. A. **54**:535 (Feb. 12) 1910.

18. Landsteiner, K., and Levaditi, C.: Ann. de l'Inst. Pasteur **24**:833, 1910.

THE VITAL CAPACITY IN A GROUP OF COLLEGE STUDENTS*

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The lessened vital capacity in intrathoracic diseases and the recommendation that vital capacity be used as a test of physical fitness have renewed interest in the question of normal standards for vital capacity. The vital capacity varies greatly even among healthy individuals, and some of the factors which accompany these variations are known. Among them are the sex, weight, height, size of the chest, age and general physical fitness. The clinician desires a normal standard with which he may compare the vital capacity of his patient. Would he do better, for example, to compare it with the average for individuals of the same height, of the same weight or of the same chest measurements; or should he use some combination of these? Obviously, that standard is best which shows the least variation among normal individuals. The convenience of the standard also deserves some consideration, for a convenient standard is more likely to be generally used.

Hutchinson [1] after examining about 3,000 men came to the conclusion that the most reliable standard for estimating the vital capacity of men was their standing height. He stated that on the average the vital capacity increased 8 cubic inches of air for every inch increase of height between the heights of 5 and 6 feet. According to Hutchinson the vital capacity increased also with the weight, but this occurred only up to an average weight of about 155 pounds. Increases of weight beyond this were not, on the average, accompanied by increased vital capacity. According to Hutchinson also the vital capacity tended to grow less after the age of about 33 years, although the chest circumference showed a slight tendency to grow greater. Peabody and Wentworth [2] grouped their normals into three classes according to height. This method has an obvious disadvantage in the case of those whose heights lie near the class borders, for they are compared with a standard that is best suited for a different height. Lundsgaard and Van Slyke [3] compared the vital capacity with certain chest dimensions;

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1. Hutchinson, J.: On the Capacity of the Lungs, and on the Respiratory Functions, with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, Med. Chir. Tr. Lond. **29**:139, 1846.

2. Peabody, F. W., and Wentworth, J. A.: Clinical Studies on Respiration, Arch. Int. Med. **20**:443 (Oct.) 1917.

3. Lundsgaard, C., and Van Slyke, D. R.: Relation Between Thorax Size and Lung Volume, J. Exper. M. **27**:65, 1918.

but West [4] found a poor correlation between these dimensions and the vital capacity of his subjects. Dreyer [5] compared the vital capacity with the weight, the stem height (measured from the top of the head to the end of the sacrum) and the circumference of the chest. So far as weight was concerned, Dreyer neglected this in individuals whose weight did not correspond to their stem height; so that for practical purposes his comparisons were based on the stem height and the circumference of the chest. Finally West [4] compared the vital capacity with the surface area, as calculated from the height and weight by the DuBois' formula.[6]

Our observations were made on 400 normal young men at Leland Stanford Jr. University between the ages of 18 and 30. All of these were active and showed no evident signs of disease. In each case the height was taken in bare feet and the weight was stripped weight. The vital capacity was determined by a spirometer which gave accurate readings. Each individual was first shown how the test was performed and was then given three trials. The highest of the three readings was recorded as his vital capacity. The body surface area was estimated from the height and weight by using the diagram of DuBois and DuBois. Unfortunately, neither the sitting height nor the stem height according to Dreyer were taken. The individual observations are shown in Table 1.

A general conception of the relation between the vital capacities and weights of our students may be gained from Figure 1. The observations were grouped according to weights, and the average vital capacity for each weight group was determined. These averages increased with increasing weights but the rate of increase was relatively rapid at low weights and relatively slow at high weights. Hutchinson noted a similar change at the higher weights. In his statistics, however, the change at higher weights was more marked. We are inclined to attribute this difference to the fact that Hutchinson's observations included men of all ages. The excess fat so often accumulated as a person grows older is probably accompanied by no corresponding increase in vital capacity. Dreyer stated that the vital capacity is proportional to the 0.72 power of the weight ($W + ^{0.72}$). Dreyer's line representing this relationship is curved in the general direction of our averages; but the curve for the weights here under consideration is hardly appreciable. For the sake of comparison we have inserted

4. West, H. F.: Clinical Studies on Respiration: Comparison of Various Standards for Normal Vital Capacity of Lungs, Arch. Int. Med. **25**:306 (March) 1920.

5. Dreyer, G.: The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

6. DuBois, D., and DuBois, E. F.: Clinical Calorimetry. Fifth Paper. The Measurement of the Surface Area of Man, Arch. Int. Med. **15**:868 (June) 1915.

TABLE 1.—Vital Capacity of Group of College Students

Vital Capacity	Height	Weight	Surface Area	Vital Capacity	Height	Weight	Surface Area
6,700	187.0	80.4	2.06	5,227	181.1	93.2	2.14
6,655	186.7	75.7	1.98	5,244	173.3	63.6	1.77
6,653	193.7	87.7	2.17	5,200	180.0	67.2	1.86
6,653	189.2	82.3	2.07	5,200	175.5	61.5	1.76
6,500	195.5	85.6	2.18	5,200	175.3	65.0	1.78
6,200	180.5	79.0	1.99	5,200	174.5	64.4	1.78
5,981	185.4	77.3	1.98	5,161	187.0	77.3	2.01
5,981	184.0	94.1	2.14	5,114	178.0	71.4	1.88
5,899	172.0	70.5	1.83	5,163	182.8	78.2	2.01
5,900	187.2	65.0	1.87	5,163	171.6	69.5	1.81
5,869	185.4	75.0	1.95	5,163	171.0	67.3	1.76
5,817	172.7	70.9	1.82	5,150	170.5	64.4	1.75
5,800	179.5	71.6	1.90	5,100	174.0	61.6	1.75
5,760	185.0	77.0	2.03	5,081	175.9	64.5	1.80
5,736	180.0	66.5	1.77	5,081	182.9	72.7	1.92
5,736	180.0	76.4	1.95	5,081	176.0	66.4	1.78
5,736	180.3	90.0	2.10	5,081	184.0	86.4	2.08
5,736	184.0	78.2	2.00	5,074	174.0	72.7	1.88
5,736	181.2	68.2	1.85	5,065	172.0	65.0	1.77
5,732	191.0	79.5	2.08	5,061	183.0	70.0	1.90
5,736	180.3	72.7	1.90	5,081	182.5	70.5	1.90
5,736	187.9	65.0	1.88	5,073	172.0	78.1	1.92
5,736	174.5	72.4	1.87	5,081	174.0	70.5	1.84
5,700	186.0	76.2	1.93	5,081	187.0	69.1	1.94
5,637	184.0	76.8	1.96	5,081	180.6	82.3	2.01
5,654	185.0	68.7	1.92	5,081	176.0	78.6	1.95
5,572	185.4	79.5	2.03	5,081	183.0	84.1	2.06
5,572	189.4	82.3	2.05	5,077	180.0	70.9	1.89
5,572	188.1	78.2	2.06	5,061	179.0	81.0	1.98
5,572	191.0	94.0	2.24	5,000	179.5	63.2	1.83
5,572	190.5	92.2	2.20	5,000	175.0	78.5	1.94
5,572	185.3	78.2	2.03	5,000	173.0	64.3	1.78
5,572	182.8	75.0	1.96	5,000	183.0	75.2	1.97
5,571	173.0	71.4	1.83	5,000	170.8	64.1	1.75
5,565	184.0	63.6	1.85	4,916	175.5	70.5	1.85
5,540	179.0	64.6	1.82	4,998	167.6	65.0	1.74
5,450	177.7	70.6	1.88	4,916	180.3	67.3	1.84
5,450	179.1	63.6	1.83	4,916	172.0	67.0	1.77
5,450	185.4	84.0	2.07	4,916	184.0	64.5	1.85
5,407	170.0	77.3	1.87	4,916	173.0	63.6	1.77
5,407	186.5	85.0	2.10	4,916	170.0	71.8	1.82
5,407	187.2	72.7	1.93	4,916	180.0	65.9	1.84
5,407	188.0	71.4	1.96	4,916	172.5	70.0	1.83
5,410	178.1	79.5	1.98	4,949	185.6	66.8	1.87
5,420	189.0	83.2	2.07	4,916	172.5	69.0	1.83
5,415	180.3	77.5	1.95	4,916	185.6	74.1	1.97
5,488	177.8	62.3	1.76	4,982	184.0	72.7	1.96
5,407	177.0	60.0	1.75	4,952	190.0	78.1	2.06
5,405	177.5	58.2	1.76	4,900	185.0	73.2	1.94
5,325	185.3	84.1	2.08	4,916	173.2	79.5	1.93
5,325	181.8	84.1	2.07	4,916	188.6	71.4	1.92
5,320	178.0	66.5	1.76	4,916	182.8	84.1	2.06
5,325	185.3	70.0	1.93	4,998	177.8	63.0	1.81
5,325	175.2	65.9	1.79	4,916	181.5	71.0	1.89
5,328	181.0	70.5	1.89	4,900	177.8	66.7	1.83
5,300	180.0	64.1	1.83	4,916	178.3	70.0	1.87
5,240	170.0	70.3	1.81	4,916	177.8	60.5	1.75
5,225	180.2	68.0	1.87	4,998	180.3	63.0	1.77
5,300	181.0	80.8	2.01	4,916	179.0	74.0	1.93
5,300	168.0	63.3	1.72	4,998	179.0	67.8	1.87
5,300	181.5	70.4	1.90	4,916	174.8	70.5	1.95
5,300	181.8	74.4	1.95	4,916	168.5	66.9	1.76
5,244	185.4	72.7	1.94	4,900	168.8	65.0	1.73
5,244	175.9	64.5	1.79	4,900	169.0	66.0	1.77
5,244	179.0	63.0	1.83	4,900	160.0	72.0	1.83
5,244	173.9	68.6	1.84	4,900	172.5	68.2	1.81
5,244	173.0	64.0	1.76	4,850	179.0	63.6	1.80
5,211	184.0	70.0	1.91	4,850	175.0	67.8	1.83
5,235	174.0	94.0	2.08	4,850	175.0	60.5	1.74
5,244	175.5	80.0	1.95	4,800	171.0	65.0	1.77
5,244	177.0	69.1	1.86	4,800	178.0	65.2	1.82
5,260	178.1	71.8	1.88	4,884	175.4	68.2	1.84
5,244	180.6	80.0	2.00	4,850	186.5	82.7	2.07
5,244	185.6	72.7	1.96	4,884	184.0	92.0	2.14
5,244	185.0	66.9	1.91	4,884	175.2	70.0	1.85
5,244	188.0	77.7	2.06	4,741	172.7	67.3	1.78
5,244	174.0	77.7	1.94	4,734	175.9	75.9	1.91
5,244	167.6	58.2	1.68	4,752	172.0	63.6	1.76
5,277	184.0	70.5	1.92	4,752	184.0	69.1	1.91
5,252	176.0	72.3	1.86	4,752	173.0	71.8	1.84
5,244	180.8	76.3	1.95	4,752	180.3	70.5	1.89

TABLE 1.—Vital Capacity of Group of College Students—(*Continued*)

Vital Capacity	Height	Weight	Surface Area	Vital Capacity	Height	Weight	Surface Area
4,752	170.0	67.5	1.80	4,425	187.2	79.5	2.05
4,734	170.0	68.2	1.80	4,425	175.8	68.2	1.85
4,752	173.0	65.0	1.77	4,425	179.0	62.8	1.82
4,788	187.2	77.3	2.00	4,425	172.0	60.5	1.71
4,700	173.0	64.0	1.76	4,420	172.7	67.3	1.77
4,752	176.0	68.0	1.85	4,416	170.0	71.8	1.82
4,752	184.0	78.1	2.02	4,425	184.0	72.7	1.94
4,734	178.0	70.6	1.87	4,425	174.0	78.0	1.94
4,752	173.0	65.4	1.78	4,425	170.0	79.5	1.92
4,752	183.0	70.0	1.91	4,425	180.3	90.9	2.10
4,752	185.4	77.7	2.03	4,425	168.2	57.0	1.63
4,752	182.8	79.5	2.02	4,416	175.0	84.5	2.00
4,752	189.0	68.2	1.95	4,425	177.4	68.7	1.86
4,752	178.0	68.2	1.84	4,457	170.0	66.9	1.78
4,752	181.0	82.3	2.06	4,440	178.0	78.2	1.97
4,746	183.0	84.1	2.06	4,409	165.5	56.0	1.62
4,752	186.5	68.5	1.94	4,463	169.0	58.6	1.69
4,760	175.7	82.7	1.99	4,425	160.0	59.1	1.69
4,760	175.6	60.0	1.74	4,440	172.5	72.3	1.83
4,752	181.0	66.9	1.86	4,450	173.8	57.6	1.69
4,759	176.0	66.0	1.81	4,400	161.5	59.5	1.63
4,700	176.0	60.2	1.74	4,400	173.5	64.8	1.78
4,700	177.0	74.2	1.91	4,409	177.8	71.6	1.89
4,700	178.0	62.4	1.78	4,400	183.0	70.8	1.92
4,700	171.0	63.5	1.75	4,343	176.0	65.5	1.80
4,700	182.0	70.5	1.91	4,343	170.1	60.5	1.70
4,700	169.0	74.4	1.85	4,343	167.0	64.5	1.69
4,670	175.9	67.3	1.81	4,343	175.7	74.5	1.90
4,670	172.7	67.3	1.79	4,343	168.0	66.4	1.76
4,670	180.3	68.2	1.88	4,350	163.5	60.0	1.65
4,670	180.3	66.4	1.84	4,300	160.0	67.4	1.78
4,600	180.0	72.7	1.92	4,300	174.0	57.2	1.69
4,670	170.0	64.5	1.75	4,300	179.0	60.2	1.77
4,490	166.0	63.2	1.69	4,300	167.5	58.8	1.67
4,670	175.4	60.0	1.74	4,300	166.0	64.8	1.72
4,670	184.0	94.5	2.18	4,251	168.0	67.5	1.78
4,676	174.0	81.2	1.94	4,250	170.0	60.0	1.70
4,670	183.3	70.5	1.93	4,250	169.0	60.5	1.69
4,612	175.2	72.3	1.85	4,250	162.0	63.2	1.64
4,662	179.0	63.0	1.82	4,251	180.0	67.8	1.87
4,670	175.2	65.9	1.79	4,251	170.1	63.6	1.75
4,650	170.4	63.6	1.74	4,251	176.4	87.7	2.06
4,600	174.0	68.0	1.82	4,211	176.0	69.1	1.83
4,600	173.5	65.2	1.79	4,250	172.6	88.8	2.03
4,600	173.5	88.9	1.84	4,250	165.0	63.0	1.73
4,588	175.9	60.5	1.75	4,211	173.0	75.0	1.88
4,588	182.9	60.5	1.79	4,251	177.0	60.0	1.75
4,588	170.2	60.5	1.70	4,251	167.6	56.0	1.63
4,588	170.0	67.5	1.78	4,250	178.0	68.7	1.87
4,588	177.2	114.5	2.29	4,242	170.0	61.8	1.72
4,506	180.0	67.3	1.85	4,245	174.0	60.5	1.73
4,568	176.0	68.6	1.86	4,250	173.6	64.5	1.77
4,506	178.0	72.7	1.93	4,250	166.5	57.7	1.66
4,588	182.5	72.7	1.92	4,250	178.0	68.2	1.87
4,589	176.0	68.2	1.86	4,250	164.0	64.5	1.72
4,572	171.0	64.5	1.76	4,250	172.5	62.2	1.74
4,589	182.0	66.0	1.84	4,210	180.2	55.5	1.71
4,568	180.5	76.8	1.95	4,200	175.6	63.8	1.81
4,572	183.1	69.1	1.90	4,200	167.5	51.4	1.57
4,506	173.8	66.4	1.78	4,200	177.0	57.3	1.68
4,589	189.0	78.2	2.06	4,200	165.0	56.3	1.62
4,506	183.0	78.0	2.01	4,200	171.0	57.4	1.67
4,597	175.1	70.0	1.82	4,100	186.0	69.0	1.82
4,560	187.0	67.3	1.92	4,179	160.0	64.5	1.68
4,596	176.0	80.4	1.96	4,170	172.6	81.2	1.94
4,560	174.0	86.8	2.02	4,170	177.8	67.3	1.83
4,506	173.8	68.2	1.84	4,180	173.5	62.7	1.77
4,588	180.3	74.0	1.94	4,180	181.5	70.5	1.89
4,588	181.5	70.5	1.89	4,180	170.0	64.5	1.73
4,589	180.3	77.2	1.96	4,100	171.5	57.0	1.67
4,506	178.0	72.3	1.88	4,100	174.0	64.0	1.78
4,539	180.0	68.2	1.88	4,087	172.7	54.4	1.65
4,506	162.0	69.5	1.75	4,087	179.1	60.4	1.77
4,596	175.2	70.9	1.85	4,080	168.9	54.5	1.63
4,588	180.3	65.9	1.83	4,087	180.3	61.8	1.78
4,588	175.5	71.4	1.84	4,087	172.0	60.5	1.72
4,520	174.0	57.0	1.69	4,080	176.0	67.3	1.83
4,500	167.0	62.5	1.70	4,087	176.0	62.7	1.77
4,500	187.5	57.6	1.79	4,087	183.0	75.6	1.97
4,500	170.0	53.5	1.62	4,070	162.0	60.0	1.64
4,500	164.3	62.2	1.68	4,087	172.6	57.3	1.68

TABLE 1.—Vital Capacity of Group of College Students—(*Continued*)

Vital Capacity	Height	Weight	Surface Area	Vital Capacity	Height	Weight	Surface Area
4,087	171.3	53.2	1.60	3,750	160.0	70.5	1.73
4,095	176.4	62.3	1.75	3,769	162.5	57.5	1.59
4,015	173.4	71.4	1.84	3,730	163.0	84.5	1.90
4,050	170.1	89.4	1.92	3,769	165.0	57.7	1.66
4,015	170.0	55.4	1.64	3,750	175.5	58.8	1.72
4,015	165.0	54.6	1.60	3,750	168.5	56.5	1.64
4,087	168.2	62.6	1.73	3,695	172.6	59.1	1.70
4,087	164.0	64.5	1.71	3,695	157.4	47.3	1.46
4,050	166.3	59.8	1.67	3,687	172.6	68.2	1.82
4,050	172.0	57.3	1.68	3,687	162.5	60.0	1.64
4,050	172.2	60.9	1.72	3,606	177.8	57.0	1.74
4,050	172.5	55.9	1.67	3,687	185.0	58.4	1.79
4,000	169.5	60.0	1.69	3,687	173.0	59.1	1.72
4,000	173.6	58.7	1.70	3,695	172.0	60.0	1.72
3,960	172.7	60.5	1.72	3,688	167.6	65.9	1.75
3,982	168.3	60.4	1.68	3,675	171.0	66.9	1.77
3,960	176.0	63.6	1.80	3,625	170.0	55.9	1.64
3,933	180.0	77.3	1.96	3,687	179.0	62.2	1.77
3,933	173.0	58.2	1.70	3,687	175.2	53.9	1.66
3,900	180.3	74.5	1.94	3,695	171.0	66.9	1.78
3,933	158.7	60.0	1.63	3,650	160.7	57.3	1.60
3,960	169.0	62.7	1.73	3,600	157.5	62.0	1.63
3,933	168.0	75.9	1.86	3,500	162.8	56.0	1.60
3,933	170.5	59.1	1.70	3,400	166.9	58.0	1.65
3,950	169.0	58.8	1.68	3,441	180.3	68.2	1.78
3,910	174.5	72.9	1.87	3,441	166.0	65.4	1.74
3,900	160.6	53.4	1.55	3,450	167.0	65.0	1.74
3,900	167.0	62.5	1.70	3,425	187.0	59.1	1.83
3,851	182.8	67.8	1.90	3,441	170.1	60.0	1.70
3,842	172.6	65.3	1.77	3,472	170.1	75.9	1.87
3,851	167.6	56.8	1.64	3,359	169.5	58.2	1.69
3,801	176.6	64.5	1.79	3,277	176.0	61.0	1.75
3,802	179.0	62.2	1.81	3,250	168.0	52.3	1.57
3,769	172.0	67.5	1.78	3,277	160.8	63.6	1.65
3,769	179.0	60.4	1.76	3,277	164.3	52.7	1.55
3,769	168.9	70.7	1.81	3,150	167.0	66.9	1.77
3,769	170.0	58.2	1.68	3,115	165.0	63.6	1.69
3,769	179.3	58.6	1.76	3,048	175.5	60.0	1.74

in Figure 1 the straight line relationship between weight and vital capacity as calculated from our data, Dreyer's line, and Hutchinson's averages of vital capacity for different weight groups. The lower averages in Hutchinson's statistics will be considered farther on.

Figure 2 indicates for our students the average vital capacities of the different height groups. We have added the similar averages of Hutchinson's cases, the straight line relationship between vital capacity and height as calculated from our data and the straight line relationship which Hutchinson proposed for his. Both in our cases and in those of Hutchinson the relationship between the height and the vital capacity for height groups approached a straight line.

The statistical methods employed are based on two assumptions. The first is that the relationship between the factors compared approaches a straight line relationship. We have shown that this is approximately the case so far as the relation between height and vital capacity is concerned. The relation between weight and vital capacity deviates somewhat from a straight line in the case of our students and this deviation is quite marked in Hutchinson's observations. The second assumption is that the data for each group of observations approximates the so-called normal distribution curve. This is true of

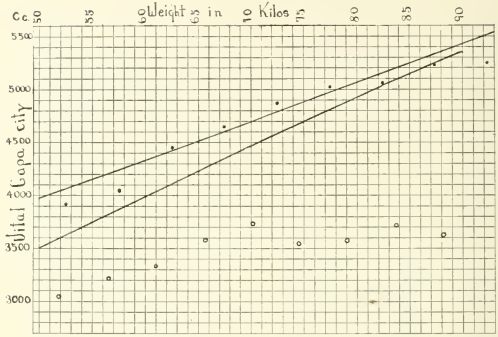

Fig. 1.—The vital capacity and weight. The dots represent the average vital capacities for different weight groups of Stanford students. The circles represent similar averages for Hutchinson's cases. The upper straight line is the calculated line for Stanford students. The line just below is Dreyer's line. Its curve is hardly perceptible.

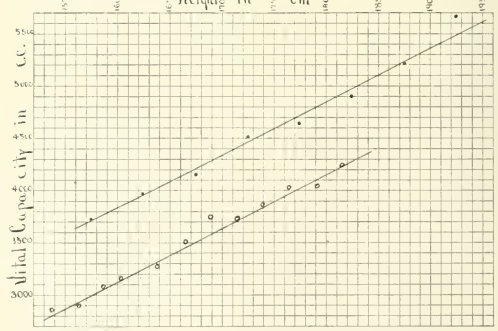

Fig. 2.—The vital capacity and height. The dots represent the average vital capacities for different height groups of Stanford students. The circles represent similar averages for Hutchinson's cases. The upper straight line is the calculated line for Stanford students. The lower straight line is that proposed by Hutchinson.

biologic measurements in general, including height and weight. It is also true of the vital capacity. Figure 3 shows the actual observations in Stanford students and the calculated theoretical distribution curve.

With the above assumption it is possible by the mathematical methods employed in statistical studies to determine the relation of vital capacity to height, to weight and to their combination. For determining these relations in college students we have used our figures on 400 Stanford students, the figures of West on eighty-five Harvard medical students and the figures of Schuster [7] on 959 Oxford students. For comparison, Hutchinson's data on 1,285 men as shown in his Table D have also been used. We have calculated from these data the standard deviations, the coefficients of correlation, and the formulas which best express the straight line relationship between vital capacity

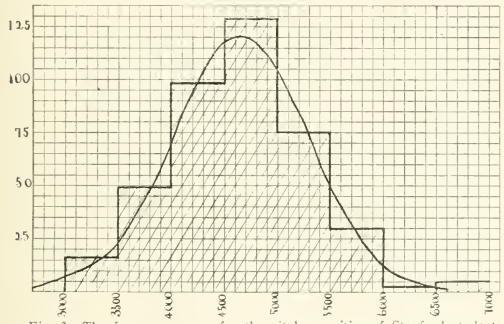

Fig. 3.—The frequency curve for the vital capacities of Stanford students. The shaded columns represent the number of observations between different limits of vital capacity. The curve represents the theoretical distribution as calculated from the standard deviation, the mean, and the total number of observations.

and various other factors. The methods used are described in Yule's "Introduction to the Theory of Statistics."

Briefly, it may be stated that the standard deviation expresses the dispersion of the data on either side of the average. It is expressed by the formula $\sigma = \sqrt{\frac{\Sigma x^2}{N}}$ where σ is the standard deviation, x is the deviation of any one point from the average, Σx^2 is the sum of the squares of these individual deviations, and N is the number of observations.

7. Schuster, E.: First Results from the Oxford Anthropometric Laboratory, Biometrika **8**:40. 1911.

The coefficient of correlation, r, indicates how closely the observations of any two sets of data on the same individuals, e. g. vital capacity and height, range themselves about a straight line relationship. It is calculated from the formula $r = \frac{\Sigma xy}{N\sigma x\sigma y}$ where x and y represent the deviations of each point from the averages of x and y, respectively, Σxy the sum of the products of these deviations, N the number of observations and σx and σy the standard deviations of the two groups of observations that are being compared, e. g., vital capacity and height. The more nearly r approaches unity the more closely do the data range themselves on a straight line, i. e., the more exact is the linear correlation. A mathematical expression for the line of relationship is given by the formula $y = a + r\frac{\sigma y}{\sigma x}x$ where for example, y represents the vital capacity, x the height, r the coefficient of correlation between height and vital capacity, σy the standard deviation of the vital capacity, σx the standard deviation of the height and a is a constant. The standard deviation of the individual observations from this calculated line is represented by the expression $\sigma y\sqrt{1-r^2}$.

TABLE 2.—Results of Comparison of Data from Three Groups of Students

	Oxford	Harvard	Stanford	S. & H.	S. H. & O.	Hutchinson
Number	959	85	400	485	1,444	1,285
Means:						
Weight	68.52	64.59	68.49	.....	68.28	68.30
Height	176.5	173.6	175.9	.....	176.2	171.5
Vital capacity	4,315	4,651	4,646	4,647	4,426	3,602
Surface area	.....	1.776	1.835	1.825	.....	.....
Standard Deviations:						
Weight	7.428	7.176	8.821	.....	7.885	8.706
Height	6.908	6.856	7.121	.....	6.805	6.627
Vital capacity	613.2	652.5	655.8	655.3	646.9	(446.3)*
Surface area	.....	0.1167	0.1332	0.1324	.....	.....
Coefficients of Correlation:						
Wt. : Ht.	0.66	0.61	0.50	.....	0.60	0.60
Wt. : V. C.	0.59	0.67	0.49	.....	0.53	(0.63)*
Ht. : V. C.	0.57	0.63	0.55	.....	0.53	(0.86)*
S. A. : V. C.	.....	0.73	0.57	0.59	.....	.....

* Calculated from Hutchinson's averages as given in his Table D. The use of averages makes the standard deviation too small and the coefficients of correlation too large.

Table 2 gives the results obtained by these statistical calculations. In the group studied by Hutchinson, which comprised men of different ages and different occupations, the average weight was the same as the average weight of the college students, whereas the average height was definitely less. On the average, then, Hutchinson's subjects were somewhat shorter and relatively fatter than our students. The average vital capacity differed considerably in the different groups. The Stanford and Harvard medical students showed the highest average vital capacity; the Oxford average was about 7 per cent. lower and Hutchinson's average group was more than 20 per cent. lower. This low average in Hutchinson's group was probably due, in part, to the fact that he studied men of all classes and all ages, whereas college students represent a picked class both as to age and general physical fitness. It seems unlikely, however, that the low average in Hutchinson's group was due entirely to this cause. Difference in technic or in the instruments used may have been partly responsible for his low figures.

Fluctuations on either side of the average are indicated by the standard deviations given in Table 2. These fluctuations were greater among the Stanford students than among the Oxford or the Harvard medical students. In all groups the fluctuations of vital capacity were relatively greater than the fluctuations of either weight or height. Thus for all students the standard deviation for vital capacity amounted to 14.6 per cent. of the mean, the standard deviation for weight amounted to 11.5 per cent. of the mean, and the standard deviation for height amounted to 3.9 per cent. of the mean. It is evident, therefore, both from the different averages and from the standard deviations that the vital capacity of normal individuals shows a rather wide range of fluctuation.

Table 2 shows also that among college students the correlation between weight and vital capacity is approximately the same as the correlation between height and vital capacity. Hutchinson did not record the individual vital capacities of his subjects and it is not possible from his data properly to calculate correlation coefficients for vital capacity and either weight or height. We have, however, made such calculations from the average vital capacities given in his Table D. From these it is evident, as he stated and as is shown in our Figures 1 and 2, that for his cases the correlation of vital capacity with height is far better than the correlation with weight. This difference between college men and men at large with respect to the correlation of weight and vital capacity may be explained on the assumption that the latter group includes some fat men whose excess weight is accompanied by no increase or perhaps by a decrease of vital capacity. It seems to us, therefore, that weight is not a reliable index of vital capacity unless one can exclude those with excess fat.

Among college students, where excess fat is not common, there is a closer correlation between vital capacity and a combination of weight and height than between vital capacity and either height or weight alone. West proposed that the body surface as calculated from the weight and height be used as an index of vital capacity and it may be seen from Table 2 that the correlation with body surface is somewhat better than the correlation with either height or the weight alone. A combination of the linear relationships of vital capacity to weight and to height was calculated. This correlation will be discussed later.

By applying the methods of statistical study to the above data, formulas may be obtained by means of which one may calculate for college students the probable vital capacity either from the height, from the surface area, or from the linear combination of height and weight. The first and last formulas are based on the combined Stanford, Oxford and Harvard medical statistics. The second is based on the correlation

coefficient between vital capacity and surface area of the Stanford and the Harvard medical groups and on the average for all students. The formulas obtained are as follows:

$$VC=50\ Ht-4{,}400$$
$$VC=2{,}900\ SA-1{,}000$$
$$VC=27\ Wt+31.5\ Ht-3{,}000$$

In these formulas vital capacity is expressed in cubic centimeters, height in centimeters, surface area in square meters and weight in kilograms.

The standard deviations of the observed vital capacities of students from vital capacities which have been calculated from the above formulas are as follows:

Standard deviation of vital capacities from height formula, 548.6 c.c.

Standard deviation of vital capacities from surface area formula, 529.1 c.c.

Standard deviations of vital capacities from weight and height formula, 521.1 c.c.

TABLE 3.—Showing Number of Students Out of Each Hundred Who May Be Expected to Have a Vital Capacity Which Falls Below the Following Percentages of Their Calculated Vital Capacity, When the Different Formulas Are Used

	Falling Below				
	90%	85%	80%	75%	70%
Height formula	21.0	11.3	5.4	2.2	0.8
Surface formula	20.1	10.3	4.8	1.8	0.6
Height-Weight formula	19.8	10.2	4.5	1.7	0.6

It will be seen that in the case of college students the fluctuations from a formula based on both height and weight are less than the fluctuations from a formula based on height alone. Between the formula based on the calculated body surface area, and the formula based on linear relationships between vital capacity and height and weight, there is no significant difference. This conclusion, of course, applies only to college students. The significance of these standard deviations can better be appreciated if one compares how many out of each hundred college students will have a vital capacity that falls below any assumed percentage of the calculated vital capacity. Table 3 gives these figures.

Of every hundred college students approximately twenty-one will have a vital capacity less than 90 per cent. of that calculated by the height formula, and approximately twenty will have a vital capacity less than 90 per cent. of that calculated by the body surface or by the height-weight formula. On the other hand, only about two will have a vital capacity less than 75 per cent. of the calculated amount. We

have compared the calculated fluctuations among Stanford students with those actually observed and find a close agreement between the two.

DISCUSSION

College students constitute an excellent group for determining normal vital capacity standards. They are young, intelligent and healthy. In this test intelligence is a factor because the test demands a maximum effort and statistics might easily be impaired if some subjects did not understand the instructions or did not make the necessary effort.

By applying statistical methods of study to the figures obtained from college students we have determined which gave the best index of vital capacity—the height, the weight or a combination of these; we have obtained formulas by which one may predict the average vital capacity for students from their heights or a combination of these with their weights; and we have defined the probable fluctuations from these calculated averages. Unfortunately, we have not the figures necessary for comparing the vital capacity with the sitting or with Dreyer's stem height, but we hope later to report on the value of this standard as judged by college statistics.

Most standards for vital capacity are based on the assumption that there is a simple ratio between the vital capacity and some body measurement or some power of this measurement. Thus the ratio to the height, to the surface area or to some power of the weight or stem length is given. Statistical formulas usually introduce an additional constant which is added to or subtracted from one side of the equation. This distinguishes our formulas from those that have been proposed.

Our formulas are strictly applicable only to college students. How far may they applied to a larger field? We have no figures which answer this question but it is evident from the work of others that they are quite inapplicable to females in general,[4] as well as boys.[8] Furthermore, our standard is a high one for men at large, partly because college students represent a picked class and, partly, because the vital capacity tends to lessen as persons grow older. Excess fat is a disturbing factor in any formula which is based on weight. For this reason we have given no weight formula and we suspect that for men in general a formula based on height and weight combined may be no better than one based on height alone.

Vital capacity varies considerably even in such a selected group as college students and even when it is compared with the height or with a combination of height and weight. The amount of these

8. Emerson, P. W., and Gue, H.: Vital Capacity of the Lungs of Children, Am. J. Dis. Child. **22**:202 (Aug.) 1921.

variations is shown in Table 3. What constitutes an abnormal reduction of the vital capacity? The answer to this question depends on whether we are comparing individuals or group averages with the standard. The difference between different groups of normal individuals is illustrated by the deviations of the Oxford average and the Harvard medical average from our standard for college students. Making allowances for height, the former is 2.5 per cent. below the average and the latter 8.7 per cent. above the average. To be significant, a group average should probably differ from the college standard by not less than 10 per cent. With respect to individual observations, our study shows that of every hundred college students about two have a vital capacity that is less than 75 per cent. of the standard. Assuming that an occasional student has some unrecognized disease, we may conclude that for men in general a reduction below 70 per cent. of the standard is almost always abnormal. Studies on heart patients and on patients with pulmonary tuberculosis indicate that in these diseases the vital capacity frequently falls below this figure.

CONCLUSIONS

1. Among college students the correlation of vital capacity with height and the correlation of vital capacity with weight are approximately equal. The correlation of vital capacity with a combination of weight and height is a little better than the correlation with either separately.

2. Formulas are given which express the average vital capacity of college students for different heights and combinations of height and weight.

3. From these formulas there is a very considerable fluctuation even among college students. The fluctuations for men in general, and the deviations in disease must necessarily be still greater.

THE LENGTH OF LIFE OF TRANSFUSED ERYTHROCYTES IN PATIENTS WITH PRIMARY AND SECONDARY ANEMIA*

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Introduction.—During recent years, and especially since the introduction of the sodium citrate method, blood transfusion has become one of the most common forms of treatment of the various types of primary and secondary anemias. Thus far, however, little is known as to the length of life of the transfused erythrocytes in patients with primary and secondary anemia, and until the recent work of Ashby[1] no observations had been made on this subject. This investigator studied the length of life of transfused red corpuscles in pernicious anemia and found the average to be about three months. Previous to this time various observers had claimed the length of life of the red corpuscles to be from fourteen to fifty-two days.[2] Information on this point seemed desirable in that it might demonstrate the practical value of transfusion, serve as an aid in deciding what the proper intervals between transfusions should be, and because of its relation to the debated problem as to whether or not there is an increase of hemolysins in the blood serum of individuals with primary and secondary anemias.

It is generally known that the transfusion of blood is a safe procedure when the donor's cells are compatible with the plasma of the recipient. The fact that the donor's plasma may agglutinate and hemolyze the cells of the recipient is negligible because the donor's plasma is diluted so rapidly as it enters the recipient's blood stream that agglutination and hemolysis are impossible. It follows then that Group IV blood (Moss classification) may be transfused without ill effects into persons whose bloods fall into Groups I, II and III. In a similar manner a recipient in Group I may be transfused with bloods of Groups II, III and IV.

* From the Medical Service of the Peter Bent Brigham Hospital.

* This paper is No. 20 of a series of studies on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed from a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1. Ashby: J. Exper. M. **29**:267. 1919.

2. Ashby: M. Clin N. America, November, 1919; J. Exper. M. **29**:267, 1919. Ward and Muller; Von Ott; Hunter, W.: Quoted by Ashby, J. Exper. M. **29**:207, 1919.

Technic.—Ashby has devised an ingenious method of following the life of the transfused red blood cells by means of group agglutination.[3] Blood is taken from the recipient's finger and mixed with citrated blood serum which will agglutinate the cells of the recipient but not the cells which have been transfused. The unagglutinated cells (i. e., those that have been transfused) may then be counted. The technic of the method is as follows (assuming a Group II recipient and a Group IV donor): The blood of the recipient is taken in a leukocyte counting pipet up to the 0.5 mark, and is diluted up to the 11 mark with the agglutinating fluid, which is made up of Group IV serum and a 4.4 per cent. solution of sodium citrate in the proportion of 1:20. The pipet is shaken and the mixture expelled into a small test tube in which it is incubated at 37 C. for forty minutes, with thorough shakings every ten minutes. It is then left in the icebox over night. Just before counting, the mixture is shaken and a drop placed in the blood counting chamber and, as directed by Ashby, "160 small squares in each of the two chambers are counted, the average of the counts taken and multiplied by 1100/2 to give the number of unagglutinated or transfused corpuscles per cubic millimeter of blood." Controls on the activity of the agglutinating serum are made by using the technic described above on blood of an untransfused individual in Group II. Theoretically, all the Group II cells should be agglutinated by the Group IV serum; practically, however, there remain unagglutinated on an average of from 20,000 to 50,000 cells per c.mm. Serum which will agglutinate the blood of a normal person in Group II, leaving only 50,000 cells per c.mm. unagglutinated may be considered to be active. When the unagglutinated cell counts in transfused individuals remain higher than these control counts, it may be assumed that the number of unagglutinated corpuscles in excess of the control count represent the number of unagglutinated donor's cells present in the circulation. Cases have been studied by us according to Ashby's method and technic. All counts have been made in duplicate, and the figures in the accompanying tables represent the average. In the cases reported, controls on the serum were made as described above, and, except in two instances, the same agglutinating serum was used throughout for all patients. Control counts of the new and old serums were shown to be practically identical before the changes were made.

Observations on Patients with Pernicious Anemia.—Four patients with pernicious anemia, whose bloods were in Group II, were transfused with citrated blood from donors in Group IV. Counts were then made of the transfused or unagglutinated cells in the bloods of these recipients, and repeated many times until the total transfused cells dropped to the level of the control counts. These patients presented the clear cut and classical signs and symptoms of primary

3. Ashby: J. Exper. M. **34**:147, 1921.

anemia, but among them were representatives of the different stages of the disease. Patient A was in the sixth year of the disease, was bedridden and had been observed in a remission during his stay in the hospital the year before, but in a series of counts taken before his transfusion his erythrocytes were found to be steadily decreasing. Patient C, in the third year of the disease, was also bedridden and his red blood cell counts showed the same general curve as the counts of Patient A. In contrast, Patients B and D were in the earlier stages of the disease, had been able to do some work and were ambulatory at the time of their transfusion.

The observations on Patient D are of especial interest in that the donor for transfusion was another patient with pernicious anemia (Group IV). When the donor was bled, 300 c.c. were withdrawn and he was immediately transfused with 800 c.c. of normal blood. The volume of cells in the 300 c.c. of pernicious anemia blood being very small, the unagglutinated cell count in this recipient never rose above 97,000 per c.mm. Frequent counts were made in this case, and the control counts which were made on untransfused normals in Group II and also on the blood of an untransfused patient with pernicious anemia in Group II, agreed closely.

REPORT OF CASES

Case 1.—Patient A (Medical No. 13211) was a man, aged 41, belonging to Group II. His symptoms began four years before his entrance to the hospital. They were weakness, pallor, distress after eating and numbness of the fingers and toes. Two years previously, while under observation in the hospital, he had a typical remission with marked improvement of all his symptoms except the numbness of the extremities. Eight months later he again began to grow steadily weaker. In the month previous to his present entrance to the hospital his red cell count dropped from 1,332,000 to 676,000. He was then transfused with 575 c.c. citrated blood of Group IV. Blood findings before transfusion were: white cell count, 2,500 per c.mm.; hemoglobin, 30 per cent.; platelets, 98,000 per c.mm.; reticulated cells, 0.5 per cent. The blood picture was typical of pernicious anemia (Table 1, Fig. 1).

TABLE 1.—Blood Picture of Patient A

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Nov. 16, 1920	1,152,000	
18	Dec. 3, 1920	Transfused 575 c.c. citrated blood, Group IV	
18	Dec. 3, 1920	1,024,000	630,000
23	Dec. 8, 1920	1,936,000	535,700
28	Dec. 13, 1920	1,800,000	601,900
49	Jan. 3, 1921	1,552,000	553,850
59	Jan. 13, 1921	1,216,000	464,200
66	Jan. 20, 1921	848,000	349,800
73	Jan. 27, 1921	1,344,000	300,300
77	Jan. 31, 1921	811,456	148,500
78	Feb. 1, 1921	884,268	228,350
79	Feb. 2, 1921	Transfused 600 c.c. citrated blood, Group II	
85	Feb. 8, 1921	1,160,000	229,300
91	Feb. 14, 1921	1,160,000	
95	Feb. 18, 1921	1,088,000	
101	Feb. 24, 1921	904,000	301,400
106	March 1, 1921	1,328,000	351,450
110	March 4, 1921	1,744,000	258,500
116	March 10, 1921	1,512,000	122,650
120	March 14, 1921	1,084,808	100,650
128	March 22, 1921	848,000	73,150

Case 2.—Patient B (Medical No. 15159), a woman aged 46, also belonged to Group II. Her illness began one year before admission to the hospital. The symptoms were gradually increasing weakness and pallor, several attacks of diarrhea and slight numbness of the fingers. She had been able to do a little work around the house. Her blood report before transfusion was as follows: Red cell count, 3,456,000 per c.mm.; reticulated cells, 0.9 per cent.; white cell count, 4,700 per c.mm.; platelets, 151,000 per c.mm. The blood smears showed the typical findings of pernicious anemia. She was transfused with 400 c.c. of citrated blood from a Group IV donor (Table 2, Fig. 2).

TABLE 2.—Blood Findings of Patient B

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Jan. 9, 1921	3,456,000	
1	Jan. 9, 1921	Transfused 400 c.c. citrated blood, Group IV	
3	Jan. 11, 1921	4,152,000	464,750
13	Jan. 21, 1921	4,648,000	381,150
19	Jan. 27, 1921	4,438,000	282,150
24	Feb. 1, 1921	4,256,000	247,500
31	Feb. 8, 1921	3,592,000	307,450
38	Feb. 15, 1921	5,446,000*	
51	Feb. 28, 1921	5,338,000	259,600
55	March 4, 1921	3,688,000	347,600
75	March 24, 1921	4,368,000	216,150
90	April 8, 1921	4,214,000	110,000
98	April 16, 1921	4,320,000	106,150
111	April 29, 1921	4,556,000	35,200

* The sudden rise in the total red blood cell curve was due to a short remission as shown by a sudden increase in the number of reticulated red cells just previous to the rise in the total red cell count.

Case 3.—Patient C (Medical No. 14705) was a woman, aged 55, belonging to Group II. Two years before entrance to the hospital, a gradually increasing weakness, pallor and gastric distress marked the onset of her illness. Then she developed numbness of the hands and feet. Her blood findings before transfusion were: hemoglobin, 45 per cent.; red cell count, 2,356,000 per c.mm.; reticulated cells, 1.5 per cent.; white cell count, 4,100 per c.mm. The stained smear was typical of pernicious anemia. She was transfused with 600 c.c. citrated blood from a Group IV donor and later had several transfusions of Group II blood (Table 3, Fig. 3).

TABLE 3.—Blood Findings of Patient C

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Jan. 18, 1921	1,268,000	
1	Jan. 18, 1921	Transfused 250 c.c. citrated blood, Group IV	
3	Jan. 21, 1921	1,928,000	238,350
7	Jan. 25, 1921	Transfused 600 c.c. citrated blood, Group II	
10	Jan. 28, 1921	2,256,000	165,000
14	Feb. 1, 1921	2,016,000	161,700
16	Feb. 3, 1921	Transfused 550 c.c. citrated blood, Group II	
17	Feb. 4, 1921	2,776,000	189,750
43	March 19, 1921	1,560,000	124,850
43	March 19, 1921	Transfused 500 c.c. citrated blood, Group II	
71	April 16, 1921	1,544,000	57,750

Case 4.—Patient D (Medical No. 15642), a man aged 50, belonging to Group II, noticed symptoms of weakness and pallor three months before admission to the hospital. One month later he had a sore tongue, distress after eating and numbness of the fingers. He had been able to work until shortly before he entered the hospital. His blood findings at entrance were as follows: hemoglobin, 18 per cent.; red cell count, 1,224,000 per c.mm.; reticulated cells, 0.9 per cent.; white cell count, 5,600 per c.mm., and platelets, 128,000 per c.mm. The smear was characteristic of pernicious anemia. He was transfused with 300 c.c. of Group IV blood from another patient who had a typical pernicious anemia (Table 4, Fig. 4).

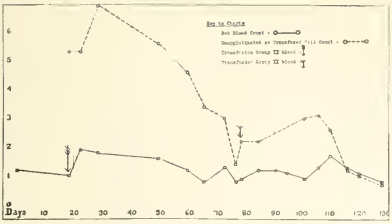

Fig. 1.—Blood findings of Patient A. In this and the accompanying charts the figures on the left border represent millions in the total red blood cell counts, and hundreds of thousands in the unagglutinated or transfused red blood cell counts.

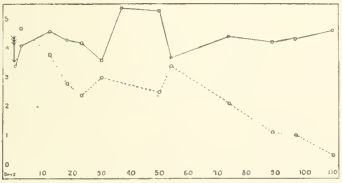

Fig. 2.—Blood findings of Patient B.

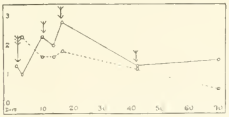

Fig. 3.—Blood findings of Patient C.

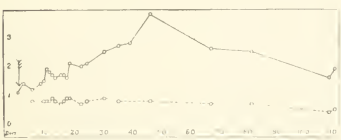

Fig. 4.—Blood findings of Patient D.

TABLE 4.—Blood Findings of Patient D

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	March 19, 1921	1,224,000	
1	March 19, 1921	Transfused 300 c.c. citrated blood, Group IV (P. A.)	
3	March 22, 1921	1,401,000	
6	March 25, 1921	1,200,000	86,350
9	March 28, 1921	1,448,000	
10	March 29, 1921	1,520,000	89,650
11	March 30, 1921	1,628,000	87,100
12	March 31, 1921	1,864,000	86,900
13	April 1, 1921	1,704,000	94,600
14	April 2, 1921	1,648,000	89,850
16	April 4, 1921	1,680,000	78,650
17	April 5, 1921	1,688,000	84,150
18	April 6, 1921	1,568,000	94,000
19	April 7, 1921	2,144,000	90,700
23	April 11, 1921	2,064,000	78,100
25	April 13, 1921	2,120,000	80,850
31	April 19, 1921	2,560,000	96,800
36	April 24, 1921	2,688,000	84,700
40	April 28, 1921	2,804,000	
47	May 5, 1921	3,320,000	82,500
68	May 26, 1921	2,600,000	75,900
82	June 9, 1921	2,928,000	74,250
109	July 6, 1921	1,600,000	47,850
111	July 8, 1921	1,372,000	54,833

Observations on Patients with Secondary Anemia.—Four cases (E, F, G and H) of secondary anemia, accompanying an advanced nephritis, were studied in the same way. Before transfusion, the patients showed progressive anemias as proved by decreasing red cell counts. Patients F and H were bleeding constantly from the kidneys and their urines showed gross blood. Patient E had a very small amount of blood in the urine, averaging from five to six red blood corpuscles per low power field when examined microscopically, while Patient G showed no evidence of hematuria or bleeding elsewhere.

Case 5.—Patient E (Medical No. 15126), a man, aged 32, in Group II, had had chronic nephritis for about six months before admission to the hospital. On entry his systolic blood pressure was 190; diastolic, 110. Phenolsulphonephthalein excretion was 42 per cent., blood urea nitrogen, 20 mg. per hundred c.c. of blood. His urine showed a few red blood cells constantly, averaging about five or six per low power microscopic field. The blood findings were: hemoglobin, 60 per cent.; red cell count, 4,060,000 per c.mm.; reticulated cells, 0.9 per cent.; white cell count, 9,650 per c.mm. The red corpuscles were practically normal in size and shape but showed definite achromia. He was transfused with 600 c.c. citrated blood from a Group IV donor (Table 5, Fig. 5).

TABLE 5.—Blood Findings of Patient E

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	Jan. 15, 1921	4,060,000	
1	Jan. 15, 1921	Transfused 600 c.c. citrated blood, Group IV	
4	Jan. 18, 1921	4,644,000	623,700
42	March 1, 1921	4,992,000	244,750
52	March 11, 1921	4,792,000	332,750
64	March 23, 1921	4,560,000	239,800
70	March 29, 1921	4,656,000	162,250
77	April 5, 1921	4,008,000	143,550
84	April 12, 1921	3,544,000	90,750
92	April 20, 1921	3,368,000	94,600
99	April 27, 1921	3,420,000	82,650
108	May 6, 1921	2,936,000	151,800
119	May 17, 1921	3,248,000	34,650

Case 6.—Patient F (Medical No. 15371), a man, aged 23, in Group II, had had influenza followed by acute nephritis two years before his entrance to the hospital. He has passed bloody urine constantly since that time and throughout his stay in the hospital the urine showed gross blood. The phenolsulphonephthalein excretion varied from 18 to 35 per cent.; blood urea nitrogen was from 26 to 61 mg. per hundred c.c. on a low protein diet. Blood findings before transfusion were as follows: hemoglobin, 65 per cent.; red cell count, 4,512,000 per c.mm.; reticulated cells, 2 per cent.; white cell count, 11,200 per c.mm. The smear showed slight achromia of the red cells but was otherwise essentially normal in appearance. He was transfused with 550 c.c. citrated blood from a Group IV donor (Table 6; Fig. 6).

TABLE 6.—Blood Findings of Patient F

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	March 28, 1921	4,572,000	
6	April 5, 1921	Transfused 550 c.c. citrated blood, Group IV	
10	April 6, 1921	3,664,000	248,050
12	April 8, 1921	3,974,000	275,550
15	April 11, 1921	4,040,000	259,000
17	April 13, 1921	4,160,000	296,450
23	April 19, 1921	4,736,000	294,850
30	April 26, 1921	3,072,000	206,450
36	May 2, 1921	3,216,000	202,950
39	May 5, 1921	3,552,000	242,000
46	May 12, 1921	3,416,000	189,200
53	May 19, 1921	3,208,000	143,000
56	May 22, 1921	4,288,000	176,550
69	June 4, 1921	2,816,000	156,750
92	June 27, 1921	3,828,000	83,600
96	July 1, 1921	3,600,000	68,750
108	July 13, 1921	3,596,448	42,185
114	July 19, 1921	4,016,000	33,000

Case 7.—Patient G (Medical No. 14976), a man, aged 33, in Group II, had had nephritis for about eight months. Physical examination revealed ascites and considerable edema of the genitals and lower extremities. The blood pressure was: systolic, 128; diastolic, 96. Phenolsulphonephthalein excretion was 13 per cent., and blood urea nitrogen was 25 mg. per hundred c.c. The urinary sediment contained many hyalin, granular and waxy casts but no red blood cells. Before transfusion the red count was 3,736,000 per c.mm.; reticulated cells, 0.9 per cent.; hemoglobin, 45 per cent. The stained smear showed practically normal red cells with slight achromia. He was transfused with 250 c.c. citrated blood (containing 10 000,000 red corpuscles per c.mm.) from a donor in Group IV (Table 7, Fig. 7).

TABLE 7.—Blood Findings of Patient G

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	March 28, 1921	3,764,000	
35	May 2, 1921	2,896,000	
45	May 22, 1921	3,736,000	45,650
57	May 24, 1921	Transfused 250 c.c. citrated blood, Group IV	
59	May 26, 1921	5,064,000	285,600
67	June 3, 1921	4,576,000	261,250
74	June 10, 1921	3,984,000	209,850
79	June 15, 1921	4,688,000	240,500
85	June 21, 1921	5,024,000	265,650
94	June 30, 1921	4,416,000	163,350
105	July 11, 1921	4,344,000	179,500
112	July 18, 1921	5,712,000	130,550
142	August 17, 1921	4,456,000	69,300
150	August 25, 1921	4,128,000	56,100
156	August 31, 1921	4,800,000	49,550

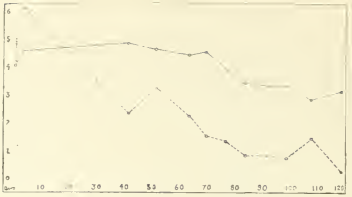

Fig. 5.—Blood findings of Patient E.

Fig. 6.—Blood findings of Patient F.

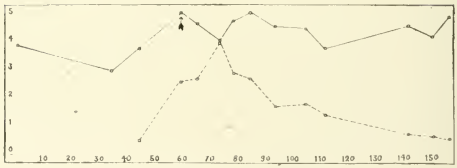

Fig. 7.—Blood findings of Patient G.

Fig. 8.—Blood findings of Patient H.

Case 8.—Patient H (Medical No. 15653), a boy, aged 16, in Group II had nephritis, of two months' duration, which followed a respiratory infection. He was not edematous and his blood pressure was: systolic, 148; diastolic, 90. The urinary sediment contained hyalin and finely granular brown casts and many red blood cells so that the blood was visible grossly from time to time. Phenolsulphonephthalein excretion was 50 per cent., and the blood urea nitrogen was 12 mg. per hundred c.c. His red cell count before transfusion was 3,360,000 per c.mm.; reticulated cells, 2.2 per cent.; hemoglobin, 52 per cent.; white cell count, 6,900 per c.mm. The stained smear showed slight achromia of the red corpuscles. He was transfused with 250 c.c. citrated blood (containing 10,000,000 red corpuscles per c.mm.) from a Group IV donor (Table 8, Fig. 8).

TABLE 8.—Blood Findings of Patient H

No. of Days	Date	Red Blood Cells	Unagglutinated or Donor's Cells
1	April 16, 1921	4,144,000	
17	May 2, 1921	3,672,000	
37	May 22, 1921	3,360,000	
39	May 24, 1921	Transfused 250 c.c. citrated blood, Group IV	
41	May 26, 1921	4,497,000	451,550
49	June 3, 1921	4,560,000	281,150
56	June 10, 1921	4,344,000	246,250
61	June 15, 1921	4,408,000	238,150
66	June 20, 1921	4,456,000	226,050
75	June 29, 1921	5,000,000	168,250
87	July 11, 1921	5,256,000	141,350
94	July 18, 1921	4,904,000	123,750
103	July 27, 1921	5,144,000	88,000
111	August 4, 1921	5,344,000	79,750
119	August 12, 1921	4,992,000	62,700
124	August 17, 1921	5,616,000	68,200
150	August 25, 1921	4,592,000	56,850
156	August 31, 1921	5,208,000	78,100
164	Sept. 8, 1921	4,688,000	48,900

DISCUSSION

Unfortunately it has not been possible in this investigation to study the length of life of cells transfused into normal individuals, but, in the light of the present findings, further studies on normals should be made. Ashby observed only one normal case until the transfused corpuscles disappeared from the circulation and found that they lived for thirty-nine days, while in her other two cases, which were followed incompletely, the cells lived about thirty-two days. In a later study, this author reports the length of life of transfused red blood cells in eight patients "without blood disease" to be very variable, some living as long as one hundred days, others disappearing in thirty days. The protocols of these patients, however, show that some of them had cancer or other malignant growths, one was in the tertiary stage of syphilis and none can be regarded as normal. Indeed, one finds included in the list patients with some of the most common and frequent causes of secondary anemia, and while in the technical sense of the term they may be "without blood disease" they show a decided disturbance of the blood.

Ashby found the length of life of the transfused erythrocytes in pernicious anemia to be about three months and concluded that there was no hemolytic toxin producing the anemia in this disease. The

results of this investigation show the length of life of the transfused corpuscles in primary anemia, and in the one type of secondary anemia studied, to be from seventy-one to one hundred and ten days, but it is felt that no conclusion regarding the presence of a hemolysin is justifiable, because these observations furnish no direct evidence on this point, and also because of the lack of accurate information as to the duration of life of red corpuscles transfused into normal persons. Furthermore, no evidence could be found to support the claim, made by Ashby, that "on the whole, blood destruction is quiescent in pernicious anemia." The results here show merely that the length of life of transfused erythrocytes is greater in patients with primary anemia and with secondary anemia due to nephritis, than in the one normal case on record; and this is only known to be true when the donor and recipient are of unlike groups. Whether or not the same would hold true when the donor and the recipient are in the same group it is not possible to say. In addition, these observations do not throw any light on what is happening to the patient's own cells during this period, and there is no reason to believe that the rate of destruction of the transfused cells is any indication of the rate of destruction of the patient's own cells, for it is possible that the transfused erythrocytes, belonging to a group foreign to the patient, are not acted on in the same manner as the patient's own cells.

It has not been proved conclusively that the transfused blood cells function during their stay in the circulation, but the fact that many of the patients show some clinical improvement after transfusion suggets that this is the case. Moreover, the observations of several investigators have shown that any foreign material, such as manganese or carbon particles and foreign blood cells, when injected into the blood stream of an animal are removed quickly.[4] This being the case, if the transfused cells were not living and functioning as normal red blood corpuscles one would expect them to be removed from the blood stream.

Several rises in the counts of transfused red cells were noted just before their final disappearance (Figs. 1 and 5). As the control counts on these days did not increase, and there was no variation in technic, differential counts of the number of microcytes were made to see if a breaking up or fragmentation of cells might account for these rises, but no evidence to support this theory was found. In view of the coincident rise of the total red blood cell count, it is not unlikely that changes in the blood volume account for the rise. One other possible explanation of this occurrence is that following transfusion there may be a definite improvement in the circulation with a resulting rise in

4. McJunkin: J. Exper. M. **21**:50, 1918. Lund, Shaw and Drinker: J. Exper. M. **33**:231, 1921. Drinker and Shaw: J. Exper. M. **33**:77, 1921.

the number of circulating cells in the periphery. This seems plausible in Case. 1.

The most striking result of these observations on the life of the transfused cells in the primary and secondary anemias is their surprisingly long stay in the circulation of the recipient. The longest period before the disappearance of the last cells was 113 days and the shortest fifty-nine days, the average for all these observed being about eighty-three days. It must be remembered that in addition to this period of life as transfused erythrocytes in a foreign circulation, that some of these corpuscles were functioning as adult cells in the donor before they were transferred, but of the length of time that they had been in the adult stage nothing is known, nor is there any accurate knowledge of the period of time required for a red blood cell to pass from its immature nucleated stage to its adult nonnucleated stage. These considerations, together with the findings of this investigation, indicate that the life of the human red blood cell is much longer than has been believed to be the case. Whether the duration of life and the stages of development of these cells would have been the same in the circulation of the individual from whom they originally came it is not possible to say.

It is also of interest that the life of the transfused red cells in both secondary and primary anemias was of the same duration. It seems almost probable that the transfused cells are adult red corpuscles of varying ages, and this, if true, would account for their steady gradual disappearance from the circulation of the recipient, also for the fact that some of the cells begin to disappear almost immediately after transfusion. This explanation is also compatible with the idea that new red corpuscles are being constantly supplied to the circulation. There were no sudden drops in the transfused cell count during these observations, but this may be due to the time intervals between counts, and in this connection it will be noted that two of the patients with pernicious anemia were women, both of whom had ceased to menstruate, so that no loss of transfused cells can be accounted for by that route, as noted by Ashby. In Case 6, in which there was constantly a large amount of blood in the urine, an attempt was made to determine the number of transfused corpuscles that were being lost in this way, but this was unsuccessful as the total unagglutinated count of the red corpuscles in the urine after centrifugalization was less than the control counts of the agglutinating serum on normal Group II blood.

Another point that is clearly brought out in this study is that due to the long life of the transfused red cells one may expect to tide patients over the acute stages of primary and secondary anemias by purely mechanical means. The improvement after some transfusions,

except when a real remission begins, might be explained by the increase in oxygen carriers. This improvement, which is generally of about two or three months' duration, is probably governed by the fact that some of the transfused corpuscles seem to function between sixty and ninety days.

CONCLUSIONS

Red blood corpuscles from donors in Group IV transfused into patients in Group II with pernicious anemia and anemia secondary to nephritis, remained in the circulation longer than has been generally believed to be the case. The last of the transfused red blood cells disappeared from the circulation in from fifty-nine to 113 days, with an average of eighty-three days.

No difference was noted in a series of observations in the duration of the stay of the transfused red blood corpuscles in the circulation between patients with primary anemia and secondary anemia (due to nephritis).

In a single observation red blood corpuscles from a patient with pernicious anemia transfused into another patient with pernicious anemia, behaved as did the corpuscles from normal donors.

BLOOD PRESSURE AND PULSE RATE LEVELS

FIRST PAPER: THE LEVELS UNDER BASAL AND DAYTIME CONDITIONS *

T. ADDIS
SAN FRANCISCO

This study is primarily concerned with the question of normal blood pressures and pulse rates under varying conditions. The observations on patients cover only a restricted field and are introduced, in the main, as illustrations of the deductions which may be drawn from comparison with the normal data. The work falls naturally into two parts, one, the measurement of the level of pressure and pulse rate under fixed conditions, with which this paper is concerned; the other, the measurement and interpretation of the changes in pressure and pulse rate induced by alteration of the conditions, which are dealt with in a succeeding paper. Most of the observations were made on soldiers at Camp Lewis, Wash. For the opportunity to do this work I am indebted to Dr. Kerr, who was in charge of the medical division of the Base Hospital, to Dr. Northington and Dr. Fulton who were successively in command, and to Lieutenant-Colonel Gibner who was camp surgeon.

The level of pressure and pulse rate under what we have called "basal" and "daytime" conditions is the subject of this paper. In work on metabolism the word basal is used to indicate that the measurements have been made in the early morning before food has been taken and before the subject has done any muscular work. In this paper it has the same significance. The observations were made in the early morning before the subjects had risen from bed. In most cases they were first awakened by the application of the arm band. By daytime observations are meant those taken at various times during the day after the subjects had risen from bed and had taken food. In all cases the readings were made while the men were lying down. Those who had recently done any strenuous muscular work were excluded. Most of the work was done on Sundays when bad weather had kept the men relatively inactive in their barracks.

The incentive to collect data on the normal basal blood pressure and pulse rate was derived from a difficulty in diagnosis in a group of patients who presented signs and symptoms resembling those seen in hyperthyroidism. While recruits from the first and second drafts were arriving at Camp Lewis, men were seen every day who combined an enlargement of the thyroid gland with tachycardia, tremor and evident

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signs of nervous instability. It was recognized from the first that only a small percentage were likely to have exophthalmic goiter for true exophthalmos was rare. The hyperthyroidism which arises in some cases of endemic goiter is uncommon at the age period of the men we were examining, and we were dealing with a condition which was not at all uncommon. It was noted also that similar signs and symptoms were found in men who had no thyroid enlargement, and on this account a statistical study was made of the incidence of tachycardia, tremor and various other abnormalities in large groups of men with and without increase in the size of the thyroid gland.[1] This survey showed that there was no definite relationship between the thyroid enlargement and the occurrence of tachycardia, tremor and other evidences of vascular and nervous instability. It appeared, then, that the thyroid enlargement was only a chance concomitant which was frequently present simply because endemic goiter was so extremely prevalent in many of the districts from which the recruits were drawn.[2] It thus seemed still more unlikely that hyperthyroidism could be a frequent cause of the condition. We felt confident that the great majority of these men were suffering from the condition described under the names irritable heart, neurocirculatory asthenia and effort syndrome. But in individual cases there was often uncertainty, and this led to a search for some objective clinical evidence of an increase in basal metabolism, to take the place of the direct measurements of oxygen consumption which we could not at that time obtain.

A relationship has been shown to exist between the pulse rate and the metabolism when they are measured under the same conditions, and for some time we placed a great deal of weight on the pulse rate counted in the early morning before the patients had risen from bed. When the pulse rate was less than 70 in patients who during the day had tachycardia and tremor, we felt that we could probably exclude hyperthyroidism. However, the relation between pulse rate and rate of metabolism is not always close. It seems likely that the reason for the relation which does exist is to be found in a more general relation between the metabolic activity of the body as a whole and the activity of the circulatory system of which the pulse rate is only a partial expression. The true measure of circulatory activity is the volume flow of blood per unit of time. It has been shown by combined circulatory and metabolic measurements that there is a close correspondence between volume flow of blood and rate of metabolism. The volume flow of blood per unit of time has been determined in man by

1. Addis and Kerr: Arch. Int. Med. **23**:316 (March) 1919.
2. Kerr: Arch. Int. Med. **24**:347 (Sept.) 1919.

Lindhard [3] and by Means and Newburgh.[4] The output of the heart was measured by gas analysis methods over a short space of time during which the pulse rate was counted. The average output at each beat of the heart was thus calculated, and the volume flow of blood per minute obtained from the product of the systolic output per beat and the pulse rate per minute. In subjects on whom measurements were made before and after exercise a remarkably close agreement was found between the increase in this product and the increase in the rate of metabolism produced by exercise. Bainbridge [5] recently pointed out that a comparison of such experiments shows that the two factors in the product which measures the volume flow of blood—the systolic output per beat and the pulse rate—may each vary, although for given metabolic conditions the product will remain constant. The required volume flow of blood may at one time be obtained mainly by increase in systolic output and at another time mainly by increasing the pulse rate. This circumstance seems to account for the absence of any very direct relation between pulse rate and rate of metabolism, and it also indicates that if we were able to get some clinical measure of the systolic output at each beat of the heart, even though it were only approximate, we might have a better index of the rate of metabolism than can be obtained from the pulse rate alone.

Measurements of systolic output by the nitrous oxid or any other blood analysis method are usually out of the question in clinical work. But von Recklinghausen [6] has shown that the pulse pressure varies directly with the systolic output per beat, except for such variations as may arise from differences in the coefficient of elasticity in the arteries. This has recently been experimentally confirmed by Bazett.[7] It appeared, therefore, that the product of the pulse pressure and the pulse rate might have a close relation to the rate of metabolism unless differences in the elasticity of the arteries in different individuals were so marked as seriously to distort the relation between systolic output and pulse pressure. Even if that should be the case the P. P. (pulse pressure) $\times$ P. R. (pulse rate) product might still be a useful clinical method for the purpose of obtaining an indication of the direction of metabolic changes in the same individual at different times.

These considerations, but especially the results of experiments on the effect of exercise on the P. P. $\times$ P. R. product which are given in the next paper, made it seem worth while to collect data on

3. Lindhard: Arch. f. d. ges. Physiol. **161**:233, 1915.
4. Means and Newburgh: J. Pharmacol. & Exper. Therap. **7**:441, 1915.
5. Bainbridge: Physiology of Muscular Exercise. 1919.
6. Von Recklinghausen: Arch. f. exper. Path. **56**:1, 1907.
7. Bazett: Proc. Roy. Soc. London, Ser. B **90**:415, 1917.

the P. P. × P. R. product in normal persons under basal conditions in order to get a control for similar observations on patients. The results, of course, do not allow of any conclusion as to whether the P. P. × P. R. product has a closer or even as close a relation to the basal metabolic rate as the pulse rate alone. That question can only by answered by direct comparison with a parallel series of determinations of basal metabolism. But the figures have an interest of their own apart from any possible significance they may have in connection with basal metabolism. In addition to these early morning observations, the pressure and pulse rate was measured on another group of normal individuals during the day under the conditions we have defined above for daytime observations.

In both the basal and daytime observations the pressure and pulse rate were observed simultaneously, the pulse rate being counted by an assistant while the systolic and diastolic pressures were being read. A mercury sphygmomanometer with a broad arm band was used. The diastolic pressure was taken at the end of the third phase or at the cessation of sound in those subjects in whom no fourth phase could be distinguished.

In Table 1 the basal and daytime results on normals are compared. The basal averages were obtained from eighty-nine observations on seventy-six persons, and the daytime figures from 300 measurements on 300 persons. Both groups comprised soldiers on active service between the ages of 21 and 31.

These results are a contribution toward the accumulation of data required for a definition of what is meant by normal pressure and pulse rate. Though a great deal of work has been done on the subject, the figures have usually been presented in such a way as to preclude the application of the statistical methods which are essential for an adequate understanding of their significance. The variability of the systolic, diastolic and pulse pressure has been admirably dealt with by Kilgore,[8] and Alvarez and his associates[9] have published a complete statistical review of a large series of measurements of systolic pressure in normal individuals. Alvarez arranged his data in groups according to the ages of the subjects, but no significant change in the systolic pressure was found between the ages of 21 and 31. We may, therefore, compare his average systolic pressure of 126.5 on 2,930 men with our average of 127.4 on 300 men, and his coefficient of variation of 12 per cent. with ours of 13 per cent. So far as the diastolic and pulse pressure are concerned, the only data available for the determination

8. Kilgore: Lancet **2**:236, 1918.
9. Alvarez, Wulzen, Taylor and Starkweather: Arch. Int. Med. **26**:381 (Sept.) 1920.

of variability seem to be the frequency distributions of Barach and Marks [10] and of Kilgore.[8] All these results were obtained under conditions similar to those we observed in our daytime observations. Only a few isolated measurements were found which were carried out under what we have called basal conditions.

TABLE 1.—Normal Data. Basal Measurements of Seventy-Six Normals Compared with Daytime Measurements on Three Hundred Normals

Averages

	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	99	71	28	63	1764
Day	127	78	50	80	3980

Standard Deviations

	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	±11.0	± 9.7	± 8.5	± 8.1	± 635
Day	±17.9	±11.1	±13.8	±12.4	±1550

Coefficients of Variation

	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	11%	14%	30%	13%	36%
Day	13%	14%	28%	16%	38%

Frequency Distributions

Systolic			Diastolic			Pulse Pressure			Pulse Rate			P. P. × P. R		
Cl. Int.	Basal	Day	Cl. Int.	Basal	Day	Cl. Int.	Basal	Day	Cl. Int.	Basal	Day	Cl. Int.	Basal	Day
71- 80	9%	—	41- 50	5%	2%	11-20	27%	1%	37- 44	1%	—	0- 999	11%	—
81- 90	16%	2%	51- 60	51%	6%	21-30	45%	9%	45- 52	13%	—	1000- 1999	61%	6%
91-100	34%	6%	61- 70	39%	28%	31-40	25%	23%	53- 60	40%	8%	2000- 2999	26%	18%
101-110	34%	11%	71- 80	39%	34%	41-50	2%	33%	61- 68	30%	13%	3000- 3999	2%	31%
111-120	5%	22%	81- 90	6%	23%	51-60	1%	20%	69- 76	10%	27%	4000- 4999	..	19%
121-130	2%	28%	91-100	—	5%	61-70	—	7%	77- 84	3%	29%	5000- 5999	..	10%
131-140	—	16%	101-110	—	3%	71-80	—	4%	85- 92	2%	14%	6000- 6999	..	4%
141-150	—	10%	.....			81-90	—	3%	93-100	—	11%	7000- 7999	..	4%
151-160	—	4%	.....			.....			101-108	—	3%	8000- 8999	..	2%
161-170	—	1%	.....			.....			109-116	—	0.6%	9000- 9999	..	0%
171-180	—	1%	.....			.....			117-124	—	0.6%	10000-10999	..	0%
									125-132	—	0.3%	11000-11999	..	0.3%

The differences between the basal and day averages show how markedly the level of pressure and pulse rate is influenced by factors associated with daytime activities. A measure which would be "normal" for the day would be unusually high if it were found under basal conditions in the early morning, so that the interpretation of the significance of any given pressure or pulse rate depends, in the first place, on a knowledge of the conditions under which the observation was made.

During the day the P. P. × P. R. product increases more markedly than the other measurements because both pulse pressure and pulse rate rise. The increase in pulse pressure occurs in spite of a slight

10. Barach and Marks: Arch. Int. Med. **13**:648 (June) 1914.

increase in diastolic pressure and is due entirely to the rise in systolic pressure. Since the systolic pressure, other things being equal, is determined by the amount of blood pumped out by the heart, we may assume that during the day the output of the heart at each systole is increased. The increase in pulse rate shows that there are a larger number of systoles per unit of time. The changes induced by daytime conditions are, therefore, such as we should expect to find if there were an increase in the volume flow of blood.

There are two factors which are certainly of importance in raising the daytime levels. One of them is the effect of food, which has been shown by Weysse and Lutz [11] to result in an increase in systolic pressure and pulse rate. The other factor is exercise. In Table 2 averages are given from a group of ten normal persons under basal and daytime conditions and after a shorter or longer period of exercise.

TABLE 2.—Effect of Exercise on Blood Pressure and Pulse Rate Levels of Normal Individuals

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	100	65	35	60	2100
Day time	121	77	44	74	3256
Short exercise	137	59	78	81	6289
Longer exercise	168	42	126	114	14360

There is another factor—excitement—which may have been equally operative under both basal and daytime conditions. In Table 3 daytime averages from a group of twenty-seven men who were not excited are compared with averages from a group of twenty-seven men who admitted that the examination excited them because they were afraid that something would be found which would prevent them going over with their regiment.

TABLE 3.—Effect of Excitement on the Daytime Levels of Pressure and Pulse Rate in Normal Individuals

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
No excitement	122	79	43	80	3440
Excitement	154	89	65	92	5980

These three factors, food, exercise and excitement, all have their most marked effect on the systolic pressure and pulse rate. The measurement which is least influenced is the diastolic pressure. Food has little or no effect; exercise lowers it, and excitement increases it, but it remains the most stable measure, so that in daytime observations on patients when all three factors are operative, an increase in diastolic

11. Weysse and Lutz: Am. J. Physiol. **37**:330. 1915.

pressure is likely to be of more significance than the same degree of increase in systolic pressure.

The significance of any measurement which deviates from the normal average depends on the variability or degree of dispersion of the normal measurements. This variability is given in the standard deviation. The relation between the actual deviation of the measurement and the standard deviation can be expressed in a concrete way as odds against the possibility that any normal subject would give as high or a higher level of pressure or pulse rate than the measurement in question. A discussion of this statistical method will be found in a recent very complete study of blood pressure and pulse rate in children by Faber and James.[12] In Tables 4 and 5 the odds for a series of measurements for basal and daytime conditions are given.

TABLE 4.—Basal Conditions. The Odds That a Normal Individual Under Basal Conditions Will Show as High or a Higher Level of Pressure and Pulse Rate as Those Given Below

Systolic	Odds	Diastolic	Odds	Pulse Pressure	Odds	Pulse Rate	Odds	P. P. × P. R.	Odds
118	1 in 24	88	1 in 25	43	1 in 26	77	1 in 24	2600	1 in 27
119	1 in 29	89	1 in 32	44	1 in 33	78	1 in 31	2650	1 in 33
120	1 in 36	90	1 in 40	45	1 in 44	79	1 in 42	2900	1 in 39
121	1 in 44	91	1 in 51	46	1 in 59	80	1 in 56	3050	1 in 47
122	1 in 55	92	1 in 67	47	1 in 80	81	1 in 76	3100	1 in 58
123	1 in 69	93	1 in 86	48	1 in 106	82	1 in 106	3150	1 in 69
124	1 in 86	94	1 in 112	49	1 in 147	83	1 in 147	3200	1 in 84
125	1 in 104	95	1 in 147	50	1 in 208	84	1 in 208	3250	1 in 104
126	1 in 141	96	1 in 204	51	1 in 306	85	1 in 293	3300	1 in 128
127	1 in 182	97	1 in 270	52	1 in 417	86	1 in 435	3350	1 in 161
128	1 in 233	98	1 in 385	53	1 in 625	87	1 in 666	3400	1 in 201
129	1 in 313	99	1 in 526	54	1 in 910	88	1 in 1000	3450	1 in 256
130	1 in 417	100	1 in 770	55	1 in 1430	.....	.....	3500	1 in 323
131	1 in 555	101	1 in 1000	.....	.....	.....	.....	3550	1 in 417
132	1 in 741	.....	.....	.....	.....	.....	.....	3600	1 in 526
133	1 in 1000	.....	.....	.....	.....	.....	.....	3650	1 in 666
								3700	1 in 833
								3750	1 in 1111

The odds given in these tables refer only to the normal, they cannot be interpreted as odds in favor of abnormality. To know the latter, we should have to measure the standard deviation of the group of abnormals to which the patient happened to belong. However, for practical purposes of classification of cases it is permissible arbitrarily to decide that any patient whose pressure exceeds a certain level shall be regarded as "abnormal." The choice of that level will depend on the nature of the work. It is sometimes desirable to have a standard so narrow that all cases with a possible pathologic tendency to hypertension will be detected. Then a level at which the odds are that only one normal out of, say, twenty-five would give as high a pressure may be taken. But at other times one may desire to separate a group of

12. Faber and James: Am. J. Dis. Child. **22**:7 (July) 1921.

cases in which it is practically certain that there are no normals. Then a level at which the chances are that only one out of 1,000 normals will be so high may be selected as the dividing point.

These statistical methods give no information as to the nature of the factor responsible for any unusually high pressure which may be found in a patient. If it is a daytime observation it may be the result of an abnormal susceptibility to purely external and evanescent causes such as food, excitement or exercise, rather than the inner and more lasting perversion of function we are accustomed to think of in connection with hypertension.

TABLE 5.—Daytime Conditions. The Odds That a Normal Individual Under Daytime Conditions Will Show as High or a Higher Level of Pressure or Pulse Rate as Those Given Below

Systolic	Odds	Diastolic	Odds	Pulse Pressure	Odds	Pulse Rate	Odds	P. P. × P. R.	Odds
160	1 in 23	97	1 in 23	74	1 in 24	102	1 in 27	6799	1 in 26
161	1 in 26	98	1 in 29	75	1 in 29	103	1 in 32	6800	1 in 29
162	1 in 29	99	1 in 34	76	1 in 33	104	1 in 38	6900	1 in 33
163	1 in 33	100	1 in 42	77	1 in 40	105	1 in 47	7000	1 in 39
164	1 in 38	101	1 in 52	78	1 in 47	106	1 in 55	7100	1 in 45
165	1 in 44	102	1 in 65	79	1 in 56	107	1 in 69	7200	1 in 53
166	1 in 51	103	1 in 82	80	1 in 67	108	1 in 84	7300	1 in 62
167	1 in 58	104	1 in 104	81	1 in 80	109	1 in 101	7400	1 in 74
168	1 in 69	105	1 in 133	82	1 in 98	110	1 in 128	7500	1 in 86
169	1 in 78	106	1 in 170	83	1 in 119	111	1 in 161	7600	1 in 104
170	1 in 91	107	1 in 222	84	1 in 145	112	1 in 204	7700	1 in 124
171	1 in 106	108	1 in 286	85	1 in 182	113	1 in 250	7800	1 in 147
172	1 in 125	109	1 in 385	86	1 in 222	114	1 in 323	7900	1 in 175
173	1 in 147	110	1 in 500	87	1 in 270	115	1 in 416	8000	1 in 208
174	1 in 175	111	1 in 666	88	1 in 333	116	1 in 526	8100	1 in 256
175	1 in 207	112	1 in 910	89	1 in 417	117	1 in 714	8200	1 in 303
176	1 in 250	113	1 in 1250	90	1 in 526	118	1 in 910	8300	1 in 385
177	1 in 294	.....	.....	91	1 in 666	119	1 in 1250	8400	1 in 455
178	1 in 345	.....	.....	92	1 in 834	.....	.....	8500	1 in 588
179	1 in 417	.....	.....	93	1 in 1111	.....	.....	8600	1 in 714
180	1 in 500	.....	.....	.....	.....	.....	.....	8700	1 in 833
181	1 in 625	.....	.....	.....	.....	.....	.....	8800	1 in 1111
182	1 in 740								
183	1 in 909								
184	1 in 1111								

The striking difference between the averages of normal individuals under basal and daytime conditions are the clearest illustration of the necessity for uniformity in the conditions under which the observations are made. It is not possible to use the basal normal for the evaluation of pressures obtained in patients in the morning if they have been out of bed even for a moment. The normal values for daytime measurements cannot be taken as a standard for observations made on patients who are standing or sitting, or on those who have just walked up a flight of stars. The variability of normal blood pressure under such conditions is not known.

1. IRRITABLE HEART

The measurements on patients were carried out under the same basal conditions as were observed with the normal controls. The cases

were in each instance tentatively diagnosed as cases of irritable heart with the exception that a reservation was made in regard to the possibility of true hyperthyroidism. These cases were selected from a larger group on the following basis. The patients all complained of one or more of three cardiac symptoms—dyspnea, palpitation, precordial pain; one or more of the three symptoms of vascular instability—dizziness, flushing, fainting, and, in addition, they gave some evidence of general nervous instability. In the great majority of cases these symptoms antedated enlistment, and often dated back to childhood. Persons presenting these symptoms following some infectious disease were excluded, and in none could a diagnosis of organic cardiac disease be made. In almost all cases, tachycardia and tremor were present at one time or another. The hands were usually cyanosed, cold and clammy. These patients thus seemed to belong to what has been called the constitutional type of irritable heart, or neurocirculatory asthenia. Basal pressure and pulse rate measurements were made on 138 of these patients. In Table 6 the averages, standard deviations and frequency distributions are given.

TABLE 6.—Basal Measurements on Patients Provisionally Diagnosed as "Irritable Heart" Cases

Averages

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
105	72	33	65	2145

Standard Deviations

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
±11.8	±10.9	±9.0	±8.9	±706

Coefficients of Variation

Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
11%	15%	27%	14%	33%

Frequency Distributions

Systolic		Diastolic		Pulse Pressure		Pulse Rate		P. P. × P. R.	
Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl.Int.	Per Cent.
71- 80	4	31- 40	1	11-20	16	37-44	1	100- 999	2
81- 90	11	41- 50	3	21-30	47	45-52	12	1000-1999	54
91-100	30	51- 60	12	31-40	26	53-60	38	2000-2999	35
101-110	30	61- 70	37	41-50	9	61-68	38	3000-3999	8
111-120	21	71- 80	34	51-60	1	69-76	12	4000-4999	1
121-130	4	81- 90	11	.....		77-84	6		
		91-100	2	.....		85-92	3		
		101-110	1						

The average level of all the measurements on the patients is slightly higher than the basal averages for normals given in Table 1. The greatest increase is in the P. P. × P. R. product. In this case the difference is statistically significant, for when the "probable difference between the averages" is determined the odds are found to be about 64

to 1 against the possibility that the increase from 1,764 for the normals to 2,145 for the patients can have arisen simply as the result of chance. It would appear, then, that some factor not operative in the normal cases had increased the P. P. × P. R. This might have been the inclusion of some cases of hyperthyroidism or the same difference might be due to a greater nervous excitability in the patients. But whatever the cause may have been, it is evidently of relatively slight importance, since all but 1 per cent. of the observations on patients fall within the range of variation of the normal. It seemed to us to be of particular significance that patients whose condition during daytime examinations showed so many points of resemblance to hyperthryroidism should in the early morning, under basal conditions, give evidence of an inactivity and quietude of the circulatory system which seemed inconsistent with the hypothesis of a state of continuing metabolic activity, such as exists in hyperthyroidism. It is true that in individual cases we were sometimes still in doubt, but the important question at the time was one of group diagnosis; and the fact that a normal basal product, as well as a normal basal pulse rate, was found in practically all these patients was of aid, in conjunction with other evidence, in leading us to reject a diagnosis of hyperthyroidism for this group of patients. At a later date Peabody, Wearns and Tompkins[13] showed the correctness of this conclusion by demonstrating that patients of this type, many of whom had been diagnosed as having hyperthyroidism, had an entirely normal rate of basal metabolism.

An increase in the P. P. × P. R. product may be found in patients in whom there is no reason to suspect any increase in the rate of metabolism. This is shown in the daytime measurements given in Table 7.

TABLE 7.—Daytime Measurements Showing Increase in P.P × P.R. Product

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Normals	127	78	50	80	3980
Patients	190	113	77	79	6083

The patients were nineteen middle aged or old people who had hypertension. They were unselected cases, except that those with cardiac decompensation or advanced renal disease were excluded. There were no indications whatsoever of any increased metabolic activity, rather the reverse. Yet their P. P. × P. R. product is markedly increased, but it is an increase due to a rise in only one factor of the product, the pulse pressure. Furthermore, it has been shown that any decrease in the elasticity of the large vessels between the heart

13. Peabody, Wearn and Tompkins: Med. Clin. N. America **2**:507, 1918.

and the brachial artery will result in an increase in pulse pressure because the pressure will rise higher at each systole, if the vessels are rigid than if they give way to some extent when the blood is forced into them by the heart.[6] Hence, when a product is found to be high only because of an increase in pulse pressure it would be well to suspect the presence of an inelastic aorta, rather than an increased output of the heart.

Daytime measurements were also made on 156 patients who were believed to have an irritable heart. This group includes the 138 persons whose basal pressures and pulse rates were obtained. The averages given in Table 8 are derived from 580 observations.

TABLE 8.—Daytime Measurements on Patients Provisionally Diagnosed as "Irritable Heart" Cases

Averages				
Systolic 131	Diastolic 75	Pulse Pressure 55	Pulse Rate 85	P. P. × P. R. 4680
Standard Deviations				
Systolic ±18.5	Diastolic ± 11.5	Pulse Pressure ±17.5	Pulse Rate ±13.4	P. P. × P. R. ±1982
Coefficients of Variation				
Systolic 14%	Diastolic 15%	Pulse Pressure 32%	Pulse Rate 16%	P. P. × P. R. 43%

Frequency Distributions

Systolic		Diastolic		Pulse Pressure		Pulse Rate		P. P. × P. R.	
Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl. Int.	Per Cent.	Cl.Int.	Per Cent.
71– 80	0.2	31– 40	1	11– 20	1	37– 44	..	0– 999	..
81– 90	0.5	41– 50	2	21– 30	7	45– 52	..	1000– 1999	2
91–100	5	51– 60	10	31– 40	17	53– 60	2	2000– 2999	13
101–110	8	61– 70	26	41– 50	27	61– 68	8	3000– 3999	23
111–120	21	71– 80	36	51– 60	20	69– 76	22	4000– 4999	23
121–130	27	81– 90	21	61– 70	15	77– 84	23	5000– 5999	15
131–140	18	91–100	4	71– 80	6	85– 92	20	6000– 6999	10
141–150	10	101–110	1	81– 90	4	93–100	14	7000– 7999	6
151–160	6	111–120	0.2	91–100	2	101–108	7	8000– 8999	3
161–170	3	.....	.....	101–110	1	109–116	5	9000– 9999	2
171–180	2	.....	.....	111–120	0.2	117–124	1	10000–10999	1
181–190	0.4	.....	.....	121–130	0.2	125–132	1	11000–11999	0.4
191–200	0.5	.....	.....	.....	.....	.....	.....	12000–12999	0.2
								13000–13999	0.2

The averages show a little increase in systolic pressure and pulse rate as compared with the normals—131 as compared with 127. There is also a somewhat greater variability in systolic, diastolic and pulse pressures and P. P. × P. R. in the patients as compared with the controls. But these differences are slight. This is of interest since it will be shown in the next paper that a marked variation from the normal can be demonstrated in this group of patients under conditions which impose a strain on the cardiovascular system.

2. HYPERTENSION IN YOUNG MEN

In eighteen soldiers between 21 and 31 years of age a systolic pressure of more than 150 was found on repeated daytime examinations.

These cases are briefly reviewed here because a comparison of their basal and day measurements brought up a point which may prove to be of some importance. They can be separated into four groups in accordance with the conditions associated with the hypertension.

The first group comprises six cases in which no other evidence of disease than the hypertension was found. The following is a summary of the record of the only case in this group in which cardiac enlargement was found.

Case 1.—Sa., aged 26; no complaint.

Mother died of heart disease. Measles and diphtheria in childhood. Pneumonia when 8 years old.

Six months ago, while doing heavy work in France, he became breathless on exertion. He reported for examination, and has been kept on light duty since then. Neither before nor since that time has he had any complaint.

The heart appeared to be enlarged and this was confirmed by roentgen-ray examination, which showed an increase in the transverse diameter. There was a systolic murmur best heard over the aortic area and audible in the neck. There was no thrill. The Wassermann was negative.

After restriction of fluids the night urine had a specific gravity of 1.025 on one occasion, and 1.030 on another. No albumin or casts were found. Phenolsulphonephthalein excretion was 80 per cent. in two hours and ten minutes after intramuscular injection.

Ophthalmoscopic examination showed a greater tortuosity than usual in the retinal vessels, but no thickening of the arteries.

TABLE 9.—Basal and Daytime Pressures and Pulse Rates on Hypertension Cases Not Associated with Any Discoverable Disease

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Sa.	170	105	65	64	4160	223	115	108	96	10380
Fr.	140	90	50	96	4800	135	80	75	122	9150
W.	133	77	56	80	4480	164	78	86	93	8000
L.	118	73	45	80	3600	164	99	65	91	5910
Sto.	130	80	50	60	3000	156	90	66	91	6006
Stoc.	120	85	35	60	2100	168	95	73	86	6278

The second group includes eight patients who were all typical instances of constitutional neurocirculatory asthemia. The record of the patient Ta is characteristic of this group.

Case 2.—Ta., aged 28; complains of dyspnea, palpitation, precordial pain, dizziness, frequent fainting and extreme "nervousness." Duration, twelve years or more.

His father is very nervous. His mother is subject to fits. His sister has heart trouble.

The only serious illness he remembers is typhoid fever when he was 16 years old.

He has never been able to do hard work. While he was in Italy he was three times drafted into the army, but each time he was discharged on account of disability.

The heart showed no evidence of enlargement. There was a faint systolic murmur at the apex. The pulse rate was always regular, but usually rapid. The hands were often blue and cold and there was a marked tremor. There was no enlargement of the thyroid or protrusion of the eyes. The urine contained no albumin or casts.

TABLE 10.—Basal and Daytime Pressures and Pulse Rates on Hypertension Cases Associated with Neurocirculatory Asthenia (Irritable Heart)

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Ta.	135	70	55	80	4400	160	91	69	94	6490
R.	135	93	42	72	3024	158	106	52	96	4980
Sch.	130	110	20	84	1680	175	106	69	154	8540
O.	120	70	50	60	3000	154	72	82	90	7380
Fri.	120	90	30	72	2160	157	88	69	83	5720
Greenw.	113	80	33	72	2380	177	97	80	90	7200
Greenb.	110	80	30	72	2160	162	97	65	97	6305

The third group contains two cases associated with active pyogenic infection.

Case 3.—Ri. had experienced some shortness of breath and palpitation on exertion two years before, but these symptoms had been greatly aggravated following a mastoid and frontal sinus infection from which he was still suffering.

Case 4.—Ch. also complained of most of the symptoms experienced by the irritable heart group, but he had a pronounced infection of the urinary tract associated with evidences of renal decompensation. His urine contained much pus and was always of low specific gravity even after restriction of fluids. His phenolsulphonephthalein excretion was 15 per cent., two hours and ten minutes after intramuscular injection. After intravenous injection, 8 per cent. was excreted in sixteen minutes from the left kidney and none from the right. Pus was seen coming from both ureters. No tubercle bacilli were found.

TABLE 11.—Basal and Daytime Pressures and Pulse Rates on Hypertension Cases Associated with Pyogenic Infections

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Ri.	135	90	45	68	3060	172	108	64	84	5380
Chi.	132	75	67	68	4556	160	72	88	80	7040

In the last group there are two cases with advanced Bright's disease.

Case 5.—R. was 21 years old. He complained of occasional headaches.

He had scarlet fever when a child. Two years ago his ankles were swollen and painful for some weeks, and a year ago there was a recurrence of this condition.

There was a diffuse retinitis in both eyes. The urine contained a moderate amount of albumin. The specific gravity never rose above 1.016 in spite of fluid restriction. The sediment showed coarsely granular and highly refractile casts, many of them three to four times broader than the usual cast. Only a trace of phenolsulphonephthalein was excreted. The blood urea concentration was 171 mg. per hundred c.c.

Case 6.—C. also complained of occasional headaches. His urine contained a moderate amount of albumin, and the sediment showed a fair number of blood casts. The phenolsulphonephthalein excretion was 25 per cent. in two hours and ten minutes.

TABLE 12.—Basal and Daytime Pressures and Pulse Rates on Hypertension Cases Associated with Advanced Bright's Disease

	Basal					Daytime				
Name	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
R.	169	118	51	60	3060	173	123	50	69	3450
C.	148	120	28	59	1652	167	107	60	66	3960

Only a few of the basal measurements on these patients would have been regarded as unusual if the low average pressure and narrow range of variation of normal individuals had not been known. But taking all these figures together, the average systolic pressure in the early morning is 32 mm. above the normal basal average as compared with a daytime systolic pressure 40 mm. in excess of the normal daytime average. As a whole, then, these hypertension cases, selected because of their high daytime systolic pressures, still showed hypertension in the early morning when the pressor stimuli of the day were no longer in action. The point, however, which seems to me to be of special clinical significance is the wide variation in the degree of reduction of pressure during the night shown by the different individuals of this series. The first case in Group I and the two nephritic cases are distinguished from the others by the relatively slight decrease of pressure in the early morning and especially by the maintenance of high diastolic pressures. In a large series of cases it might be possible to distinguish two types of hypertension, one in which there is a pronounced fall in pressure under basal conditions and another in which the decrease is only slight. It is true that such a distinction would be one of degree only and would not necessarily depend on any difference in etiology. But from the point of view of prognosis it is surely of importance. In the patient Greenw., for instance, the average daytime pressure of 177 systolic and 97 diastolic will be more easily borne than the systolic of 167 and the diastolic of 107 in the patient C. with Bright's disease, because in the first case the cardiovascular system is rested each night by the fall to the basal levels of 113 and 80, whereas in the renal case there is no remission, and the heart has continually to work against a high diastolic pressure.

SUMMARY

1. The blood pressure and pulse rate of normal persons were measured under what are called basal conditions, i. e., in the early morning before the subjects had risen from bed or taken food. These results

are contrasted with similar measurements on normal persons under what are called daytime conditions, i. e., at any time during the day after the subjects had risen from bed and had had food, but in all cases in the recumbent position and with the exclusion of those who had recently undergone any muscular exertion, such as stair climbing or drilling. The averages obtained are shown in Table 13.

TABLE 13.—AVERAGES OF PULSE PRESSURE AND PULSE RATE

Conditions	Systolic	Diastolic	Pulse Pressure	Pulse Rate	P. P. × P. R.
Basal	99	71	28	63	1764
Day time	127	78	50	80	3980

2. The variability of normal basal and daytime pressures and pulse rates is defined by statistical methods and probability tables for use in clinical work are given.

3. The significance of the difference between basal and daytime pressures and pulse rates is discussed, and data on the influence of exercise and of psychic disturbance on pressure and pulse rate levels are given.

4. Measurements of basal and daytime levels were made on patients, and the deductions which may be drawn from comparison with the normal data are discussed.

BOOK REVIEWS

DIAGNOSTISCHE WINKE FUR DIE TAGLICHE PRAXIS. Dr. E. Graetzer. Verlag von S. Karger, Berlin, 1920.

Books of this type are intended for the medical student and the general practitioner. They have a certain value and are a type of reference a busy and perplexed practitioner will most readily consult. This text will appeal because it deals largely with the atypical forms and symptoms of various diseases. These are given in considerable detail. A brief résumé of the normal train of symptoms of a given disease precedes the description of the atypical forms. This should prove a valuable feature of the book. Differential diagnoses are generally only mentioned. It is obviously difficult and probably hardly intended that a text of this kind should cover any subject in detail. Its function is limited and chiefly lies in the fact that it serves as a quick reference and that it emphasizes the unusual features of a given disease. The frequent allusions throughout the book to other sources of reference should prove very helpful.

THE EVOLUTION OF DISEASE. By Prof. J. Danysz. Translated by Francis M. Rackemann, M.D. Philadelphia: Lea & Febiger, 1921.

The subtitle of Professor Danysz' book, which is "A Discussion of the Immune Reactions Occurring in Infectious and Noninfectious Disease. A Theory of Immunity, of Anaphylaxis and of Antianaphylaxis," indicates, in a general way, the scope of the subject matter. In effect, it is an argument for the selective rather than the specific action in the process of immunity and anaphylaxis. Throughout most of the book the reviewer follows the argument with considerable interest. As long as the discussion is largely theoretical, in spite of the fact that it is an illustration of special pleading, and that it is somewhat involved with specialized terms, the argument is somewhat convincing. The effect of the illustrative cases reported by Professor Danysz, many of which are tactfully omitted by the translator, is, however, to shake the confidence in the earlier theoretic discussion. The results from the administration of a bacterial vaccine derived from certain bacteria of the intestinal flora in a wide variety of conditions, including neurasthenia, psoriasis, and asthma, are too strikingly successful. It should be stated, however, that Danysz particularly emphasizes the fact that the successful issue in these cases is not dependent on the theoretical assumption of any specific therapy, but depends rather on the theoretic assumption of a selective action of these bacterial antigens. Furthermore, Danysz does not believe that these conditions are due to any of the components of the bacterial antigens. The book represents an interesting speculation on the nature of the obscure processes of immunity and anaphylaxis, rather than the record of scientific achievement, or of sound application of the theory.

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STUDY OF SOME CASES OF DIABETES INSIPIDUS WITH SPECIAL REFERENCE TO THE DETECTION OF CHANGES IN THE BLOOD WHEN WATER IS TAKEN OR WITHHELD*

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Several years ago[1] we published a study of a case of diabetes insipidus in which, among other points, attention was directed to the question, whether any well marked changes could be detected in the blood when the water intake was greatly restricted or water taken at discretion. The patient had an enormous diuresis and a correspondingly great thirst, so that the conditions seemed unusually favorable for the inquiry. The conductivity of the serum and the relative volume of the serum and corpuscles were selected for study because the conductivity can be measured with great accuracy, and from the conductivities of the serum and blood the percentage volume of serum can also be obtained to a close approximation. Even when great changes were taking place in the rate of absorption, elimination and transportation of water, it was found that the two quantities measured altered only very slightly, although there seemed to be a small increase in the conductivity and a small decrease in the relative volume of the serum when water was severely restricted. But the extreme variation for the conductivity of the serum was only 5 per cent. in observations made at an interval of five days (from 78.6 to 82.5 were the extreme values of $K \times 10^4$ at 5 C.). The percentage volume of serum varied from 83 to 79, again about 5 per cent. The woman had a severe anemia. In the absence of a greater number of observations than it proved possible to obtain on this patient, we cannot be quite sure that even the small differences observed were directly related to the changed intake or output of water.

We have since observed two additional cases. In neither case, however, was the diuresis as great as in the first case. Only in one of the cases (Case 1) were we able to obtain what we considered a fairly sufficient number of observations. They are summarized in Table 1.

*From the Department of Medicine of Lakeside Hospital and the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Christie, C. D., and Stewart, G. N.: Arch. Int. Med. **20**:10 (July) 1917.

TABLE 1.—Conductivity and Relative Volume of Blood Serum in C. S.

Date	K × 10⁴ at 5 C.		Percentage Volume of Serum		Remarks
	Serum	Blood	Electrical Method	Hematocrit	
Feb. 6, 9:30 a. m.	74.6	21.8	44.4	26.5 (10 m.), 40.5 (40 m.), 43 (60 m.)	After 25½ hours without food or water. Duplicate blood samples
	74.6	21.7	44.3		
10:00 a. m.	75.4	21.0	42.6	38 (30 m.), 39 (40 m.), 40 (55 m.), 41 (65 m.)	Food and 2,000 c.c. water taken from 9:30 to 10 a. m. Water taken thereafter as desired
3:30 p. m.	76.4	25.9	50.2	37 (15 m.), 47 (45 m.), 48 (61 m.)	Duplicate blood samples
	76.4	25.9	50.2		
Feb. 7, 9:30 a. m.	75.9	28.8	55.1	45.5 (15 m.), 51.5 (45 m.), 52.5 (55 m.)	Abstention from water and food begun at 9:30 a. m. Means of duplicate blood samples
Feb. 8, 10:45 a. m.	76.8	29.4	55.3	41 (10 m.), 51.5 (40 m.), 53.5 (60 m.)	After 25¼ hours without food or water. Means of duplicate blood samples
11:15 a. m.	75.7	28.1	54.1	41.5 (10 m.), 53 (40 m.), 54 (60 m.)	Food and 2,440 c.c. water taken from 10:45 to 11:15 a. m. Duplicate blood samples
	75.7	28.1	54.1		
3:00 p. m.	77.0	33.5	61.1	50 (10 m.), 57 (25 m.), 60 (50 m.)	Means of duplicate blood samples. Water at discretion since 10:45 a. m
Feb. 9, 9:30 a. m.	76.8	31.6	58.6	50 (10 m.), 55 (25 m.), 58 (50 m.)	Abstention from water and food begun at 9:30 a. m.
Feb. 10, 11:00 a. m.	75.4	30.2	57.6	41 (10 m.), 52 (35 m.), 54 (50 m.)	After 25½ hours abstention
11:30 a. m.	75.6	28.2	54.4	41 (10 m.), 50 (25 m.), 52 (50 m.)	After taking food and 2,500 c.c. water from 11 to 11:30 a. m. Thereafter at discretion
5:45 p. m.	77.5	35.2	63.0	38 (10 m.), 54 (35 m.), 55.5 (50 m.)	
Mar. 10, 11:00 a. m.	73.5	31.3	60.7	50 (10 m.), 58 (25 m.), 58.5 (35 m.)	Abstention from water and food begun
		32.1*			
Mar. 11, 11:00 a. m.	80.7	34.5	59.6	52.5 (10 m.), 57 (25 m.), 58 (40 m.)	After 24 hours abstention
	81.0*	35.2*	60.3		
Apr. 20, 11:00 a. m.	75.4	30.0	57.3		Abstention from water and food begun
Apr. 21, 11:00 a. m.	72.8	29.3	58.2		
	72.0*	28.5*	57.6*	49 (11 m.), 55 (31 m.)	After 24 hours abstention
Apr. 26	78.0	32.3	58.7	45.5 (10 m.), 52 (20 m.), 53.5 (31 m.)	After 24 hours abstention from food and water
	78.5*	33.1*	59.4*		

* Specimens obtained after injection of 12 c.c. congo red solution.

The observations were made at different times during eleven weeks, and the relative constancy of the serum conductivities, in spite of the changes imposed in the intake of water and the accidental changes which might be expected to occur over so long a period, is quite striking. The greatest variation was from 72.8 to 80.7, and the average of all the observations 76. The values obtained after injection of congo red solution for estimation of the blood volume are left out in calculating the average, although there would be practically no change if they were included, since the quantity injected causes no sensible alteration in the conductivity. The variation in the percentage of serum was greater than that in the serum conductivity, from 42.6 to 63 per cent., the average percentage for all the observations being 55.7. It so happens that all the serum percentages in the first series of observations (February 6) are lower than in any of the other series. It is not known that this was due to any experimental error. The only error which could possibly have caused such a result, so far as we can see, would be the loss of some of the serum in the manipulations before the blood was brought to the laboratory. But it is very difficult to understand how this could have affected all the specimens. Also duplicate specimens were taken in two observations, and the duplicate determinations are identical. It seems, therefore, more likely that the observations are correct, and that, for some reason unknown to us, there was a considerable increase in the relative volume of serum between February 6 and February 7. The hemoglobin content was seen to diminish somewhat throughout the series of experiments, accompanied by a slight diminution in the erythrocyte count. The average quantity of blood taken for each determination was not less than 20 c.c., so that it is possible that the mere loss of blood might, in part at least, account for this. The conductivities of the serum specimens of February 6 are not out of line with those of the rest of the series. If the serum percentages of February 6 are omitted the variation for the rest of the observations is from 54.1 to 63 per cent. and the average 58. There was only slight anemia in this patient, the erythrocyte count being in the neighborhood of 5,000,000, at the beginning, declining to 4,500,000 toward the end of the period.

As in the previously reported case, the percentage of serum was determined by the hematocrit as well as by the electrical method. It will be seen, as before, that the longer the centrifuge is turned the closer does the hematocrit reading approximate to the result of the electrical determination. The number of minutes rotation of the hematocrit (at about 4,000 turns a minute) is given in parentheses after the corresponding serum percentages.

The general plan of the observations was as follows: The patient being on his usual diet and taking water at discretion, a blood sample

(or generally two samples for duplicate determinations) was obtained, and the blood defibrinated. The electrical conductivity of the blood and serum and the percentage volume of serum were determined. The patient was then deprived of food and water, in the case of C. S. (Case 1) for twenty-four hours or longer, as he bore the deprivation well. Blood samples were obtained at the end of the period. Then he was allowed food and as much water as he could drink, and blood drawn at the end of thirty minutes, and again at the end of five or six hours, water and food being taken. Several sets of observations of this type were made on C. S. In none was there any material difference in the percentage of serum in the samples taken before and at the end of the period of abstention from water. The conductivity of the serum was also practically unchanged, except in the observations of March 10 to 11, when there was an apparent increase of about 10 per cent. at the end of twenty-four hours abstention from water.

The samples taken half an hour after renewed water ingestion showed practically no change in the serum conductivity, while in several of the sets of observations it seemed that a slight diminution in the percentage of serum occurred. More striking was the increase in the percentage of serum in the samples drawn from five to six hours after the taking of water had been resumed. This is seen in the observations of February 6, February 7 to 8, and February 9 to 10. The increase in the relative volume of the serum was not apparently accompanied by any diminution in the concentration of the salts, since the serum conductivity remained unaltered, or if anything, underwent a slight increase.

In Case 2 (U.A.), like Case 1, one of medium severity, the range of variation in the conductivity of the serum in all the observations was from 77.3 to 86.8. Although the mean of all the observations (82.2) was somewhat higher than in Case 1, the maximum range was about the same. However, the number of observations obtained in Case 2 was smaller than in Case 1, and they were spread over a much shorter period. In the most complete series in Case 2 (May 5 and 6) (Table 2) there was an increase in the conductivity of the serum after abstention from water for twelve hours (from 79.2 to 86.8. This was accompanied by a more marked diminution in the percentage volume of the serum (from 70.9 to 58.3 per cent.). On taking water, the proportion of serum increased. However, in the first experiment (April 20 to 22) when abstention was carried to the possible limit in this case (twenty-seven hours) a slight diminution of the conductivity was seen (from 82.0 to 77.3) accompanied by a marked increase in the proportion of the serum, while on April 30 the ingestion of 2 liters of water in twenty minutes after twelve hours abstention was associated with a slight increase in the conductivity of

TABLE 2.—Conductivity and Relative Volume of Blood Serum in U. A.

Date	K × 10⁴ at 5 C.		Percentage Volume of Serum		Remarks
	Serum	Blood	Electrical Method	Hematocrit	
Apr. 20	82.0	34.7	58.0	34 (14 m.), 45 (19 m.), 48 (20 m.), 56.5 (24 m.), 53 (49 m.)	Before abstention from water
Apr. 22	77.3	44.1	74.0	63 (14 m.), 65.5 (20 m.), 68 (30 m.), 68.5 (25 m.).	After 27 hours abstention
Apr. 26	79.0	53.4	90.5	52 (15 m.), 56 (23 m.), 58 (35 m.)	Water taken at discretion since April 22
Apr. 30 10:00 a. m.	82.8	59.1	60.0	45 (10 m.), 52.5 (20 m.), 54.5 (30 m.)	After 12 hours abstention from water
10:20 a. m.	85.6	80.1	59.6	20 (10 m.), 39 (20 m.), 43.5 (30 m.), 46 (40 m.)	After 2,000 c.c. water had been taken in 20 minutes
May 5	79.2	42.8	70.9	60 (10 m.), 64.5 (20 m.), 66 (27 m.)	Before abstention from water
May 6, 10:20 a. m.	86.8	59.9	88.2	53 (10 m.), 55.5 (20 m.), 56 (25 m.)	After 24 hours abstention from water
11:00 a. m.	84.8	47.9	66.8	53 (10 m.), 60 (20 m.), 61.5 (25 m.), 63 (30 m.), 64.5 (37 m.)	After 1,575 c.c. water had been taken in 39 minutes

TABLE 3. Conductivity and Relative Volume of Blood Serum in C. V.

Date	K × 10⁴ at 5 C.		Percentage Volume of Serum		Remarks
	Serum	Blood	Electrical Method	Hematocrit	
Nov. 29	80.2	28.5	65.1	43.5 (32 m.), 47 (38 m.), 49 (25 m.)	Before abstention from water and food
Nov. 30	....	....	....	42 (22 m.), 44 (32 m.), 45 (38 m.)	At end of 24 hours abstention from water
Nov. 30	87.1	50.9	49.4		After food and water had been taken at discretion for 1 hour

the serum, and a distinct diminution in the proportion of serum. We prefer not to attempt a hypothetic explanation of these variable results, simply pointing out that in Case 2 the relative volume of the serum was more variable than in Case 1, the extreme range being from 50.6 to 74 per cent. and the average of all the observations 62 per cent. It should be noted that in Case 2 deprivation of water was not nearly as well borne as in Case 1, the patient complaining much more of thirst. Also U.A. (Case 2) was allowed food during the period of deprivation of water, although he ate less than usual.

The observations in these cases illustrate, perhaps, even more clearly than those previously published, how trifling the changes in the concentration of the blood plasma, as regards the electrolytes, may be when great changes in the ingestion, excretion and transportation of water are in progress. So far as our experience goes it would seem that it is only in exceptionally favorable circumstances that even minute changes in the conductivity of the serum, a quantity capable of being measured to so considerable a degree of accuracy, can be detected with certainty. Observations which profess to demonstrate considerable and constant variations, associated with the taking or withholding of water should, we think, be received with reserve.

The relative volume of the blood plasma may undergo somewhat greater variations. This agrees with the conclusion of Farkas,[2] in an extensive research on the influence of water and salt given with the food on the water content of the organs in some of the domestic animals. In sheep caused to drink large quantities of water with or without sodium chlorid, the osmotic pressure and the concentration of the electrolytes remained the same; but the water content of the blood was increased in the sheep which received salt as well as water. According to Adolph,[3] the drinking of isotonic salt solution by normal persons is accompanied by a measurable diminution in the hemoglobin content of the blood, indicating some increase in the water content. The possibility should not be lost sight of that in cases of diabetes insipidus the variations may be even less than in normal individuals, the urine secreting mechanism being, perhaps, even more responsive to slight changes in the blood, or the tissues less capable of storing any excess of water.

We do not intend to discuss the mechanism by which the osmotic pressure and the concentration of electrolytes in the plasma (as measured by the electrical conductivity) are maintained relatively constant during the absorption or excretion of large quantities of water. The exchange between the erythrocytes and the plasma, as well as the exchange between the tissue liquids and the plasma through the

2. Farkas, K.: Mitth. aus. d. Königl. Ungar. Tierphysiol. Versuchsstation in Budapest, No. 3, Berlin, 1908; Landwirtschaftliche Jahrb., 1908.

3. Adolph, E. F.: J. Physiol. **55**:114, 1921.

capillary walls, must play a part. As to the relative volume of plasma and corpuscles, although the changes were probably greater than those in the conductivity of the serum, they were too small in amount, and not constant enough in sign, to permit the assumption that when water was withheld, any important part of the water which continued to be excreted could have been credited to a diminished water content of the blood, or that when water was again taken, any important part of it went to recoup the blood for its previous loss. The chief changes must have been in the tissue water. The slight apparent diminution in the percentage of serum in the first half hour after resumption of water intake, if it is a genuine diminution, might possibly have been associated with a preliminary speeding up of the diuresis. The increase in the proportion of serum a few hours later, perhaps to something more than the amount present at the beginning of the period of abstention, is most naturally associated with a rapid absorption slightly outstripping the diuresis. However, this is not the only possible explanation, and as has been previously said, speculations founded on such data as we have been able to obtain would, in the present state of our knowledge, be of little value. This is well illustrated by the marked increase in the proportion of serum, accompanied by a slight decrease in the conductivity, seen in the observations of April 20 to 22 in Case 2, after twenty-seven hours abstention from water. Whether the fact that some solid food was taken in this case influenced the result, it is impossible to say.

REPORT OF CASES

Case 1.—C. S., male, married, aged 39, was admitted to the Lakeside Hospital medical service, Feb. 3, 1921.

Past History.—Essentially negative, aside from an attack of pneumonia five years ago. No history of any venereal infection.

Present Illness.—The patient dates his present trouble from July, 1920, when he noticed that he was becoming more irritable and much more easily fatigued. He had been an active man, but he now became so tired that his one desire was to lie down and sleep. He arose late each morning and retired early, and usually spent most of his Sundays in bed. Four months ago he began to have headaches, which he described as "heavy aches," coming every two or three days and lasting from a few minutes to half a day. They seemed to distress him more at night, and would sometimes awaken him. About one month after the headaches started, he noticed that he was gradually drinking more water each day and was passing an excessive quantity of urine. He said that his thirst reached such a degree that he would drink from three to four glasses of water every half hour and pass a corresponding amount of urine.

Physical Examination.—The patient is a well developed and well nourished man, and gives the appearance of being in good health. He is extremely neurotic, apprehensive, prone to complain and very restless. There is considerable dryness of the skin and a slight anemia. The eyes and eye grounds are normal. There is no evidence of cardiac enlargement. Blood pressure is not elevated. There is no acceleration of the pulse rate; no abnormal physical signs about the abdomen or the extremities. A complete neurologic examination revealed no abnormal findings.

Urine.—The urine was pale and of low specific gravity; no albumin or sugar. The quantity varied from 6 to 10 liters in the twenty-four hours.

Blood.—The blood showed: hemoglobin from 80 to 90 per cent. (Tallquist); white blood count, from 5,000 to 7,000; red blood count varied from 4,500,000 to 5,000,000. Blood sugar estimations showed from 0.085 to 0.050 gm. per hundred c.c. (by Lewis and Benedict method); blood urea varied between 0.025 and 0.032 gm. per hundred c.c.

Spinal Fluid.—Lumbar puncture revealed no increase in pressure; fluid normal in color; no cells. The Wassermann, globulin and gold chlorid tests were negative.

Head.—Roentgenograms of the region about the sella turcica showed no evidence of a pathologic process.

Kidneys.—Renal test meals, given when the patient was getting three daily intramuscular injections of 1 c.c. of a pituitary extract (pituitrin) showed an output of from 2 to 3 liters and that the patient's kidneys were quite able to concentrate the urine.

Dec. 15, 1921, the patient, who had become insane, shot himself in the left chest and died December 25. Diagnosis: "encysted hematoma, empyema and collapse of the left lung." The necropsy gave no information as to the possible cause of the polyuria. The pathologic examination of the brain, including the pituitary, showed nothing abnormal.

Case 2.—U. A., male, single, aged 16; admitted to Lakeside Hospital medical service, April 7, 1920.

Past History.—He had had when a child the ordinary diseases.

Present Illness.—He dates his present trouble from the time he was 5 years old, when he had a cold and was feverish one night, and began drinking water excessively and urinating frequently. He was apparently worse at that time, from the statement of his parents, as he was not allowed to enter school until he was 7 years of age because of the trouble. Since the complaint began, eleven years ago, there has been no marked abatement of symptoms.

Physical Examination.—The patient is well developed and well nourished, and does not have the appearance of being ill. There are a few small brown pigmented areas over the face. The eyes are normal; the pupils react to light and accommodation; eye grounds are normal; no disturbance in the field of vision. The heart is not increased in size, and the pulse is regular and of good volume. The systolic blood pressure varied between 130 and 120 and the diastolic between 79 and 60. Examination of the abdomen and extremities was negative. A complete neurologic examination revealed nothing pathologic.

Urine.—The urine varied between 5 and 10 liters per twenty-four hours. It was pale, and the specific gravity varied between 1.002 and 1.005, except when the fluid intake was restricted or when the patient was given pituitary extract (1 c.c. three times daily, intramuscularly), and then the output was cut down and the specific gravity elevated. No albumin, casts or sugar.

Blood.—The blood showed: hemoglobin, 90 per cent. (Tallquist); white cells, 10,000; red cells, 5,200,000. Blood sugar, 0.10 gm. per hundred c.c., and blood urea, 0.030 gm. per hundred c.c.

Head.—Roentgenograms of the region about the sella turcica revealed nothing abnormal.

Kidneys.—The phenolsulphonephthalein excretion was 78 per cent. in two hours.

Discussion of the Clinical Aspects of Cases 1 and 2.—There was nothing unusual about these cases other than that the patients had a diabetes insipidus of medium severity. Nothing was made out, either on physical examination or from the laboratory procedures, which gave us any clew to a possible etiology.

Both Cases 1 and 2 responded to the intramuscular injection of pituitary extract when given in 1 c.c. doses. The thirst and diuresis promptly subsided, and if three daily injections of 1 c.c. were given, the urine output could be cut down from 5 to 12 liters to below 2½ liters in the twenty-four hours. Feeding of the fresh pituitary gland to the patients had no effect, and the oral administration of commercial pituitary extract did not modify the diuresis. There was no evidence obtained from any of the tests for kidney function to bear out the contention of Erich Meyer [4] and others that the diuresis in diabetes insipidus is in any way associated with, or dependent on, a pathologic alteration in the kidneys. Both our patients had perfectly normal phenolsulphonephthalein excretions. There was no evidence of nitrogen retention in the blood; and when the diuresis was lessened by pituitary extract and the patients were put on a renal test meal their kidneys showed ample ability to concentrate the urine. These clinical observations bear out in the main the findings which we have reported in another case.[1]

In these two cases the condition was chronic, of long standing and of unknown etiology. A third case (C.V.) was studied in which the polyuria, apparently associated with a lesion of the base of the brain, came on suddenly, and disappeared after lumbar puncture.

Case 3.—C. V., male, married, aged 28, was admitted to the Lakeside Hospital medical service, Nov. 27, 1920.

Past History.—This patient had had the ordinary diseases of childhood, and typhoid fever when about 11 years of age (?). At 25 years he had pneumonia, and for some time after was weak. He was thought to have tuberculosis of the lungs at that time and was advised to go to California, which he did. He came back apparently in good health, and then had influenza in February, 1920.

Present Illness.—April 29, 1920, after moving his household effects, at which he had worked very hard, riding around most of the day in a truck, he felt numb over the whole left side of his body. He said that he felt as if the left side of his body belonged to someone else. He was totally unable to move his left arm and hand and also his left leg. This paralysis disappeared in about two hours. It had never appeared prior to that time.

Since the attack of influenza and paralysis the patient enjoyed good health until last night (November 26) at 4 a. m., when he awakened with a dull headache, which he had not had for two years at least, and a slight vertigo, both of which persisted until today (November 27). As he awoke last night he says he had a most extreme sense of thirst in the interior of his nose and not in his mouth. He has since emphasized the fact that the thirst was in his nose and very intense. He also noticed that he had a markedly overfull bladder, which caused him pain above the pubic crest. When he voided urine he said he was sure that he passed more than a quart. His thirst persisted all day yesterday and is still present today in the same intensity. Yesterday he voided from 12 to 14 quarts of urine, and he says that he is maintaining the same average of urine output today. Today he feels weak and tired, in addition to his other complaints, and has a general soreness over his abdomen, which he attributes to his frequently overdistended bladder.

4. Meyer, Erich: Deutsch. Arch. f. klin. Med. **83**:1, 1905; Ztschr. f. klin. Med. **74**:352, 1912.

Physical Examination.—The patient is an intelligent young man, well proportioned and of healthy appearance. There were no abnormalities about the head, eyes, ears, nose and throat, except those detailed under the neurologic examination. There were a few enlarged lymph glands and a moderate uniform hypertrophy of the thyroid gland. Aside from a slight impairment in the movement of the left upper chest, the examination of the lungs was negative. The heart showed no evidence of enlargement or valvular defect. The pulse was not accelerated; systolic blood pressure was 125, diastolic, 80. The abdomen was normal and an examination of the rectum, genitalia and extremities revealed nothing abnormal.

Neurologic Examination.—The mentality of the patient is good and he cooperates well. Cranial Nerves: There was a loss of the sense of smell in the left side of the nose. The gross vision not impaired. There was a concentric limitation of the left visual field. The left pupil reacts more slowly to accommodation than the right. The external muscles of the eye were normal. There was impairment in the sense of touch and pain over the left forehead and zygomatic area. The lower and lateral part of face were unaffected. There was slight paresis of the left facial nerve. There was a diminution in both bone and air conduction in the left ear. There was impairment in the sense of taste and common sensation on the posterior third of the tongue, but muscles of palate and pharynx seemed intact. There was some atrophy of the left side of the tongue.

Sensory Examination.—There was a very gross impairment in all sensations over much of the left side of the body. This included primarily touch, but there was a corresponding diminution to pain, heat and cold and to vibration. The areas which were most markedly involved were the left forehead, left zygomatic area, left neck, left finger tips, distal phalanx of all toes on the left foot and the medial surface of left leg, etc. There was no ataxia; gait and station normal, and no impairment in complemental opposition; muscles were normal. Both skin and deep reflexes were apparently normal. There was nothing made out to suggest any involvement of the sympathetic nervous system.

Our conclusion from the neurologic examination was that the patient had a basilar lesion which was either a tumor or a serous meningitis.

Urine.—The urine was pale, with a specific gravity of 1.005. The urine never contained any pathologic elements.

Blood.—Blood examination showed hemoglobin, 100 per cent. (Tallquist); white blood cells, 7,000; red blood cells, 5,800,000.

Spinal Fluid.—About 8 c.c. of clear colorless fluid was removed by lumbar puncture. It contained 2 cells to the field; no increase in pressure or in the globulin content. The Wassermann was negative. Blood Wassermann was also negative.

Head.—Roentgenograms of the area about the base of and of the whole skull were negative.

Kidneys.—Phenolsulphonephthalein excretion was 57 per cent. in two hours, and a renal test meal, given after the diuresis had subsided, showed that the kidneys had ample ability to concentrate the urine.

Discharge Note.—This patient had polyuria for less than three days. It made its appearance early in the morning of November 27, and November 29 a lumbar puncture was done for diagnostic purposes, after which the polyuria disappeared, even though nothing pathologic was found in the spinal fluid and there was no increase in pressure. The patient, while the polyuria existed, excreted about 12 liters of urine per day. He had a severe headache for several days following the lumbar puncture. He was discharged from the hospital Dec. 7, 1920. His urine output had not exceeded 1,300 c.c. in any twenty-four hours after the lumbar puncture. There were no demonstrable changes in the neurologic signs on discharge.

Case 3 was one of severe polyuria of very acute onset. There was evidence that the patient had an intracranial lesion which was probably located at the base of the brain. It had apparently involved the olfactory nerve, the optic nerve peripheral to the chiasma and the fifth, seventh, ninth and twelfth cranial nerves, the involvement probably being nuclear, with, perhaps, also some encroachment on the sensory areas in the thalamic region. Our impression was that there was either a tumor or a serous meningitis at the base. A lumbar puncture was decided on for aid in diagnosis. Although the cerebrospinal fluid was not under increased pressure and its examination was negative, after this procedure the increased thirst and diuresis disappeared. In Case 1 lumbar puncture was also done, but there was no effect on the thirst or diuresis.

There has been no return of the diuresis since C. V. (Case 3) left the hospital, and for some months he appeared to be in good health. However, after from three to four months, he began to show signs of loss of mental balance, the derangement taking largely a religious turn, and he had to be discharged from his work. He is now (October, 1921) in a sanitarium, suffering from "nervous breakdown."

Any hypothesis which we could advance as to the cause of the polyuria in this case would be mere conjecture. The course of the onset, the recovery following the lumbar puncture and the fact that there has probably been no increase in the neurologic signs since he left the hospital, make the diagnosis of serous meningitis seem the most likely. Herrick [5] reported a case in 1912 in which the polyuria ceased after lumbar puncture, and in 1918 Cammidge [6] reported a case. Cammidge thought his patient had a serous meningitis due to a parasyphilitic state.[7]

It had been intended to study the blood in the same way as in the other cases. But owing to the disappearance of the polyuria after lumbar puncture only two sufficient samples of blood were obtained, one before abstention from water was begun and the other one hour after the taking of water had been resumed. The first specimen was secured on the day when lumbar puncture was done and the second on the following day when the diuresis had already subsided. The conductivity of the serum (Table 3) in the second sample was somewhat greater than in the first and the percentage of serum was somewhat less. The blood specimen obtained at the end of the twenty-four hour period of abstention was so small that only a hematocrit determination could be made. The percentage of serum after thirty-eight minutes rotation was 45, whereas in the sample taken before

5. Herrick: Arch. Int. Med. **10**:1 (July) 1912.
6. Cammidge, P. J.: Practitioner **105**:244, 1918.
7. We desire to express our thanks to Dr. R. G. Pearce, Akron, Ohio, for referring Case 3 to us for study.

abstention it was 49 after twenty-five minutes rotation. Probably, therefore, there was some diminution in the serum percentage at the end of the period of abstention. At any rate there was no increase. It is impossible from the hematocrit determination alone to say more than this.

SUMMARY

The regulation of the excretion of water by the kidneys was studied in two cases of diabetes insipidus presenting the typical features, and in one case of polyuria of acute onset, apparently associated with a brain lesion. In the last case the polyuria disappeared permanently after lumbar puncture, but the patient eventually developed symptoms of mental derangement.

Blood specimens obtained immediately before and immediately after a long period of complete deprivation of water (twenty-four hours or more) showed no definite differences in the electrical conductivity of the serum, which could be associated with changes in the rate at which water was being absorbed, transported and excreted, although the conductivity can be measured with great accuracy. The same was true of the percentage volume of serum.

Comparison of blood specimens procured within half an hour, and again after five or six hours, after the resumption of water drinking with the specimens obtained just before or just at the end of the period of water deprivation also revealed differences in the conductivity of the serum so slight and so inconstant that it was impossible to connect them definitely with changes in the intake of water.

The percentage of serum, in the observations which we were able to carry out completely, seemed to be somewhat greater in the specimens taken after five or six hours, than in the specimens taken half an hour after resumption of water drinking.

The regulation of the concentration of electrolytes in the plasma and of the relative volume of plasma and corpuscles in the blood was, therefore, at any rate as fine in these cases of diabetes insipidus, in spite of the great variations induced in the quantity of water transported, as in normal persons. It is possible, indeed, that in this condition the renal excretory mechanism is even less tolerant than normal of any excess of water in the blood, or the tissues less capable than normal of storing an excess of water.

As in the case previously published,[1] no evidence was obtained that the condition was associated with any pathologic change in the kidneys. The various tests of efficiency of renal function gave normal results. When pituitary extract was administered the kidney showed normal power of concentrating the urine.

CLINICAL CALORIMETRY. XXX. METABOLISM IN ERYSIPELAS*

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In the study of fever in the human subject it is difficult to select a disease which lends itself well to experimental conditions. Patients with certain fevers, such as pneumonia, are so seriously ill that one hesitates to make even the simplest observations. Some of the other fevers are so mild that they do not give one a chance to study high temperatures. In others, the possibility of contagion must be considered and it is hardly justifiable, for instance, to study measles or scarlet fever in a room adjoining a general ward. Typhoid fever, which is in many respects ideal for experimental work in the respiration calorimeter, was thoroughly investigated by Shaffer and Coleman [1] and later by the staff of the Russell Sage Institute of Pathology.[2]

It seemed desirable to determine whether other acute infectious diseases present phenomena similar to those of enteric fever. For this purpose erysipelas was chosen. There were several reasons for its selection. In the first place, the inflammatory process can be observed and a fairly good prognosis can be made from day to day. The temperature is high and the toxemia often severe and yet the patient is not exhausted by simple movement such as the necessary transfer from the bed to the calorimeter. Moreover, temperature fluctuations are often rapid. It was hoped that further information might be obtained concerning temperature regulation in the body.

In many respects, erysipelas was a disappointment from an experimental standpoint. Some of the patients were of alcoholic habits which dulled their intelligence and accentuated the usual delirium of the disease. Cooperation in the collection of twenty-four hour specimens was obtained with difficulty. The mental state of the patient often rendered calorimetric observations impossible at times when it would have been otherwise desirable to make them. The appetite was

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Shaffer and Coleman: Protein Metabolism in Typhoid Fever, Arch. Int. Med. 4:538 (Oct.) 1909.

2. Coleman, W., and Gephart, F. C.: Clinical Calorimetry, Paper 6. Notes on the Absorption of Fat and Protein in Typhoid Fever. Arch. Int. Med. **15**:882 (May) 1915; Coleman, W., and Du Bois, E. F.: Paper 7, Calorimetric Observations on the Metabolism of Typhoid Patients with and Without Food, Arch. Int. Med. **15**:887 (May) 1915.

always capricious and it was many times impossible to induce the patients to take the requisite amount of food. Furthermore, the expected wide fluctuations of temperature were not observed in the calorimeter. Special efforts were made to observe these changes. Experiments were undertaken at night in the hope of obtaining the usual sharp drop in temperature during the morning hours. For some reason, however, fluctuations in temperature always seemed to be less marked when the patients were in the calorimeter than when they were in the erysipelas ward. The same difficulty was experienced in the study of falling temperature in tuberculosis.

Several determinations of the total heat production have been made in facial erysipelas by Riethus [3] and Grafe.[4] Riethus found an increase of 41 per cent. in the metabolism, Grafe, in one case with a temperature of 39.5 F, found the heat production 40 per cent. above the level which it assumed after recovery. Loening,[5] in a comparative study of the nitrogen losses in various fevers, published the results in eight cases of erysipelas. Rolland [6] in one case with a range of temperature between 37.5 and 39 C. gave 46 calories per kilo in the food with 12.1 gm. protein daily and found a negative nitrogen balance averaging 0.67 gm. per day. She considered this as evidence against a toxic destruction of body protein. Kocher [7] was able to administer to four erysipelas patients diets containing from 3,200 to 4,300 calories with only 1.8 to 2.2 gm. nitrogen. On such diets, normal men excrete only from 2 to 4 gm. nitrogen even though they perform severe muscular exercise. The nitrogen excretion of the erysipelas patients was from 9 to 20 gm. even after several days of this diet. Grafe,[8] one of the chief opponents of the theory of toxic destruction, confirmed these results. He gave an erysipelas patient a diet containing 66 calories per kilo and no protein. The urinary nitrogen dropped from 25.9 gm. to 7.7 gm. on the fifth day of the diet but would not fall below this point.

The various urinary constituents have been determined by most of the investigators who have studied the nitrogen metabolism. Unusually complete analyses were made by Kocher.[7] He found during the febrile

3. Riethus, O.: Beobachtungen über den Gaswechsel kranker Menschen und den Einfluss antipyretischer Medicamente auf denselben, Arch. f. exper. Path. u. Pharmak. **44**:239, 1900.

4. Grafe, E.: Untersuchungen über den Stoff- und Kraftwechsel in Fieber Zur Genese des Eiweisszerfalls bei Fieber und bei Arbeitsleistung, Deutsch. Arch. f. klin. Med. **101**:209, 1911.

5. Loening, K.: Experimentelle und klinische Untersuchungen über Eiweiss und Stoffwechsel im Fieber, Klin. Jahrb. **18**:199, 1908.

6. Rolland, A.: Zur Frage des toxogenen Eiweisszerfalls im Fieber des Menschen, Deutsch. Arch. f. klin. Med. **107**:440, 1912.

7. Kocher, R.: Ueber die Grösse des Eiweisszerfalls bei Fieber und bei Arbeitsleitung, Deutsch. Arch. f. klin. Med. **115**:82, 1914.

8. Grafe, E.: Zur Genese des Eiweisszerfalls im Fieber, Deutsch Arch. f. klin. Med. **116**:328, 1914.

periods a considerable increase in the excretion of creatinin. At the height of the disease, this reached from 2.4 to 2.6 gm. per day, the uric acid from 0.8 to 2.0 gm. and the ammonia from 1.8 to 3.0 gm.

Our own work includes eight observations on the basal metabolism of five patients during the acute stage of the disease. Two of the five were studied on the first day of normal temperature. The respiration calorimeter of the Russell Sage Institute of Pathology was employed. The methods have been described in Paper 4 [9] of this series. Observations were also made on the nitrogen equilibrium and on the weight curves during the infection.

The character of the cases studied can be judged from the following histories.

REPORT OF CASES

Case 1.—Erysipelas of neck and back.

History.—Arshel A., a peddler, born in Russia, 29 years of age, was admitted Oct. 9, 1916, and discharged cured Oct. 24, 1916. He drinks one glass of beer a day and smokes cigarets to excess.

September 25 a boil developed on the left side of the back of the neck. It was incised on the twenty-eighth but the area of incision became red and swollen. The inflammation spread very rapidly until it covered the neck and back. He felt feverish but had no chill.

Physical Examination.—The patient is an undersized, fairly well developed and nourished young Jew, acutely ill but mentally alert and rather apprehensive. The tongue is moderately dry with a thick white coat. Lymph nodes are not enlarged. On the back of the neck is a small incision nearly healed. The area of inflammation extends from the hair line to two inches below the inferior angles of the scapulae and from the right to the left deltoid. The area is brawny and dark red in color and is sharply demarcated from the surrounding skin, but without a definitely raised edge. There are many broken blebs. The spleen is not palpable.

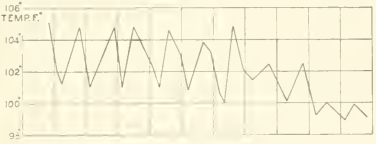

Fig. 1.—Arshel A. (Case 1) Temperature chart.

Laboratory Examination.—The urine shows a trace of albumin; no casts. Blood: October 16: Leukocytes, 25,000; polymorphonuclears, 93 per cent.

October 13 he was in the calorimeter from 10:30 a. m. to 2:30 p. m. October 14 the inflammation had extended to the elbow on the left side to within two inches of the elbow on the right. The inflammation of the back was

9. Gephart, F. C., and Du Bois, E. F.: Clinical Calorimetry, Paper 4, The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. **15**:835 (May) 1915.

less marked, and his general condition was improved. From 6 p. m. October 15 to 2:45 a. m. October 16 he was again in the calorimeter. By the twenty-first all active inflammation had disappeared and he was discharged as cured October 24.

Case 2.—Facial erysipelas.

History.—James W., a fireman born in the United States, 51 years of age, was admitted Oct. 11, 1916, and discharged as cured on Oct. 21, 1916. He had gonorrhea in 1896 without complications. He denies syphilis and says he does not drink.

October 9 he had noticed that the left side of his nose was swollen and red. He had a chill in the afternoon. During the next twenty-four hours the swelling spread rapidly over the left side of the face.

Physical Examination.—Patient is a well developed, poorly nourished, rather surly American, acutely ill. His tongue is red at the edges, shows a white coat and is very dry. Over the bridge of the nose and spreading over the entire left side of the face is a diffuse, red, hot area of inflammation. The edge is raised, firmly and sharply demarcates the area from the surrounding skin. The pulse is slow, full and dicrotic. The spleen is not palpable. Lymph nodes are not enlarged.

Fig. 2.—James W. (Case 2) Temperature chart.

Laboratory Examination.—Urine is negative. Blood Pressure: Systolic, 130 mm.; diastolic, 70 mm.

October 13 the area of inflammation had spread to include the left ear. The left eyelid was swollen and shut. On the fifteenth the right forehead and ear were swollen, tender and red. The condition of the left side of the face was much improved. October 17 he was placed in the calorimeter from 10:15 a. m. to 1:15 p. m. At that time his temperature was normal and most of the signs of inflammation had disappeared. Both ears were slightly swollen. The left ear was desquamating. He was discharged as cured October 21.

Case 3.—Facial erysipelas.

History.—Odysseus B., a cigaret maker, born in Greece, 46 years of age, was admitted Oct. 24, 1916, and discharged cured Nov. 1, 1916. He was operated on for fistula in ano in March, 1916, at an Italian hospital. He drinks two glasses of beer a day; no whisky.

October 20 he had a slight pain in the abdomen. On the afternoon of October 21 he had a severe chill with high fever. On the morning of October 22 he noted a slight redness on the right side of the nose. This spread gradually to the left side and ultimately covered his cheek and forehead.

Physical Examination October 27, 1916.—Patient is a well developed, fairly well nourished man, acutely ill. The tongue is moist with a thick, white coat. Over the left cheek, ear, forehead and scalp and over the right forehead, is a diffuse swelling, hot and tender, dark red in color, showing over a portion

of its periphery, particularly in the scalp, a distinct raised edge. The nose shows no abrasion. However, there is an occasional slight nasal hemorrhage. The throat is red but not swollen. The lymph glands of the neck are not enlarged. Over both lungs are a few scattered rales. Coughing is frequent. The spleen is not palpable.

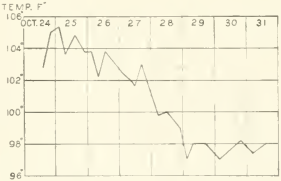

Fig. 3.—Odysseus B. (Case 3) Temperature chart.

Laboratory Examination.—Urine shows a faint trace of albumin; no casts. Blood: Leukocytes, 22,000; polymorphonuclears, 84 per cent.

October 27 he was in the calorimeter from 10:30 a. m. to 1:30 p. m. By the twenty-eighth the area of inflammation had increased in extent to cover the scalp to the occipital prominence and the neck for two inches posterior and inferior to the left ear. The inflammation, however, had decreased in intensity, desquamation had begun and recovery from that time was rapid. He was discharged, cured, October 31.

Case 4.—Facial erysipelas.

History.—Robert H., a waiter, born in Germany, 38 years of age, was admitted Oct. 31, 1916, discharged as cured Nov. 10, 1916. He has been in this country since 1902. He drinks moderately of beer; no whisky. He has had gonorrhea several times; had a chancre in 1915, no secondaries.

October 27 he had some fever and muscular pains but no chill. He remained in bed until October 30, when he went to a choral club rehearsal. It was first noted there that his face was red and swollen. The swelling began on the nose and spread rapidly to both cheeks.

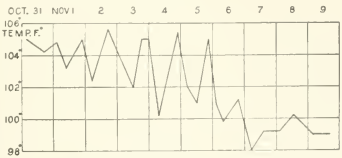

Fig. 4.—Robert H. (Case 4) Temperature chart.

Physical Examination.—Patient is a well developed and well nourished man, very nervous, acutely ill. The tongue is slightly dry and covered with a brown coat. Over the nose, the lower half of the forehead and the cheeks down to the angles of the mouth there is an edematous, red, hot, slightly tender area of inflammation, the edges of which are moderately raised and indurated and sharply demarcated from the surrounding skin. The eyelids are swollen and shut. The conjunctivae are red and edematous. At the angle of

the left jaw there is a moderately tender, nonfluctuating lymph node. The throat is slightly red. The lungs shows no signs although the patient coughs frequently. The spleen is easily palpable two finger breadths below the costal margin.

Laboratory Examination.—Urine shows a trace of albumin; no casts. Blood: Wassermann is negative.

November 3 the inflammation had spread to involve the whole face. From 11:22 a. m. to 4:22 p. m. he was in the calorimeter. November 4 the ears were involved but the severity of the inflammation of the face was less marked. Desquamation had begun. During the night, from 11:30 p. m. November 4 to 2 a. m. November 5, he was in the calorimeter. On the sixth a large grayish patch appeared on the uvula. A culture was negative for diphtheria. By the eighth the redness and swelling had disappeared from the face. A new area of inflammation had appeared on the back of the neck similar in character to the first one. Lymph nodes were no longer palpable. He was in the calorimeter from 11:30 a. m. to 2:30 p. m. By the tenth practically all signs of inflammation of the skin and the grayish patch on the uvula had disappeared. The spleen was still palpable below the costal margin. The heart murmur was still present. He was discharged as cured on November 13.

Case 5.—Facial erysipelas.

History.—Joseph S., a sailor born in Russia, 25 years of age, was admitted Feb. 27, 1917, and discharged cured March 23, 1917. He had smallpox in Russia in 1902. He drinks moderately. He denies venereal infection.

During a boxing match February 25 he received a severe blow over his left eye and left ear. Two days later he was admitted to Bellevue Hospital with a hematoma and a marked cellulitis of the left eyelid and ear. By March 3 the wound of the eyelid had become definitely erysipelatous.

Fig. 5.—Joseph S (Case 5) Temperature chart.

Physical Examination March 6 (after development of erysipelas).—Patient is a muscular, well nourished, very surly young Russian, prostrated by disease; very toxic. The conjunctivae of both eyes are swollen, bright red and are exuding pus. There is a slight cloudiness of the right cornea. In the left upper eyelid there is a badly infected cut, extending the width of the lid and exuding pus. The erysipelatous area extends over the nose, both cheeks to the angle of the mouth on the right, to the neck on the left. The skin is red and indurated and there are numerous blebs containing purulent serum. In the upper part of the pinna of the left ear is a hematoma the size of a walnut. There is a wide sinus extending deep into the mass and exuding pus. There is no sign of rupture of the drum membrane, no evidence of infection of middle ear. The cervical nodes are enlarged and on each side is a diffuse, tender swelling about the region of the parotids. The tongue is dry and coated with brownish pus. Fauces are red and slightly swollen. The heart shows marked overaction. Lungs show a few scattered râles. The soft edge of the spleen is palpable one finger breath below the costal margin.

Laboratory Examination.—The urine is negative. Blood (March 6, 1917): Leukocytes, 7,000; polymorphonuclears, 75 per cent. Roentgen ray showed no fracture of skull.

March 6 he was in the calorimeter from 12 noon to 1 p. m. March 12 the cut on the eyelid was practically healed. The inflammation of the conjunctivae and the diffuse redness and swelling of the skin had almost disappeared. There was, however, a localized swelling over the upper right cheek and the bridge of the nose. When this was opened it discharged considerable amounts of pus. Following this he recovered rapidly and was dicharged as cured March 23.

The data of the calorimeter experiments are presented in Table 1. A summary of results will be found in Table 2.

DISCUSSION OF RESULTS

Basal Metabolism.—In the ten experiments the agreement between the total calories measured by direct and indirect calorimetry is deceptive. The calories by the direct method totaled 2,152.9 by the indirect method 2,118.6, a divergence of only 1.1 per cent. In the individual experiments, however, the divergence ranged between + 9.6 and — 13.5 per cent. Perhaps this discrepancy may be explained, in part, by the necessarily short periods during which some of the patients were observed. In typhoid fever,[9] it was found that during the first hour, some heat was probably lost in warming the bed frame and bedding. This, however, cannot explain the discrepancy on the plus side and can answer only for a part of the minus divergence. We must look elsewhere for complete explanation. In the work on malaria,[10] it was demonstrated that the rectal temperature is a rather inaccurate measure of general body conditions. It may rise more rapidly or less rapidly than the average body temperature during sudden changes in heat elimination and production. In the calculation of the heat production by direct calorimetry the rectal temperature is assumed to represent accurately the temperature conditions of the whole body. This assumption is not valid during rapid fluctuations of temperature, but probably holds where the temperature rises and falls gradually as in the cases of erysipelas studied. In Figures 11 and 12 the curves of both rectal and average body temperature are charted. It will be seen that they are practically parallel.

One of the patients observed on the first day of normal temperature after the subsidence of fever exhibited a basal metabolism 8 per cent. below the average normal level. The other afebrile patient, also observed on the day following the crisis, still showed a heat production 12 per cent. above the normal. During the course of the fever, the metabolism was always high, the variations being between 19 and 42 per cent. above the average normal basal.

Relation of Basal Metbolism to Temperature.—In typhoid fever and tuberculosis [11] the increase in heat production was found to be roughly

10. Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry. Paper 28, The Metabolism in Malarial Fever. Arch. Int. Med. **21**:627 (May) 1918.

11. McCann, W. S., and Barr, D. P.: Clinical Calorimetry. Paper 29, The Metabolism of Tuberculosis. Arch. Int. Med. **26**:663 (Nov.) 1920.

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Arshel A. .... 10/13/16 56.4 Kg. 1.58 Sq. M.	Prelim.	11:35	....	....	....	....	....	....	....
	1	12:35	23.5	23.1	0.74	34.4	0.60	....	76.4
	2	1:35	24.7	24.3	0.74	37.1	0.60	....	79.6
	Aver	.....	....	....	....	....	....	77.3	....
Arshel A. ..... 10/15/16 55.6 Kg. 1.57 Sq. M.	Prelim.	6:47	....	....	....	....	....	....	....
	1	7:47	25.2	23.5	0.78	39.9	0.49	....	83.5
	2	8:47	24.0	24.0	0.73	35 8	0.49	....	81.5
	3	9:17	11.5	10.8	0.77	16.1	0.49	....	38.6
	4	10:47	36.3	35.1	0.75	50.2	0.49	....	125.0
	5	12:47	45.6	44.2	0.75	61.7	0.49	....	164.0
	6	2:47	43.5	43.6	0.73	61.6	0.49	....	163.9
	Aver.	.....	....	....	....	....	....	74.2	....
James W. .... 10/17/16 54.8 Kg. 1.67 Sq. M.	Prelim.	11:32	....	....	....	....	....	....	....
	1	12:32	21.3	17.9	0.87	32.8	0.45	59.7	64.4
	2	1:32	20.4	18.3	0.81	33.0	0.45	60.9	65.9
	Aver.	.....	....	....	....	....	....	....	....
Odysseo. B. ..... 10/27/16 54.0 Kg. 1.59 Sq. M.	Prelim.	11:07	....	....	....	....	....	....	....
	1	12:07	27.0	25.9	0.76	42.6	0.66	85.2	83.4
	2	1:08	28.9	27.5	0.76	39.0	0.66	90.3	85.5
	Aver.	.....	....	....	....	....	....	....	....
Robert H. ..... 11/1/16 60.0 Kg. 1.67 Sq. M.	Prelim.	11:24	....	....	....	....	....	....	....
	1	12:24	28.3	27.4	0.75	43.5	0.65	89.6	93.5
Robert H. ..... 11/3/16 59.9 Kg. 1.67 Sq. M.	Prelim.	11:22	....	....	....	....	....	....	....
	1	12:22	30.3	44.1	0.78	38.4	0.60	145.7	90.7
	2	12:52	16.9			19.4	0.60		47.7
	3	1:22	15.4	14.9	0.75	13.9	0.60	43.0	43.3
	4	2:22	27.6	26.5	0.76	36.6	0.60	86.8	81.5
	5	3:22	29.7	27.8	0.78	39.8	0.60	91.6	90.9
	6	4:22	31.1	29.3	0.77	41.5	0.60	96.5	93.1
	Aver.	.....	....	....	....	....	....	93.9	....
Robert H. ..... 11/5/16 60.4 Kg. 1.67 Sq. M.	Prelim.	12:11	....	....	....	....	....	....	....
	1	1:11	29.1	28.6	0.74	37.2	0.73	93.9	100.0
Robert H. ..... 11/8/16 59.0 Kg. 1.67 Sq. M.	Prelim.	11:42	....	....	....	....	....	....	....
	1	12:42	24.0	22.0	0.79	33.1	0.39	73.2	78.2
	2	1:42	24.1	22.7	0.77	37.9	0.39	75.0	75.3
	Aver.	.....	....	....	....	....	....	....	....
Joseph S. ..... 3/6/17 69.0 Kg. 1.81 Sq. M.	Prelim.	11:59	....	....	....	....	....	....	....
	1	12:52	32.1	29.9	0.78	40.9	0.33	99.3	93.2
Joseph S. ..... 3/9/17 67.5 Kg. 1.81 Sq. M.	Prelim.	11:37	....	....	....	....	....	....	....
	1	12:37	28.4	27.2	0.76	43.2	1.05	....	88.8
	2	1:37	29.7	25.7	0.84	39.3	1.05	....	87.3
	Aver.	.....	....	....	....	....	....	86.9	....

Direct Calorimetry (Rectal Temp., Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	39.3	..	..	....	..	..	..	....	....	Basal
79.7	39.4	100	5	....	..	..	..	....	....	Very quiet
84.3	39.5	96	8	....	..	..	.	....	....	Very quiet
....	....	..	..	0.72	21	74	5	1.37	48.9	
....	40.0	..	..	....	..	..	..	....	....	Falling temperature
75.4	39.9	90	17	....	..	..	.	....	....	Very quiet, voided twice
78.0	39.8	..	12	....		..		....	....	Very quiet
37.4	39.8	..	3	....		.		....	....	Very quiet
107.8	39.4	85	..	....	.			....	....	Very quiet
148.6	39.1	..	14	....	.		.	....	....	Very quiet
151.2	38.9	80	8	....			.	....	....	Very quiet
.. .	....	..	..	0.73	17	75	8	1.33	47.3	
....	36.4	62	..	....	.	..	..	....	....	Basal
68.6	36.5	58	..	0.88	20	35	45	1.10	....	Slightly restless
64.6	36.5	58	..	0.81	20	51	29	1.11	....	Fairly quiet
....	....	..	..	....	..	..	..	....	36.6	
....	38.7	..	..	....	.	..	..	....	....	Basal
86.5	38.8	67	21	0.74	21	70	9	1.57	....	Fairly quiet
90.3	38.9	67	62(?)	0.75	20	68	12	1.65	....	Restless, coughing
....	....	..	..	....	..	..	..	....	54.6	
....	39.5	106	..	....	..	..	..	....	....	Basal
98.0	39.6	102	43	0.74	19	72	9	1.49	53.7	Somewhat restless
....	39.7	91	..	....	..	..	..	....	....	Rising temperature
105.1	40.2	91	20	0.77	..	..	..	1.63	....	Fairly quiet, shivering 12:10–1:10 p. m.
51.4	40.3	105	18							Slightly restless
46.0	40.3	..	16	0.74	..	..	..	1.64	....	Slightly restless
91.0	40.5	104	10	0.75	.	.	..	1.45	....	Quiet, sleeping
91.8	40.6	115	23	0.77	..	..	..	1.53	....	Fairly quiet
87.3	40.5	119	35	0.77	..	.	..	1.62	....	Slightly restless
....	....	..	..	....	17	66	17	....	56.2	
....	39.5	102	..	....	..	..	..	....	....	Basal
86.9	39.1	108	33	0.72	20	75	.	1.53	56.0	Restless
....	37.3	..	..	....	..	..	..	....	....	Basal
75.9	37.2	88	26	0.79	14	67	19	1.24	....	Slightly restless
72.3	37.2	78	17	0.77	14	68	18	1.27	....	Fairly quiet
....	....	..	..	....	..	..	..	....	44.3	
. ..	40.1	..	..	....	..	..	..	....	....	Basal
100.7	40.3	94	30	0.78	9	68	23	1.44	54.8	Rather restless
.. .	39.0	..	.	....	..	..	..	....	....	Basal
91.1	39.0	82	16	. ..	..	..	..	....	....	Fairly quiet dozed, 5 minutes
89.0	39.1	..	11	....	.	..	..	....	....	Quiet
....	....	..	..	0.79	28	48	24	1.29	48.0	

TABLE 2.—Summary of Results in Erysipelas

Subject	Date	Surface Area, Sq. M.	Stage of Disease	Rectal Temperature, C.	Length of Period	Average R. Q.	Heat Eliminated, Cal.	Heat Produced, Cal.	Per Cent. Divergence of Direct from Indirect	Average Calories per Sq. M. per Hour, Indirect	Rise Above Average Normal, Basal Linear	Per Cent. of Total Heat Elimination Lost in Vaporization of Water
Arshel A.	10/13/16	1.58	Febrile period, rising temperature	39.3-39.5	2 hours	0.74	156.0	164.0	+6.2	48.9	+23	26.8
Arshel A.	10/15/16	1.57	Febrile period, falling temperature	40.0-38.9	8 hours	0.75	656.5	598.4	+0.8	47.3	+19	23.6
James W.	10/17/16	1.67	First day, normal temperature	36.4-36.5	2 hours	0.84	129.4	133.3	+9.6	36.6	— 8	29.7
Odysseo B.	10/27/16	1.59	Febrile period, rising temperature	38.7-38.9	2 hours	0.76	168.9	176.8	+0.8	54.6	+38	28.
Robert H.	11/ 1/16	1.67	Febrile period, high temperature	39.5-39.6	1 hour	0.75	93.5	98.0	+9.3	53.7	+35	27.2
Robert H.	11/ 3/16	1.67	Febrile period, rising temperature	39.7-40.6	5 hours	0.77	437.2	472.5	+0.6	56.2	+42	26.0
Robert H.	11/ 5/16	1.67	Febrile period	39.5-39.1	1 hour	0.74	100.0	80.9	—13.5	56.0	+41	33.4
Robert H.	11/ 8/16	1.67	First day of low temperature	37.3-37.2	2 hours	0.78	153.5	148.2	0	44.3	+12	30.8
Joseph S.	3/ 6/17	1.81	Febrile period, high temperature	40.1-40.3	1 hour	0.78	93.2	100.7	+1.4	54.8	+38	25.6
Joseph S.	3/ 9/17	1.81	Febrile period, high temperature	39.0-39.1	2 hours	0.80	176.1	180.1	+3.2	48.0	+20	27.4

proportional to the degree rise in rectal temperature. The same relation is found in erysipelas. Figure 6 expresses this relationship graphically according to the method used by McCann and Barr in tuberculosis. The abscissas show the level of metabolism in percentage of the average normal, the ordinates show the rectal temperature in degrees Centigrade. The line 90 means 10 per cent. below the average normal;

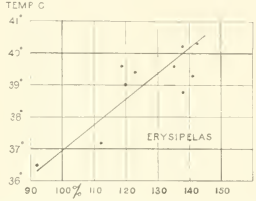

Fig. 6.—Relationship of basal metabolism to temperature in erysipelas. Ordinates represent rectal temperature in degrees Centrigrade; abscissae the metabolism expressed in percentages of the average normal. Each dot represents an experimental period in the calorimeter.

150 means 50 per cent. above the average. Each dot represents a calorimetric experiment. The diagonal line represents the average. Figure 7 expresses the same relation for the more numerous observations on typhoid fever. The heat production in typhoid increases a little more rapidly for each degree rise in temperature but on the whole the curves are strikingly similar.

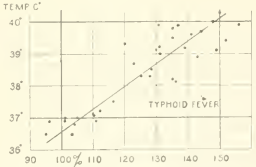

Fig. 7.—Relationship of basal metabolism to temperature in typhoid fever.

Nitrogen Equilibrium and Weight.—The observations on the nitrogen metabolism are disappointing and inconclusive. In spite of the determined efforts of a well trained staff of nurses, it was impossible to induce the patients to take nourishment sufficient for their caloric need during the fever. In figures 8, 9, and 10, the temperature, weight,

nitrogen intake and output together with the total food intake are represented graphically. The dashes of the dot dash line at the foot of the charts represent the heat production as calculated from actual observations in the calorimeter. The clinical data from which the charts are drawn will be found in Table 3. It will be seen that during the febrile course the expenditure of energy was always in excess of the caloric intake. No conclusions, therefore, may be drawn concerning toxic destruction of the body protein. Even normal individuals may show a nitrogen loss during an insufficient caloric intake.

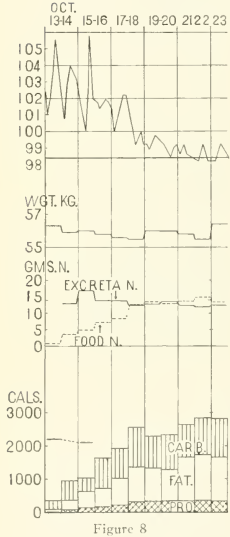

Figure 8

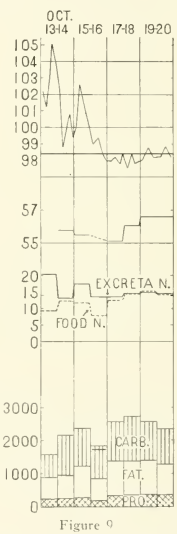

Figure 9

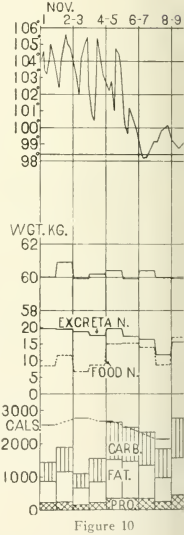

Figure 10

Fig. 8.—Arshel A. (Case 1) Temperature, body weight; food nitrogen dotted line; excreta nitrogen, continuous line. At the base of chart, columns representing total calories of food. The dot dash line represents the estimated heat production for twenty-four hours. The dashes are placed on days of the observations in the calorimeter.

Fig. 9.—James W. (Case 2) Temperature, body weight, food and excreta in nitrogen, food calories and dot dash line showing estimated heat production.

Fig. 10.—Robert H. (Case 4) Temperature, body weight, food and excreta nitrogen, food calories and dot dash line showing estimated heat production.

TABLE 3.—Clinical Calorimetric Data in Four Cases of Erysipelas

Name and Date	Body Weight	Food				Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	Nitrogen Balance, Gm.	Urine Volume, C.c.
		Total Calories	Carbohyd., Gm.	Fat, Gm.	Alc., Gm.					
James W.										
10/13/16	....	1,598	174	69	...	9.5	19.4	20.3	—10.8	1,730
10/14/16	55.8	2,195	278	84	...	10.6	12.2	13.3	— 2.7	1,840
10/15/16	55.5	2,363	273	100	...	12.0	16.5	17.7	— 5.7	1,640
10/16/16	....	1,832	236	71	...	8.0	13.1	13.9	— 5.9	1,355
10/17/16	55.1	2,045	301	116	...	12.7	12.4	13.7	— 1.0	1,800
10/18/16	56.2	2,741	317	114	...	14.7	13.3	14.8	— 0.1	1,980
10/19/16	56.6	2,573	271	115	...	13.3	13.5	15.0	+ 0.3	2,200
10/20/16	56.6	2,378	240	92	...	14.3	13.2	14.6	— 0.1	1,520
Arshel A.										
10/13/16	56.4	346	57†	10	...	9.9	13.9	14.0	—13.1	1,213
10/14/16	55.9	972	144	31	...	3.6	12.7	13.1	— 9.5	1,210
10/15/16	56.0	1,049	100	55	...	5.0	12.6	12.1	— 7.1	1,070*
10/16/16	....	1,020	118	58	...	7.2	13.4	14.1	— 6.9	2,380*
10/17/16	55.6	1,958	228	87	...	8.5	12.9	13.8	— 5.3	2,480
10/18/16	55.5	2,576	291	115	...	12.4	11.4	12.6	— 0.2	1,520
10/19/16	56.0	2,305 ?	259 ?	106 ?	...	13.4 ?	11.5	12.8	+ 1.6	2,200
10/20/16	56.0	2,333	272	104	...	13.0	12.4	13.7	— 0.7	2,570
10/21/16	....	2,656	296	114	...	13.7	12.4	13.7	± 0.0	2,800
10/22/16	55.5	2,863	272	47	...	14.7	11.6	13.1	+ 1.6	2,300
10/23/16	56.4	2,855	282	14	...	13.3	11.2	12.6	+ 0.9	2,220
Odysseo B.										
10/26/16	54.5	1,371	134	68	...	7.4	15.7	16.4	— 9.0	690
10/27/16	53.9	933	108	38	54	3.2	14.3	14.3	—11.1	676
10/28/16	54.1	2,475	187	127	162	14.4	14.9	16.3	— 1.9	870
10/29/16	54.0	2,493	259	117	54	14.7	12.4	13.6	+ 1.1	510
10/30/16	54.4	2,493	270	106	...	15.6	14.2	15.6	.....	1,090
10/31/16	55.4	2,116	192	105	...	13.7	13.6	15.0	— 1.3	1,180
Robert H.										
11/1/16	60.0	1,429	137	69	...	8.4	18.0	19.8	—11.4	2,325
11/2/16	60.9	1,808	176	96	...	10.6	15.7	19.5	— 8.9	1,320
11/3/16	59.8	1,109	105	54	...	6.5	17.1	18.8	—12.3	1,555
11/4/16	60.1	1,537	174	65	...	8.3	16.0	17.6	— 8.3	1,390
11/6/16	60.3	2,656	282	119	...	15.1	18.1	19.9	— 4.8	2,080
11/6/16	59.9	2,315	257	115	...	15.1	15.6	17.2	— 2.1	1,120
11/7/16	60.3	2,339	241	106	...	14.0	15.2	16.7	— 2.7	2,570
11/8/16	59.1	1,861	216	80	...	8.8	10.7	11.8	— 3.0	1,477
11/9/16	59.8	2,753	292	121	...	17.9	14.2	15.6	+ 1.4	1,523
11/10/16	59.5	2,496	258	112	...	15.2	13.6	15.0	+ 0.2	1,740

* Excreta nitrogen estimated as urine nitrogen plus 10 per cent. of food nitrogen.
† Approximate.

The weight curves are of some interest. In studying pneumonia, Sandelowsky [12] found that, during the acute febrile course of the disease, many patients maintained their weight or even gained a considerable amount. At the crisis and during the early convalescence, on the other hand, there was a rapid loss in weight. This, he attributed to a storage of water in the body during fever and a rapid loss of water following it. He supported this hypothesis with refractometric studies of the serum proteins by which he demonstrated to his own satisfaction that there was a dilution of blood during the fever and a concentration or return to normal following it. In the light of Sandelowsky's contention, the weight curves in erysipelas are significant. During the acute course of the fever, it is a little surprising that the weight remains practically constant in spite of the insufficient food. At the crisis,

12. Sandelowsky, J.: Blutkonzentration bei Pneumonie, Deutsch. Arch. f. klin. Med. **96**:445, 1909.

and in convalescence, however, the fall of weight noted by Sandelowsky in pneumonia is not observed.

Regulation of Body Temperature.—In the chills of malarial fever,[9] it was found that the sharply rising temperature was accomplished by a great increase in the production of heat while the elimination of heat remained at the level which had existed before the chill. Following the paroxysm there was a period of high continuous temperature. In this stage, the heat production fell while the heat elimination increased until the two were equal to each other. Both, however,

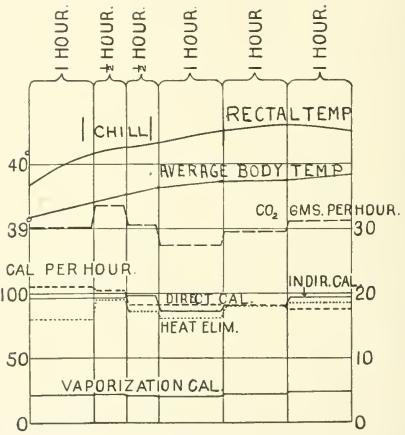

Fig. 11.—Metabolism chart. Robert H (Case 4) curves showing relationship of heat production to heat elimination.

were maintained at a level high above the normal basal metabolism. The conditions under which the erysipelas patients were studied may be considered analogous to the high constant temperature following the malarial paroxysm. Both heat production and elimination are at a high level, which, as we have seen, varies with the degree of fever. In erysipelas, however, the temperature is seldom truly continuous. There are usually frequent remissions, sometimes intermissions. It would be interesting to know how these fluctuations are brought about and whether the mechanism of the rise and fall of temperature during

a high fever is similar to that of malaria in which the temperature is originally normal. It was with these questions in mind that the study of erysipelas was undertaken. Unfortunately our data are not sufficient to answer them. Only two long observations were made during significant changes in temperature. In both, the changes were so gradual that it is impossible to draw conclusions from them. Figure 11 represents graphically the results of studies made on Robert H. during a rising temperature while Figure 12 shows in a similar manner the results of studies made on Arshel A. during a falling temperature. It is interesting to note that the rather sharp rise during the first two

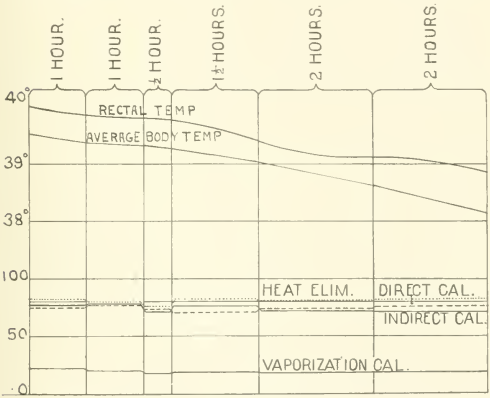

Fig. 12.—Metabolism chart. Arshel A. (Case 1) curves showing relationship of heat production to heat elimination.

hours of the observation on Robert H. was accompanied by shivering which amounted to a moderate chill. During these periods, the heat production was high. After the shivering ceased, the production of heat diminished while the heat elimination increased in a manner quite comparable with that observed in malaria. During the falling temperature shown in Figure 12, the heat elimination remained at a practically constant level throughout the seven and a half hours of the observation. The heat production gradually fell.

Heat Loss by Vaporization of Water.—The question of water utilization in fever is of great importance. Because of its ability to

absorb heat and its fluid character water offers the chief means of carrying heat from the cells where it is produced to the surface of the body where it may be eliminated. Heat loss both through radiation and conduction and through vaporization is therefore dependent on the proper mobilization of water within the body. Because of the dry skin, concentrated urine and other phenomena of fever, it has been argued that the water supply of the body is depleted or cannot be mobilized. This has been considered a possible cause of fever by Balcar, Sansum and Woodyatt.[13] Facts concerning the heat lost in vaporization of water from skin and lungs are relevant to this question.

Under the constant temperature conditions of the calorimeter, normal subjects accomplish about 24 per cent. of their total heat elimination by vaporization of water. The average percentage was slightly lower, about 22 per cent. in typhoid fever. In erysipelas, on the other hand, the heat lost in the vaporization of water is high in proportion to the total elimination. During the rising temperature observed in Robert H. (Fig. 11), it constituted 26 per cent. The limits of variation for all the observations were from 23.6 to 33.4 per cent.

SUMMARY AND CONCLUSIONS

1. Ten calorimetric experiments have been made in five cases of erysipelas. Two of these were taken on the day following the crisis. The others were made during the febrile course of the disease.

2. During the fever, the metabolism is increased from 19 to 42 per cent. above the average normal basal. The increase in metabolism is roughly proportional to the degree of fever. A temperature of 40 C. involves a heat production of about 40 per cent. above the average normal.

3. The change in rectal temperature is not always an accurate index of the change in average body temperature in erysipelas

4. The regulation of body temperature is similar to that observed in malaria during the stage of high continuous temperature. Both heat production and heat elimination are maintained at a high level.

5. The heat lost in the vaporization of water constitutes from 23.6 to 33.4 per cent. of the total heat elimination. During rising, constant and falling temperatures the percentge of heat eliminated in the vaporization of water was greater than in normal individuals.

6. No specific differences were found between the metabolism in erysipelas and in typhoid fever. Both fevers show approximately the same increases in the level of heat production for the same increase in body temperature. The protein metabolism is greatly increased in both diseases.

13. Balcar, J. B.; Sansum, W. D., and Woodyatt, R. F.: Fever and Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

CLINICAL CALORIMETRY. XXXI. OBSERVATIONS ON THE METABOLISM OF ARTHRITIS *

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NEW YORK

In recent years, bacteriologists have made important contributions to the etiology of arthritis, especially in regard to the part played by focal infections. The large mass of evidence which has gradually accumulated indicates that most cases of arthritis are infectious in origin. In spite of this, however, some practitioners have held to the belief that arthritis, particularly in its chronic form, is an expression of a disturbance in metabolism. The relationship between gouty arthritis and an abnormal purin metabolism gave some ground for this theory, and for many years the various forms of acute and chronic arthritis were supposed to be dependent on the retention in the body of uric acid or some kindred substance. For this reason rheumatic patients were often put on a reduced nitrogenous diet, but the results obtained by this mode of treatment were not encouraging. Pemberton [1] has advocated a lowered carbohydrate intake for arthritis patients.

Comparatively little experimental work was done on the metabolism of arthritis before the extensive studies of Pemberton and his associates [2] published in 1920. Indeed, it is only within the last few years that the development of newer and more accurate methods in biochemistry have made reliable investigations along this line possible. Tileston and Comfort,[3] who studied the nonprotein nitrogen and urea in the

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Pemberton, R.: The Metabolism and Treatment of Rheumatoid Arthritis, Fourth Paper, Am. J. M. Sc. **153**:678, 1917.

2. Pemberton, R., and Robertson, J. W.: Studies on Arthritis in the Army, Based on Four Hundred Cases. I. Preamble and Statistical Analysis, Arch. Int. Med. **25**:231 (March) 1920. Pemberton, R., and Tompkins, E. H.: Ibid. II. Observations on the Basal Metabolism, Arch. Int. Med. **25**:241 (March) 1920. Pemberton, R., and Foster, G. L.: Ibid. III. Studies on the Nitrogen, Urea, Carbon Dioxid Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood Renal Function, Blood Sugar and Sugar Tolerance, Arch. Int. Med. **25**:243 (March) 1920. Pemberton, R., and Buckman, T. E.: Ibid. IV. Studies in the Relation of Creatin Metabolism to Arthritis, Arch. Int. Med. **25**:335 (April) 1920. Pemberton, R.: Ibid. V. Roentgen-Ray Evidences, Clinical Considerations, Treatment, Summary, Conclusions and Clinical Abstracts of Cases Studied, Arch. Int. Med. **25**:351 (April) 1920.

3. Tileston, W., and Comfort, C. W., Jr.: The Total Nonprotein Nitrogen and the Urea of the Blood in Health and Disease, as Estimated by Folin's Methods, Arch. Int. Med. **14**:720 (Nov.) 1914.

blood in various diseases, obtained low figures in rheumatic fever. Pemberton and Foster [2] estimated the blood urea and nonprotein nitrogen in seventeen cases of chronic arthritis and found that the figures in every case were well within the normal limits. Pemberton and Buckman [2] made determinations of the nonprotein nitrogen in the blood in forty cases of arthritis and found an abnormal elevation in only two cases. Folin and Denis [4] found an increase of uric acid in the blood in nongouty arthritis. Similar results were obtained by McClure and Pratt.[5] Pemberton and Buckman [2] carried out observations on the creatin and creatinin of the blood and urine in forty cases of arthritis. About one-half of the cases showed an abnormally high value for blood creatinin. Pemberton and Foster [2] also estimated the carbon dioxid combining power of the blood, the calcium of the circulating blood and the total fat and cholesterol of the fasting blood. In all cases the figures were well within normal limits. These authors did find evidence of an abnormal rise in the blood sugar following the ingestion of 100 gm. glucose.

Pemberton and Tompkins [2] studied the basal metabolism in a series of twenty-nine cases of arthritis, the observations being made by indirect calorimetry, using the Tissot apparatus. Of the cases studied, 80 per cent. showed a metabolism within normal limits, in 20 per cent. the rate was slightly below normal limits. From the respiratory quotients no abnormality could be detected in the percentage of calories obtained from the three classes of foodstuffs.

The present investigation, carried out in 1916-1917, deals with the metabolism in two cases of acute arthritis, two cases of subacute arthritis, one case of gouty arthritis and four cases of chronic arthritis. Circumstances prevented the study of a larger series but it seemed desirable to publish the data at hand in order to complement the report of Pemberton and Tompkins and to render the records accessible to future workers.

METHODS

The experiments reported in this study were carried out on patients in Bellevue Hospital. The calorimeter of the Russell Sage Institute of Pathology was employed. The heat production was measured by both the direct and indirect methods. The actual details of technic have been described fully in previous articles in this series.[6]

The basal metabolism of four cases of acute and subacute arthritis was determined. Edward C. (Case 1) had a typical case of acute

4. Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Determinations in Blood, Arch. Int. Med. **16**:33 (July) 1915.

5. McClure, C. W., and Pratt, J. H.: A Study of Uric Acid in Gout, Arch. Int. Med. **20**:481 (May) 1917.

6. Clinical Calorimetry, Arch. Int. Med. **15**:793-945 (May) 1915; **17**:855-1059 (June) 1916; **19**:823-957 (May) 1917.

rheumatic fever. John Bl. (Case 2) was considered to have subacute rheumatic fever. John Br. (Case 3) had acute arthritis associated with gonorrheal urethritis and a conjunctivitis of gonococcus origin. Joseph McC. (Case 4) had a subacute arthritis and an intermittent urethral discharge of several years duration. Observations concerning the nitrogen equilibrium were made on one patient, John Br. (Case 3).

REPORT OF CASES

Case 1.—Acute Rheumatic Fever.

History.—Edward C., a waiter, born in Ireland, 33 years of age, was admitted, Jan. 13, 1917, and discharged unimproved, Jan. 29, 1917. Since childhood he has had frequent attacks of severe sore throat, and he has had quinsy four times. In 1906, he had symptoms of scarlet fever and was treated at a contagious hospital. During the course of the disease, he developed a very severe joint attack which lasted two weeks. In July, 1912, he was operated on for appendicitis, and in November, 1912, he was operated on for ulcer of the stomach. He was kept on a diet for one year after the operation. He was a convivial drinker, but denied venereal disease.

November 24 an operation was performed on his nose. Following this he had a severe hemorrhage from the nose lasting four hours. November 29 he was seized with a severe quinsy which was lanced December 1. He rapidly recovered from the throat trouble, but December 20 he was seized with pain in the muscles and joints which remained severe for about a week. Vague pains were present until January 13 when they again became very severe.

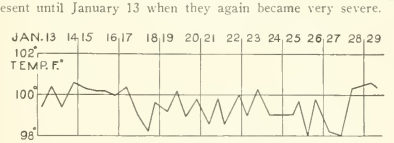

Fig. 1.—Edward C. (Case 1). Temperature Chart.

Physical Examination.—The patient was a rather pallid, poorly nourished young Irishman of cheerful disposition. The tonsils were much enlarged, the right being larger than the left. The crypts are deep but there are no follicles present. The teeth are in fair condition.

Heart: The left border of dulness in the fifth space is 11.5 cm. from the median line; the right border is beneath the sternum. There is a definite, short, soft systolic murmur, heard best at the apex, transmitted to the mid-axilla and the sternum.

Abdomen: Shows scars of previous operations. Rectal examination disclosed a normal prostate and seminal vesicles. There was some pain, on motion, in both shoulders, but no swelling or redness.

Laboratory Examination.—Urine: Moderate trace of albumin; no casts. Blood pressure: Systolic, 140 mm.; diastolic, 85 mm. Blood cultures: Negative. Tonsil cultures: *Streptococcus viridans* (blood agar plates); from right tonsil, *S. viridans* and a moderate number of *Staphylococcus aureus* colonies and a diphtheroid bacillus from the left tonsil. Wassermann test: Negative. Gonococcus fixation test: Negative.

January 22 he was in the calorimeter from 10:50 a. m. to 1:50 p. m. He had moderate pain in both shoulders, in the right wrist and in both knees. None of the joints showed swelling, tenderness or redness. This condition was practically unchanged when he was discharged January 29.

Case 2.—Subacute Rheumatic Fever.

History.—John Bl., a bookkeeper, born in Scotland, 58 years of age, was admitted Jan. 22, 1917, and discharged cured Feb. 7, 1917. In 1914 he had an attack of joint pain similar to the present one. He had pneumonia in 1912. Thirty years ago he had gonorrhea without complications. He drinks one glass of whiskey and three glasses of beer daily but is rarely intoxicated. His father died of "rheumatism and heart trouble."

January 8 he began to have vague pains in the muscles. January 18, following exposure to the weather, both knees became very painful and swollen. He felt chilly during the day and was nauseated. Two days later his ankles began to swell, and finally his arms and hands became stiff and swollen.

Physical Examination.—The patient was a large, robust Scotchman, not very ill. The tongue showed a moderate white coat. The tonsils were atrophic but red with chronic congestion. Most of the teeth were missing, although there was no definite pyorrhea. Heart: Not affected. Lungs: Show signs of a moderate emphysema. At the right base are many coarse, leathery friction rubs and diminished breathing. There was swelling and exquisite tenderness of the right and left knee joints; wrists and, to a lesser extent, of the ankles. On the right shin is the scar of an old varicose ulcer.

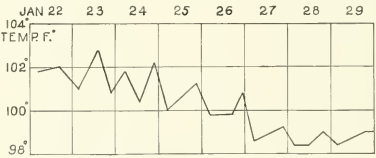

Fig. 2.—John Bl. (Case 2). Temperature Chart.

Laboratory Examination.—Urine: Negative. Blood pressure: Systolic, 130 mm.; diastolic, 90 mm. Blood culture: Negative. Blood: Leukocytes, 12,000; polymorphonuclears, 80 per cent.; hemoglobin, 80 per cent. Wassermann test: Negative. Gonococcus fixation test: Negative. Culture of each tonsil shows abundant and almost pure growth of *Streptococcus viridans* and a few colonies of *Staphylococcus aureus.*

January 26, from 10:45 a. m. to 1:45 p. m., he was in the calorimeter. At that time the hands, wrists and knees were moderately hot and swollen. The elbows and shoulders were tender and painful on motion. The joints improved gradually and he was discharged as cured February 7.

Case 3.—Acute Gonococcus Arthritis.

History.—John Br., a clerk, born in the United States, 19 years of age, was admitted Jan. 25, 1917, and discharged improved March 23. Both his mother and his father had rheumatism. The mother died in 1916 of chronic alcoholism. He had chorea in early childhood. He says that between the ages of 5 and 13 he averaged one attack of "rheumatism" a year, but has had none since. The attacks were usually mild and did not force him to go to bed. He never had tonsillitis.

January 7, seven days after intercourse, he began to have a urethral discharge. January 13 he had severe pains in the right knee. Later, the right foot, left foot and right thumb were affected. Pains became very severe and motion was limited.

Physical Examination.—The patient was a well developed, somewhat emaciated boy, acutely ill, rather toxic. The tongue was slightly dry with a brown coat. The eyes showed a moderately severe conjunctivitis. The tonsils were small with deep crypts and no signs of inflammation. The heart was not involved. The left knee joint was distended with fluid, hot, slightly tender and held in semiflexion. Considerable motion was possible without great pain. The right knee showed signs of inflammation and contained some fluid. Both ankles were swollen, the left more than the right. There was marked tenderness

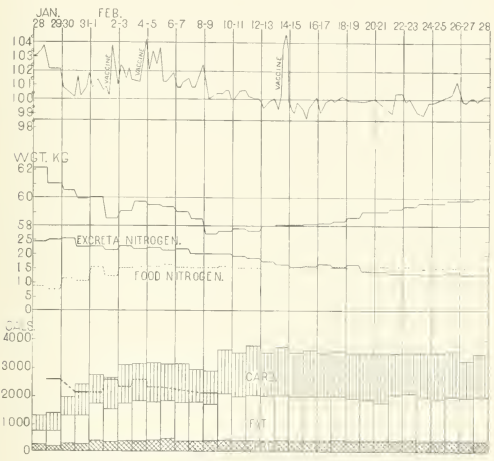

Fig. 3.—John Br. (Case 3). Acute arthritis, gonococcus origin. Temperature, body weight; excreta nitrogen, continuous line; food nitrogen, dotted line. At base of figure, columns representing total calories of food. The dot dash line represents the estimated heat production in calories for twenty-four hours. The dashes are placed on days of the observations in the calorimeter. Note that the calories of the food exceed the estimated heat production except for the first two days of observation.

over the tarsometatarsal joints of both feet; tenderness and pain on motion in the metatarsophalangeal joint of the great toe and of the metacarpophalangeal joint of the thumb. There was a moderate, white, purulent urethral discharge containing gonococci in large numbers. The prostate was not enlarged. The urine from the posterior urethra was clear and contained only an occasional pus cell. The urine from the anterior urethra contained many pus cells but no albumin or casts.

Laboratory Examination.—Blood: February 2 (before vaccine), leukocytes 11,000; polymorphonuclears, 75 per cent. Blood culture: January 30 and February 3, sterile. Wassermann negative. Gonococcus fixation test: January 26, doubtful; January 31, negative. Tonsil culture, February 3: Both tonsils showed *Streptococcus viridans* predominant but with scattering colonies of *Staphylococcus aureus* and *Micrococcus paratetragenus.*

January 29 he was in the calorimeter from 11 a. m. to 3 p. m.; January 31, from 10:30 a. m. to 2:10 p. m. February 2 a faint presystolic murmur was heard for the first time, just medial to the apex of the heart. On the same day, at 10:50 a. m. he was given intravenously a 25 million dose of the New York Board of Health typhoid vaccine and was observed in the calorimeter from 11 a. m. to 3:15 p. m. February 4 he received a second dose of typhoid vaccine. February 5, 10 c.c. of cloudy fluid was removed from the left knee joint. The smear showed large numbers of polymorphonuclear cells and a few endothelial cells. Occasional gram-negative intracellular bodies, resembling gonococci, were seen. The cultures were negative on ascitic glucose agar plate, deep ascitic glucose agar tube, blood broth, ascitic and plain broth. February 9, from 11 a. m. to 2:15 p. m., he was in the calorimeter. February 14 he received a third injection of typhoid vaccine. He remained in the metabolism ward until March 1 when he was discharged to the general service.

January 29 he weighed 137 pounds; February 9, 126 pounds; March 1, 131 pounds. During the time of observation none of the joints originally affected were cured. There was frequently marked improvement with equally frequent relapse, sometimes following the administration of typhoid vaccine by twenty-four hours, sometimes by thirty-six hours, more frequently occurring spontaneously without reference to treatment. During the last three weeks, however, there was a very slow, general tendency to improvement. The heart murmur, which was first heard February 2, became much louder by February 9. March 1 it was again very feeble and March 5 it could be heard only after exercise. During the month the right side of the heart increased moderately in size. The electrocardiogram taken March 2 showed well marked right sided enlargement. The urethral discharge lessened with local treatment but never disappeared entirely. It remained localized to the anterior urethra.

In the general ward, from March 3 to 13, he received gonococcus vaccine intravenously in doses of from 20 to 30 million. His improvement was remarkable. The temperature, which had been continually elevated since entrance to the hospital, became normal and remained so except during the reactions following vaccinations. The pain disappeared. A moderate amount of fluid in the knee joints, however, remained unabsorbed. He received bakes and massage until March 23, when he was discharged. Both knee joints contained small amounts of fluid but there were no other symptoms. He was seen again in April. His right knee still contained a small amount of fluid but he was otherwise in excellent health.

Case 4.—Subacute Gonorrheal Arthritis.

History.—Joseph McC., an elevator operator, born in the United States, 27 years of age, was admitted Jan. 14, 1917, and discharged unimproved March 1, 1917. In 1910 he had an attack of gonorrheal urethritis followed by epididymitis. Since then he has had a urethral discharge several times, the last in November, 1916. In 1912 he had an acute arthritis involving all the joints, and he was ill for nine weeks. A second attack of the same character, in 1914, lasted two months. He has never had sore throat, chorea or other manifestations of acute rheumatic fever.

Jan. 3, 1917, he began to have a dull pain in the lower end of the spine and in the lumbosacral muscles, which radiated down the right thigh. His right heel became so painful that he could not walk. About the same time the urethral discharge recommenced.

Physical Examination.—This shows an undeveloped, poorly nourished man. He held himself very stiff because of pain in the back. There was pain on pressure over the sacrococcygeal joint and marked tenderness over the spine of the ninth dorsal vertebra. The under surface of the right heel was exquisitely tender. There was a considerable watery, purulent urethral discharge, a smear of which showed gonococci. The prostate was moderately enlarged. The right seminal vesicle was palpable.

Laboratory Examination.—Urine from both anterior and posterior urethra contained pus but no albumin or casts. Gonococcus fixation test was negative. Wassermann reaction was negative. The roentgenogram showed periosteal exostosis of the os calcis of both heels.

His symptoms remained unchanged during the first seven days in the hospital. February 1 he was given intravenously 40 million of the New York City Board of Health typhoid vaccine. February 3, 5 and 7 similar doses were given. The character of the reactions following the injections appears on the temperature chart. The chills began from thirty to seventy-five minutes after injection. February 13 a dose of 50 million was given.

February 7 and 13 the patient was observed in the calorimeter. No noticeable improvement resulted from the vaccine therapy. On the first day following each injection he was more stiff and uncomfortable. On the second day the condition returned to that which obtained before the vaccine was given. Except at the times when he was given vaccine this patient had a normal temperature.

Results of the study of basal metabolism in the cases of acute and subacute arthritis will be found in the summary, Table 4, the detailed calorimeter data in Table 1.

It will be noted that the patients studied showed but slight elevation in the basal metabolism as measured by the surface area standards of Aub and Du Bois. All but one determination came within 12 per cent. of the average normal figure. This single exception was found in the case of John Br. who showed a basal metabolism 26 per cent. above the average normal when he was slightly restless with a constant temperature of 38.4 C. This case deserves mention from another standpoint.

In Figure 3 and Table 2, it will be seen that during the period of high temperature, 100-104 F., there was a persistent negative nitrogen balance similar to that observed by Coleman and Du Bois[7] in typhoid fever. This occurred during a time when he was receiving a well balanced ration greatly in excess of his heat production as measured by several calorimeter observations. This phenomenon was so distinctly abnormal that it is necessary to assume a toxic destruction of body protein caused by the gonorrheal arthritis. Since this negative nitrogen balance continued during a period when the temperature was comparatively low, it is natural to infer that the destruction of protein was due to toxins rather than the hyperpyrexia.

7. Coleman and Du Bois: Clinical Calorimetry. Paper 7.—Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food. Arch. Int. Med. **15**:882 (May) 1915.

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
William B.	Prelim.	12:14	....	....	....	....	....	....	....
12/6/16									
63.7 Kg.	1	1:14	26.2	24.2	0.79	31.1	0.39	80.2	78.6
1.80 Sq. M.	2	2:18	28.9	25.3	0.83	35.1	0.49	84.7	82.6
	Aver.	.....	....	....	....	....	....	80.0*	....
William B.	Prelim.	11:50	....	....	....	....	....	....	....
12/11/16									
63.6 Kg.	1	12:50	23.9	21.3	0.82	28.3	0.48	....	77.0
1.80 Sq. M.	2	1:50	24.2	22.2	0.79	29.8	0.48	....	76.4
	Aver.	.....	....	....	....	....	....	72.0	....
William B.	Prelim.	11:57	....	....	....	....	....	....	....
12/8/16									
62.6 Kg.	1	12:57	27.6	21.5	0.93	31.7	0.58	73.7	75.0
1.80 Sq. M.	2	1:57	28.8	21.8	0.96	31.7	0.58	74.9	75.6
	3	2:59	33.0	24.5	0.98	37.0	0.58	82.3	84.6
William B.	Prelim.	11:16	....	....	....	....	....	....	....
12/13/16									
64.5 Kg.	1	12:17	30.7	24.1	0.93	35.7	1.00	79.7	84.2
1.80 Sq. M.	2	1:16	31.8	28.4	0.81	46.8	1.00	92.6	91.9
	3	2:16	33.9	29.6	0.84	55.2	1.00	96.9	99.8
	4	3:16	32.9	29.5	0.81	58.2	2.24	96.0	102.0
Edward R.	Prelim.	12:06	....	....	....	....	....	....	....
1/3/17									
37.8 Kg.	1	1:06	15.7	14.8	0.77	23.5	0.12	....	48.4
1.42 Sq. M.	2	2:06	15.8	14.5	0.79	21.7	0.12	....	49.1
	Aver.	.....	....	....	....	....	....	48.8	....
Edward R.	Prelim.	12:19	....	....	....	....	....	....	....
1/9/17									
38.8 Kg.	1	1:19	23.7	16.8	1.03	34.7	0.09	59.1	57.9
1.42 Sq. M.									
	2	1:59	....	....	....	....	....	....	....
	3	2:59	25.2	19.0	0.97	40.9	0.94	66.4	66.6
Edward McK.	Prelim.	12:03	....	....	....	....	....	....	....
1/5/17									
38.0 Kg.	1	1:03	19.3	17.0	0.82	23.8	0.10	....	56.7
1.37 Sq. M.	2	2:03	20.6	17.4	0.84	24.2	0.10	....	58.2
	Aver.	.....	....	....	....	....	....	58.1	....
Edward C.	Prelim.	11:52	....	....	....	....	....	....	....
1/22/17									
51.7 Kg.	1	12:52	21.1	20.1	0.77	33.1	0.43	....	70.7
1.56 Sq. M.	2	1:52	20.1	19.4	0.75	30.2	0.43	....	68.7
	Aver.	.....	....	....	....	....	....	64.4	....
John Bl.	Prelim.	11:46	....	....	....	....	....	....	....
1/26/17									
84.4 Kg.	1	12:46	26.8	25.7	0.76	33.4	0.63	....	76.9
2.01 Sq. M.	2	1:46	26.9	26.0	0.75	34.7	0.63	....	83.2
	Aver.	.....	....	....	....	....	....	84.7	....
John Br.	Prelim.	11:58	....	....	....	....	....	....	....
1/29/17									
61.2 Kg.	1	12:58	30.6	29.3	0.76	42.3	0.93	95.6	94.0
1.80 Sq. M.	2	1:58	30.2	28.3	0.78	40.6	0.93	92.8	93.8
	3	2:58	30.6	29.2	0.76	41.9	0.93	95.3	95.0
	Aver.	.....	....	....	....	....	....	....	....

* Average calories per hour.

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	37.1	..	..	....	..	..	..	....	....	In chair
81.7	37.2	60	16	....	..	..	..	....	44.6	Apparently quiet, patient says he exercised fingers constantly
82.4	37.2	64	28	....	..	..	..	....	44.1	Second period prolonged because of falling barometer
....	....	..	..	0.81	10	55	29	1.26	44.4	
....	37.0	..	..	....	..	..	..	....	....	Basal, in chair
76.6	37.0	60	11	....	..	..	..	....	....	Quiet
82.4	37.1	64	20	....	..	..	..	....	....	Quiet, voided
....	....	..	..	0.81	18	53	29	1.13	40 0	
....	37.2	..	..	....	.	..	..	....	....	Dextrose 212 gm., 10:56–11:07 a. m.
69.9	37.1	65	17	0.96	16	12	72	1.16	40.9	Quiet, asleep 15 min.
76.3	37.1	64	21	0.99	16	2	82	1.18	41.6	Quiet
85.1	37.2	74	21	1.01	16	0	84	1.25	44.3	Quiet
....	37.6	68	..	....	..	..	..	....	....	Chopped beef, 662 gm. (24.3 gm. N)
76.8	37.4	.	22	1.03	.	.	.	1.25	44.3	Moderately quiet
90.9	37.4	68	26	0.82	28	44	28	1.48	53.0	Moderately quiet
98.7	37.4	..	24	0.85	27	38	35	1.53	54.6	Quiet
101.4	37.5	69	21	0.82	62	23	15	1.48	52.9	Quiet
....	36.9	..	..	....	..	..	..	....	....	Basal
47.9	36.9	90	6	....	..	..	..	....	....	Very quiet
42.6	36.9	..	12	....	..	..	..	....	....	Very quiet
....	....	..	..	0.78	7	70	23	1.29	34.4	
....	37.2	.	..	....	..	..	..	....	....	Dextrose, 212 gm., 10:19 a. m.
57.3	37.2	..	3	1.04	4	0	96	1.52	41.8	Very quiet, pain; uncomfortable at start of second period
....	37.1	145	..	....	..	..	..	....	....	Removed from calorimeter, pillows shifted
63.0	37.0	..	6	0.97	3	10	87	1.71	46.7	Very quiet, pain
....	36.9	57	..	....	..	..	..	....	....	Basal
52.4	36.7	..	12	....	..	..	..	....	....	Fairly quiet
57.6	36.7	82	2	....	..	..	..	....	....	Very quiet
....	....	..	..	0.83	4	55	41	1.53	42.4	
....	37.4	..	..	....	.	..	.	....	....	Basal
60.5	37.2	76	22	....	..	..	..	....	....	Somewhat restless
71.0	37.3	..	13	....	..	..	..	....	....	Quiet
....	....	..	..	0.75	19	68	13	1.25	41.3	
....	37.7	..	..	....	..	..	..	....	....	Basal
73.9	37.6	80	6	....	..	..	..	....	....	Very quiet
81.5	37.6	..	4	....	..	..	..	....	....	Very quiet
....	....	..	..	0.74	20	70	10	1.05	42.2	
....	38.4	92	..	....	..	..	..	....	....	Basal
89 9	38.4	87	21	0.75	26	64	10	1.57	....	Restless, voiding
95.9	38.4	84	14	0.76	27	59	14	1.52	....	Fairly quiet
96 0	38.4	80	18	0.75	26	63	11	1.56	..	Fairly quiet
....	....	..	..	....	.	.	..	....	52.6	

TABLE 1.—Calorimeter—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
John Br.	Prelim.	11:58	....	....	....	....	....	....	....
1/31/17 59.7 Kg. 1.78 (Ht.-Wt.)	1	12:58	26.4	24.1	0.76	47.0	0.72	....	87.8
	2	1:58	26.8	24.0	0.81	35.2	0.72	....	81.9
	Aver.	.....	....	....	....	....	....	80.8	....
John Br.	Prelim.	11:51	....	....	....	....	....	....	....
2/9/17 57.1 Kg. 1.74 (Ht.-Wt.)	1	12:47	25.2	22.6	0.81	28.2	0.57	....	73.9
	2	1:51	28.6	25.6	0.81	32.2	0.57	....	88.5
	Aver.	.....	....	....	....	....	....	80.2	....
Timothy S.	Prelim.	12:12	....	....	....	....	....	....	....
4/26/17 53.4 Kg. 1.64 Sq. M.	1	1:12	26.1	24.0	0.79	31.2	0.57	....	78.7
	2	2:12	26.1	24.2	0.79	30.2	0.57	....	78.1
	Aver.	.....	....	....	....	....	....	79.5	....
Timothy S.	Prelim.	11:33	....	....	....	....	....	....	....
4/27/17 53.4 Kg. 1.64 Sq. M.	1	12:33	23.6	21.1	0.82	28.6	0.62	....	69.2
	2	1:33	24.0	21.5	0.81	27.7	0.62	....	70.1
	Aver.	.....	....	....	....	....	....	70.6	....
Timothy S.	Prelim	11:06	....	....	....	....	....	....	....
5/12/17 52.4 Kg. 1.64 Sq. M.	1	12:06	21.9	18.1	0.88	25.7	0.53	....	61.0
	2	1:06	23.2	20.3	0.83	25.8	0.53	....	65.0
	Aver.	.....	....	....	....	....	....	64.3	....
Joseph McC.	Prelim.	11:09	....	....	0.82	27.8	0.27	62.4	61.5
2/7 17, 51.4 Kg. 1.46 Sq. M.	1	12:09	20.9	18.6	....	....	....	....	....

* Average calories per hour.

METABOLISM IN GOUT

The basal metabolism in one case of gout was determined.

Case 5.—

History.—Timothy S., a laborer, born in Ireland, 42 years of age, was admitted April 21, 1917, and discharged improved May 12, 1917. He has never had any serious illness and says that he is not alcoholic. Attacks of gout began in 1905 when he was 30 years of age. The first attack involved both great toes. Since that time the attacks have occurred at intervals of from two months to one year. The toes, knees and fingers have been involved. The present attack involved both knees and the small joint of the right hand.

Physical Examination.—The patient was a moderately emaciated, fairly well developed man. The pinnae of both ears showed large and small tophi. There were small tophaceous spots in the ear drum. The throat was moderately congested. The heart was not enlarged. Blood pressure: Systolic, 155 mm.; diastolic, 105 mm. The arteries were palpable but not sclerosed. The metacarpophalangeal joints of the thumb and the first three fingers of the right hand were tender, swollen and painful on motion. The right wrist and elbow were slightly involved. The left hand showed marks of deformity but no active

—DATA—(Continued)

Direct Calorimetry (Rectal Temp., Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from: Protein	Fat	Carbohyd.	Calories per Hour: Per Kg.	Per Sq. M. (Linear)	Remarks
....	38.1	78	..	....	..	..	..	....	....	Basal
74.5	37.9	76	21	....	..	.	..	....	....	Fairly quiet
77.4	37.8	74	12	....	..	..	..	....	...	Quiet
...	....	..	..	0.78	24	52	24	1.35	45.4	
....	37.8	..	..	....	..	..	..	....	....	Basal
69.7	37.7	82	27	....	..	..	..	....	....	Restless
90.1	37.7	80	27	....	..	..	..	....	....	Restless
.. ..	....	..	..	0.81	19	52	29	1.40	46.1	
....	37.7	..	..	....	..	..	..	....	....	Basal
74.8	37.6	80	13	....	..	..	..	....	....	Very restless
80.9	37.7	..	12	....	..	..	..	....	....	Unsatisfactory because of pain and restlessness
....	....	..	..	0.78	19	59	22	1.49	48.5	
....	37.4	..	..	....	..	..	..	....	....	Basal
67.1	37.3	75	13	....	..	..	..	....	....	Very quiet, turned twice
71.1	37.4	..	8	....	..	..	..	....	....	Very quiet
...	....	..	..	0.81	23	49	28	1.32	43.1	
.. .	37.6	..	..	....	..	..	..	....	....	Basal
62.4	37.6	76	2	....	..	..	..	....	....	Very quiet
67.8	37.7	..	10	....	..	..	.	....	....	Very quiet until 20 min. before end
...	....	..	..	0.87	12	74	14	1.23	39.2	
.. .	37.5	..	..	....	..	..	..	....	....	Basal
66.3	37.5	64	13	0.82	.	..	.	1.21	40 0	Very quiet

inflammation. The left knee joint was slightly swollen, exquisitely tender and very painful on motion. The left great toe showed marked deformity and moderate tenderness.

Laboratory Examination.—Urine showed a trace of albumin with many granular casts. Phenolsulphonephthalein test: 17 per cent. Blood: leukocytes, 11,000; polymorphonuclears, 66 per cent. Blood uric acid: 7.9 mg. Roentgen-ray examination showed hypertrophic osteoarthritis of all the joints affected.

April 26 he was observed in the calorimeter. His metabolism was found to be 23 per cent. above the average normal. He was restless and suffered much pain. On the following day he had less pain and was quiet. He was again observed and the metabolism was found to be 10 per cent. above the average normal basal. By May 12 he had entirely recovered from the symptoms of his attack. He was again observed in the calorimeter. This time his metabolism was found to be normal. He was discharged May 12, 1917.

The results of the study of basal metabolism will be found in Tables 1 and 4. The first observation on April 26 was unsatisfactory because of the pain and restlessness of the patient. In the two sub-

sequent observations, the metabolism was 12 per cent. and 22 per cent., respectively, above the average normal level, practically within the limits of normal.

TABLE 2.—Clinical Data on John Brown

Date	Body Weight	Estimated Heat Production per 24 Hours	Food			Food N. Gm.	Urine N. Gm.	Excreta N.* Gm.	Nitrogen Balance Gm.	½-Hour Urine Volume, C.c.
			Total Calories	Carbohydrate, Gm.	Fat, Gm.					
1/28 17	62.4	.....	1,270	138	52	8.4	23.5	24.3	—15.9	1,670
1/29/17	61.3	2,600	1,229	156	53	7.3	24.4	25.1	—17.8	1,490†
1/30/17	60.5 av.	.....	1,910	156	105	11.3	24.3	25.4	—14.1	1,460
1/31 17	59.7	2,130	2,344	261	109	10.2	21.3	22.3	—12.1	1,250
2/ 1/17	60.0	.....	2,709	243	141	15.4	21.1	22.6	— 7.2	1,510
2/ 2/17	58.5	2,690	2,760	302	138	12.2	20.2	21.4	— 9.2	1,150
2/ 3/17	59.1	.....	3,080	337	141	15.1	21.3	22.8	— 7.7	2,420
2/ 4 17	59.7	.....	3,130	322	153	15.2	20.3	21.8	— 6.6	1,760
2/ 5/17	59.5 av.	.....	3,130	340	144	15.7	20.6	22.2	— 6.5	2,250
2/ 6/17	59.4	.....	3,080	320	146	16.2	19.8	21.4	— 5.2	1,080
2/ 7/17	59.0	.....	3,100	336	144	15.1	20.3	21.8	— 6.7	2,080
2/ 8/17	58.5	.....	2,920	288	147	15.0	18.5	20.0	— 5.0	1,880
2/ 9/17	57.4	2,120	2,880	292	139	15.2	18.7	20.2	— 5.0	1,250
2/10/17	57.6 av.	.....	3,040	381	177	15.6	18.3	20.1	— 4.5	1,560
2/11/17	57.8	.....	3,200	378	168	15.2	17.7	19.2	— 4.0	1,370
2/12/17	57.7	.....	3,760	428	173	15.3	17.4	18.9	— 3.6	1,790
2/13/17	58.0 av.	.....	3,510	380	169	15.0	15.9	17.4	— 2.4	1,580
2/14/17	58.3	.....	3,730	416	176	15.2	14.6	16.1	— 0.9	1,300
2/15/17	58.3 av.	.....	3,500	378	169	15.1	13.7	15.2	— 0.1	1,960
2/16/17	58.2	.....	3,610	402	169	15.3	14.2	15.7	— 0.4	1,450
2/17/17	58.2 av.	.....	3,500	377	168	15.1	13.0	16.5	— 1.4	1,470
2/18/17	58.3	.....	3,500	389	169	15.5	14.0	15.6	— 0.1	1,100
2/19/17	58.6	.....	3,480	381	165	15.2	14.7	16.2	— 1.0	1,800
2/20 17	59.0	.....	3,470	375	167	15.2	12.6	14.1	+ 1.1	1,300
2/21 17	59.1 av.	.....	3,490	389	165	15.4	12.7	14.2	+ 1.2	1,470
2/22/17	59.3 av.	.....	3,520	368	174	15.3	11.7	13.2	+ 2.1	1,290
2/23/17	59.4 av.	.....	3,520	353	179	15.6	11.5	13.1	+ 2.5	1,360
2/24 17	59.6	.....	3,500	382	167	14.9	11.5	13.0	+ 1.9	1,390
2/25/17	59.6	.....	3,530	388	167	15.1	11.5	13.0	+ 2.1	1,490
2/26/17	59.8	.....	3,560	398	166	15.2	11.9	13.4	+ 1.8	1,530
2/27/17	59.8 av.	.....	3,220	323	162	15.0	11.3	12.8	+ 2.2	1,300
2/28/17	59.9	.....	3,460	368	168	15.2	11.5	13.0	+ 1.5	1,240

* Urine nitrogen plus 10 per cent. food nitrogen.
† About 30 c.c. lost by patient.

METABOLISM IN CHRONIC DEFORMING ARTHRITIS

The basal metabolism of three cases of arthritis deformans was studied. Four cases were examined for evidence of the toxic destruction of protein. The effect of the ingestion of large amounts of protein and carbohydrate was determined in two of the patients. The histories of the four patients follow:

Case 6.—Arthritis Deformans.

History.—Wm. M., a traveling salesman, born in the United States, 50 years of age, was admitted Oct. 16, 1916, and discharged improved Jan. 17, 1917. In 1899 he had gonorrhea followed by epididymitis. The discharge lasted for two weeks. In 1900 he was told that he had syphilis and was treated for a week. As far as he knows, he never had a chancre nor has he shown any secondary symptoms. His wife had three miscarriages at about three months. He has had occasional slight sore throat but no previous attacks of joint pain.

July 21, 1916, he was awakened in the middle of the night by severe pain in the left arm, left wrist and right ankle. He thinks he had some fever. Two days later he went to St. Vincent's Hospital where he was treated until

TABLE 3.—Clinical Data on Arthritis Deformans

Name and Date	Body Wt.	Estimated Heat Production per 24 Hrs.	Food Total Calories	Food Carbohydrate, Gm.	Food Fat, Gm.	Urine N, Gm.	Urine Gm.	Excreta N.* Gm.	Nitrogen Balance, Gm.	Urine Volume, C.c.	Length of Period
William B.											
11/21/16	....	....	2,510	257	115	15.0	14.7	16.2	−1.2	2,300	24 hrs.
11 22/16	65.1	....	2,610	275	118	15.1	15.7	17.3	−2.2	2,250	24 hrs. 10 min
11/23/16	65.3	....	2,470	252	113	14.6	12.7	14.2	+0.4	1,550	23 hrs. 50 min.
11 24/16	65.2	....	2,320	261	113	14.8	13.4	14.9	+0.1	2,090	24 hrs.
11/25/16	64.7	....	2,460	250	114	15.1	12.5	14.0	+1.1	1,840	24 hrs.
11/26/16	65.0	....	2,520	258	115	15.1	13.3	14.8	+0.3	2,080	24 hrs.
11 27/16	....	....	1,710	164	84	11.2	13.3	14.4	−3.2	2,080	24 hrs.
11/28/16	....	....	2,530	257	116	14.9	14.7	16.2	−1.3	2,170	24 hrs. 10 min.
11/29/16	64.1	....	2,530	259	116	15.2	16.1	17.6	−2.4	1,110	23 hrs. 50 min.
11/30/16	64.8	....	2,240	2754	84‡	13.8	14.8	16.2	−2.4	2,030	24 hrs.
12/ 1/16	64.2	....	2,510	260	114	15.0	11.7	13.2	+1.8	2,150	24 hrs. 5 min.
12/ 2/16	....	....	2,470	246	115	15.2	12.4	13.9	+1.3	2,070	23 hrs. 55 min.
12/ 3/16	63.4	....	2,520	258	116	15.2	13.2	14.7	+0.5	2,740	24 hrs.
12/ 4/16	63.2	....	2,520	310	114	15.9	11.8	13.4	+2.5	2,500	24 hrs.
12/ 5/16	64.6	....	2,520	266	113	14.6	11.8	13.3	+1.3	1,830	24 hrs.
12/ 6/16	63.7	2,110	2,180	207	108	15.1	11.3	12.6	+0.5	2,030	24 hrs.
12/ 7/16	64.2	....	2,520	271	106	15.8	12.2	13.9	+1.9	1,890	24 hrs.
12/ 8/16	63.6	2,033	2,000	193	97	13.1	10.6	11.9	+1.2	1,855	24 hrs.
12/ 9/16	64.4	....	2,690	293	117	15.8	13.2	14.8	+1.0	2,170	24 hrs.
12/10/16	64.8	....	2,540	261	113	15.1	12.9	14.4	+0.7	2,080	24 hrs.
12/11/16	63.6	1,900	2,550	257	120	15.0	13.2	14.7	+0.3	2,070	24 hrs.
12/12/16	64.6	....	2,510	260	113	15.2	13.3	14.8	+0.4	1,630	24 hrs.
12/13/16	64.4	2,230	2,300	152	113	24.5	20.7	22.8	+1.3	2,560	24 hrs.
12/14/16	68.6	....	2,580	296	122	9.4	10.1	10.3	+1.3	1,410	24 hrs.
12/15/16	64.2	....	2,530	300	132	2.7	6.8	7.1	−4.4	1,201	24 hrs.
12/16/16	65.1	....	2,520	297	132	2.7	5.7	6.0	−3.3	1,670	24 hrs.
12/17/16	65.2	....	2,600	346	154	3.4	4.5	4.8	−1.4	1,470	24 hrs.
12/18/16	65.3	....	2,970	355	154	2.9	3.8	4.1	−1.2	1,290	24 hrs.
12/19/16	66.0	....	3,020	366	154	3.2	4.0	4.3	−0.3	2,100	24 hrs.
12/20/16	65.9	....	2,970	355	153	3.4	3.3	3.6	−0.2	1,430	24 hrs.
12/21/16	66.3	....	2,860	339	150	2.8	3.2	3.5	−0.7	1,700	24 hrs.
12/22/16	66.6	....	2,830	351	153	2.9	2.9	3.2	−0.3	1,540	24 hrs.
12/23/16	66.5	....	3,060	369	158	2.2	3.1	3.4	−1.2	1,850	24 hrs.
12/24/16	66.2	....	2,980	356	154	3.4	3.0	3.3	+0.1	1,700	24 hrs.
12/25/16											
12/26/16	67.0	....	2,660	296	113	15.2	5.1	6.6	+8.6	2,040	24 hrs.
12/27/16	....	....	2,530	266	113	15.0	7.1	8.6	+6.4	2,400	24 hrs.
12/28/16	....	....	3,030	333	136	15.7	7.1	8.7	+7.0	1,320	24 hrs.
12/29/16	65.8	....	2,800	269	141	15.3	11.2	12.7	+2.3	2,450	24 hrs.
12/30/16	65.7	....	3,050	328	141	15.1	9.8	11.3	+3.8	1,770	24 hrs.
* 12/31/16	66.7	....	3,060	337	142	15.4	12.6	14.1	+1.3	3,280	24 hrs.
1/ 1/17	66.1	....	3,020	318	143	14.8	11.7	13.2	+1.6	2,210	24 hrs.
1/ 2/17	65.4	....	3,010	318	142	15.2	11.3	12.6	+2.6	1,950	24 hrs.
1/ 3/17	65.3	....	3,010	317	142	15.2	8.9	10.4	+4.7	1,401	24 hrs.
1/ 4/17	66.5	....	3,010	317	142	15.0	10.2	11.7	+3.3	1,450	24 hrs.
1/ 5/17	66.3	....	3,000	318	141	14.9	10.7	12.2	+2.7	1,600	24 hrs.
1/ 6/17	66.5	....	3,040	319	141	15.1	10.6	13.1	+2.0	1,580	24 hrs.
1/ 7/17	66.4	....	3,060	336	141	14.7	11.4	12.9	+1.8	2,000	24 hrs.
1/ 8/17	65.8	....	2,960	318	137	14.9	7.6	9.1	+5.8	1,270	24 hrs.
1/ 9/17	67.1	....	2,940	315	137	14.6	9.9	11.4	+3.2	1,720	24 hrs.
1/10/17	65.7	....	1,780	138	102	10.2	8.6	9.6	+0.6	1,976	24 hrs.
1/11/17	65.6	....	3,020	316	143	15.2	9.7	11.2	+4.0	1,500	24 hrs.
1 12/17	66.8	....	2,990	318	138	15.4	10.1	13.6	+1.8	1,700	24 hrs.
1 13/17	66.6	....	3,050	319	145	15.3	11.6	13.4	+2.2	2,316	24 hrs.
1 14/17	66.5	....	3,010	323	140	14.9	10.6	12.1	+2.8	2,030	24 hrs.
1/15/17	66.2	....	1,970	207	91	10.2	9.1	10.2	+0.7	2,310	24 hrs.
Edward McK.											
12/21/16	37.5	....	1,910	181	97	10.2	7.9	8.9	+1.3	815	24 hrs. 40 min.
12/22/16	....	....	1,950	159	54	7.4	6.8	7.5	−0.1	1,160	24 hrs. 5 min.
12/23/16	....	....	1,340	152	59	6.5	7.3	8.0	−1.5	1,550	22 hrs.
12/24/16	....	....	1,220	123	57	7.6	7.4	8.2	−0.6	850	24 hrs. 5 min.
12/25/16											
12/26/16	39.1	....	1,250	133	56	7.5	7.1	7.9	−0.4	780	24 hrs.
12/27/16	....	....	1,210	148	57	2.6	4.0‡	....	....	540	17 hrs.
12/28/16	....	....	....	....	....	....	5.1	....	....	1,020	35 hrs. 40 min.
12/29/16	....	....	....	....	....	....	4.5	....	....	1,550	24 hrs. 10 min.
12/30/16	....	....	1,500	174	77	2.6	3.6	3.8	−1.2	1,230	
12/31/16–1/1/17	....	....	1,490	174	77	2.6	3.3	3.6	−1.0	1,980	
1/1/17	....	....	1,490	174	77	2.6	3.1	3.4	−0.8	1,370	
1/2/17	....	....	1,490	174	77	2.6	3.4	3.7	−1.1	800	
1/3/17	....	....	2,050	244	106	2.3	3.1	3.6	−1.3	1,240	24 hrs. 30 m n.
1/4/17	....	....	2,180	244	121	2.4	3.2	3.4	−1.0	1,500	23 hrs. 45 min
1/5/17	38.1	1,535	1,940	241	96	2.2	2.7	2.9	−0.7	1,740	24 hrs. 15 min.
1/6/17	....	....	1,990	255	104	2.4	2.7	2.9	−0.5	1,030	23 hrs. 50 min.
1/7/17	....	....	1,880	232	103	2.7	2.6	2.9	−0.2	900	23 hrs. 50 min.
1/8/17	38.6	....	1,530	163	72	7.4	3.3	4.0	+3.4	1,340	24 hrs.
1/9/17	....	....	1,530	164	73	7.5	5.9	6.7	+0.8	1,220	23 hrs. 50 min
1/10/17	....	....	1,530	160	73	7.6	4.9	5.7	+1.9	1,540	24 hrs.
1/11/17	....	....	1,500	176	72	7.6	5.1	5.9	+1.7	550	24 hrs.
1/12/17	....	....	1,520	162	71	7.6	5.5	6.3	+1.3	890	24 hrs.
1 13/17	....	....	1,550	161	74	7.7	5.9	6.7	+1.0	700	23 hrs. 50 m n.
1/14/17	....	....	1,560	162	76	7.4	6.3	7.0	+0.4	830	23 hrs. 50 min.
1 15/17	....	....	....	....	....	....	5.3	....	....	1,220	

* Urine nitrogen plus 10 per cent. of food nitrogen.
† Approximate.
‡ Incomplete specimens.

TABLE 3.—Clinical Data on Arthritis Deformans—(*Continued*)

Name and Date	Body Wt.	Estimated Heat Production per 24 Hrs.	Food			Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	Nitrogen Balance, Gm.	Urine Volume, C.c.	Length of Period
			Total Calories	Carbohydrate, Gm.	Fat, Gm.						
Edward R.											
12/21/16	39.5	.....	1,990	196	99	10.6	7.3	8.4	+1.1	450	24 hrs. 15 min.
12/22/16	....	.....	1,340	159	54	7.5	6.6	7.4	+0.1	660	23 hrs. 55 min.
12/23/16	....	.....	1,410	162	58	7.8	5.9	6.7	+1.2	800	24 hrs. 10 min.
12/24/16	....	.....	1,220	123	57	7.6	6.6	7.4	+0.2	1,400	23 hrs. 50 min.
12/25/16											
12/26/16	38.8	.....	1,376	170	59	7.6	5.5	.....	.....	420†	20 hrs. 10 min.
12/27/16	....	.....	1,264	147	57	2.6	3.9	.....	.....	940†	21 hrs. 55 min.
12/28/16	....	.....	1,58	168	57	2.1	3.8	.....	.....	1,870†	22 hrs. 25 min.
12/29/16	....	.....	1,498	174	77	2.6	2.4[1]	.....	.....	600†	24 hrs. 45 min.
12/30/16	....	.....	1,500	174	77	2.6	4.23	.....	.....	1,400	11 hrs. 20 min.
12/31/16	39.2	.....	1,490	174	77	2.6	3.1	3.4	−0.8	1,800	24 hrs. 35 min.
1/ 1 17	....	.....	1,498	174	77	2.6	3.1	3.4	−0.8	1,610	23 hrs. 50 min.
1/ 2/17	....	.....	1,498	174	77	2.6	3.4	3.7	−1.1	1,750	23 hrs. 40 min.
1/ 3/17	....	1,288	2,060	242	108	2.4	2.3	2.6	−0.2	665	22 hrs. 40 min.
1/ 4/17	....	....	2,180	244	121	2.4	2.7	2.9	−0.5	1,450	22 hrs. 30 min.
1/ 5/17	....	.....	1,970	231	104	2.3	2.6	2.8	−0.5	1,340	36 hrs. 15 min.
1/ 6/17	....	.....	1,990	235	104	2.3	2.3	2.5	−0.2	1,250	21 hrs. 55 min.
1/ 7/17	37.0	.....	1,770	169	81	12.5	5.3	6.6	+5.9	1,330	23 hrs. 50 min.
1/ 8/17	....	.....	1,450	155	67	7.2	5.4	5.9	+1.3	1,500	16 hrs. 55 min.
1/ 9/17	....	1,564	.....	.....	.....	.....	3.4[1]	.....	.....	1,050†	17 hrs. 30 min.
1.10/17	....	.....	1,550	161	74	7.8	5.6[1]	.....	.....	1,810†	18 hrs.
1.11/17	....	.....	1,496	175	73	8.1	6.0	6.8	+1.3	1,550	24 hrs. 30 min.
1/12/17	....	.....	1,530	163	72	7.5	4.3	5.1	+2.4	1,700	21 hrs. 25 min.
1/13/17	....	.....	1,540	161	73	7.6	5.2	6.0	+1.6	1,250	24 hrs. 10 min.
1/14 17											
1/15/17	....	....	1,602	170	77	7.4	5.5	6.2	+1.2	1,440	24 hrs.
Frank H.											
11/24/16	40.9	.....	2,520	258	115	14.8	8.9	10.4	+4.4	1,150	24 hrs.
11/25/16	41.1	.....	2,500	277	114	15.3	9.8[1]	11.3	+4.0	785†	24 hrs.
11/26/16	41.1	..	2,520	260	115	15.1	11.22	12.7	+2.4	1,050†	24 hrs.
11/27/16	41.6	.....	2,470	249	114	15.0	12.6	14.1	+0.9	1,200	24 hrs.
11/28/16	....	.....	2,470	249	112	15.7	12.6	14.2	+1.5	980	24 hrs.
11/29/16	41.5	.....	2,520	259	117	14.6	12.8	14.3	+0.3	980	24 hrs. *
11/30/16	41.3	.....	2,140	242	80	13.6	12.8	14.3	−0.6	880	24 hrs.
12/ 1 16	41.5	.....	2,500	255	115	15.6	12.3	13.8	+1.2	900	24 hrs.
12/ 2 16	....	.....	2,450	253	112	15.0	12.1	13.6	+1.5	1,000	24 hrs.
12/ 3 16	42.2	.....	2,450	256	114	14.8	13.4	14.9	−0.1	1,000	24 hrs.
12/ 4/16	42.8	.....	2,520	304	101	2.4	14.5	14.7	−12.3	1,200	24 hrs.
12/ 5/16	41.8	.....	2,580	268	185	3.4	4.7	4.9	−2.5	700	24 hrs.
12/ 6/16	42.3	.....	2,620	290	144	3.1	5.22	5.4	−3.3	980‡	24 hrs.
12/ 7/16	41.4	.....	2,520	301	152	2.6	4.0	4.3	−1.7	850	24 hrs.
12/ 8/16	42.0	.....	2,200	268	132	2.4	4.0	4.2	−1.8	780	24 hrs.
12/ 9/16	41.7	.....	2,220	700	132	2.7	4.6	4.9	−2.2	960	24 hrs.
12/10/16	41.6	.....	2,520	301	132	2.6	3.6	3.9	−1.3	1,050	24 hrs.
12/11/16	....	.....	2,540	304	132	2.6	3.5	3.8	−1.2	1,080	24 hrs.
12/12/16	41.4	.....	2,250	317	132	2.7	3.6	3.9	−1.2	930	24 hrs.
12/13/16	....	.....	2,340	304	132	2.6	3.5	3.8	−1.2	1,300	24 hrs.
12/14/16	41.4	.....	2,510	297	132	2.7	3.3	3.6	−0.9	675	24 hrs.
12/15/16	41.5	.....	2,480	286	133	2.7	4.2	4.5	−1.8	800	24 hrs.
12/16/16	41.1	.....	2,520	298	133	2.6	3.4	3.7	−1.1	660	24 hrs.
12/17/16	42.0	.....	2,700	299	166	14.4	6.5	7.9	+6.5	1,450	24 hrs.
12/18/16	40.7	.....	2,700	268	117	15.7	7.8	9.4	+6.3	1,000	24 hrs.
12/19/16	42.0	.....	2,630	296	113	15.2	8.6	10.1	+5.1	1,300	24 hrs.

* Urine nitrogen plus 10 per cent. of food nitrogen.

† Incomplete specimens.

October 16. During this time, his left ankle and right hand were involved. The right ankle improved slightly but the elbows caused great pain. The right elbow gradually stiffened until only slight motion was possible.

Physical Examination.—He was poorly nourished, well developed, rather apathetic man. He had no temperature and was not toxic. The teeth showed moderate pyorrhea. The tonsils were small with rather deep crypts. The right elbow was the site of very painful inflammation. The joint was swollen; the forearm was held at a right angle to the arm. Movement was impossible: the effort was very painful. All of the muscles of the arm and forearm were flabby and wasted. There was but little redness about the swollen parts. The

fingers of the right hand could not be flexed. There was no sign of inflammation, the stiffness probably being due to disuse. There was some limitation of motion, but no pain, in the right shoulder. The left elbow showed thickening of the soft parts but no pain or active inflammation. The right ankle was swollen and slightly painful but not red or hot. The actual involvement of the joint was hidden by a diffuse superficial edema of the foot and ankle. There was slight limitation of dorsal and plantar flexion and some limitation of eversion and inversion. The left ankle was normal. Massage of the prostate caused no discharge. The seminal vesicles were not palpable.

TABLE 4.—SUMMARY OF BASAL METABOLISM STUDIES IN ARTHRITIS

Subject and Diagnosis	Date of Observation	Age, Yrs.	Surface Area, sq. M.	Average Rectal Temp. C.	Average R. Q.	Average Calories per Hour, Indirect	Per Cent. Deviation from Normal	N* Minimum	Remarks
Edward C. ..... Acute rheumatic fever (mild)	1/22/16	33	1.56	37.2	0.76	64.4	+ 5	.....	Slightly restless
John Br. ..... Gonococcus arthritis	1/29/17	19	1.80	38.4	0.77	94.6	+29	.....	Slightly restless
John Br. ..... Gonococcus arthritis	1/31/17	19	1.78	37.9	0.79	80.8	+11	.....	Quiet
John Br. ..... Gonococcus arthritis	2/ 9/17	19	1.74	37.7	0.81	80.2	+12	.....	Restless
John Bl. ..... Rheumatic fever	1/26/17	38	2.01	37.6	0.76	84.7	+12	.....	Very quiet
Joseph Mc. ..... Gonococcus arthritis	2/ 7/17	27	1.46	37.5	0.82	62.4	+ 8	.....	Very quiet
Timothy S. ..... Gout	4/27/17	42	1.64	37.4	0.82	70.6	+12	.....	Very quiet
Timothy S. ..... Gout	5/12/17	42	1.64	37.6	0.85	64.3	+ 2	.....	Quiet
William B. ..... Severe arthritis deformans	12/11/16	50	1.80	37.0	0.80	72.0	+ 7	2.9-3.3	Quiet
Edward R. ..... Severe arthritis deformans	1/ 3/17	32	1.42	36.9	0.78	48.8	—13	2.6-3.1	Very quiet
Edward McK. ..... Severe arthritis deformans	1/5/17	28	1.37	36.7	0.83	58.1	+ 7	2.6-2.7	Quiet

* Urinary nitrogen for 24 hours on low nitrogen intake.

Laboratory Examination.—Urine: Negative. Blood: Leukocytes, 6,000; polymorphonuclears, 80 per cent.; erythrocytes, 5,000,000; hemoglobin (Sahli) 90 per cent. Nonprotein nitrogen: 57 mg. per 100 c.c. Uric acid: 4 mg. per 100 c.c. Wassermann: negative. Gonococcus fixation test: once positive; twice doubtful.

Roentgen-Ray Reports The teeth showed a considerable amount of alveolar recession, with accentuation of the pericemental membrane, suggesting pyorrhea. There was also an area of rarefaction around the root of the second right upper bicuspid, with imperfect root canal filling. The ankles showed a moderate amount of periarticular atrophy, with a narrowing and clouding of joint spaces,

most marked in the right ankle joint and tarsometatarsal joint, the appearance suggesting an atrophic adhesive osteoarthritis. A similar condition was noticeable in the right elbow.

October 30 the second right bicuspid was extracted. The tooth was dead and somewhat carious in the root canal. On extraction there was a marked putrid pus odor. A culture from the cavity of the gum was negative.

November 27 he had an acute attack of follicular tonsillitis. The temperature rose to 103 F. The right elbow was more swollen and extremely painful. There was pain on any motion of the right shoulder. A tonsil culture showed a pure growth of a nonhemolytic streptococcus. A blood culture was sterile.

December 8, after receiving 200 gm. glucose, he was observed in the calorimeter. On the following day, the joint condition was unchanged. Basal observations were made December 6 and 11. December 13 he was given meat in large quantities and was afterward observed in the calorimeter. From December 19 to January 15 he received frequent doses of Jobling's proteose, the observations on which are mentioned in another article. The joint condition improved very gradually. With constant baking and massage he regained motion in the fingers of the right hand. Motion in the elbow was not increased.

Fig. 4.—William Bl. (Case 6). Roentgenogram of right elbow.

The ankles caused little pain but the edema of the right foot and ankle continued to the time of his discharge on January 17. He was seen again in February. The disease had not advanced. He was working every day but had regained no motion in the elbow.

Case 7.—Arthritis Deformans (many ankyloses).

History.—Edward R., a machinist, born in Austria, 32 years of age, was admitted Dec. 19, 1916, and discharged unimproved Jan. 16, 1917. A sister has deforming arthritis. The patient is a skilled mechanic who had excellent working and home conditions. His habits have been good. He had diphtheria in early childhood. For about one year preceding the onset of the arthritis he expectorated large amounts of foul smelling material which came from the nasal passages and which ceased about the time the joint trouble began. He persistently denies any venereal infection.

In the winter of 1911 he began to have pain in his right great toe. Two weeks later pain appeared in the other toes of the right foot. Soon afterward pain developed in the other foot and before a year had passed both knees were affected. During this time he was able to continue with his occupation but

required help in going to and from work. During the next eight months he was treated in a hospital where traction was applied to his legs. Roentgenograms were taken of his teeth as a result of which one tooth was extracted. While in the hospital the shoulders, elbows, hands, jaws, hips and the sacroiliac synchondroses were involved. In each new joint affected there was some swelling and pain, very severe in the wrists, ankles and toes, moderate in the other joints. The swelling and pain gradually subsided and stiffening occurred. Subsidence was a matter of months or years. So far as he knows, he has never had fever. During the first two years of the illness his weight dropped from 148 to 96 pounds.

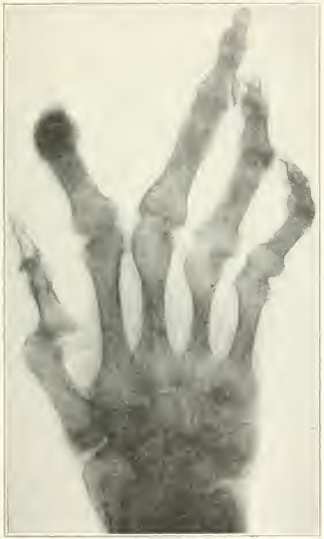

Fig. 5.—Edward R. (Case 7). Roentgenogram of left hand.

Physical Examination.—His face was that of a well nourished man. Complexion florid. There was, however, tremendous wasting of the muscles which gave his body the appearance of extreme emaciation. He laid in dorsal decubitus, the thighs in line with the body, the knees extended, the elbows flexed. His skin was moist, shiny and of very fine texture. He was of a cheerful, philosophic disposition. Ears were normal. The teeth and gums appeared healthy. There was no pyorrhea. The tongue and throat could not

be seen because of ankylosis of the jaw. The joints showed many deformities. The jaws could be opened only a quarter of an inch. No lateral motion was possible. There was no tenderness but distinct crepitus over the temporomandibular joints. The right shoulder and wrist, both elbows, hips, knees and ankles were ankylosed but still tender. The sacroiliac joints were tender; very limited motion was possible in the right shoulder. The hands showed extreme deformity which was best demonstrated by the roentgen ray. In both hands were numerous subluxations. There was complete ankylosis of all joints except the distal interphalangeal joints of the right thumb, right fifth finger and left ring finger, which were not at all affected, and the metocarpophalangeal joint of the thumb, which showed free motion but was swollen, very painful and tender. The toes of the left foot were ankylosed. Those of the right foot showed very little motion.

Laboratory Examination.—Urine: Faint trace of albumin; no casts. Blood: Leukocytes, 7,000; polymophonuclears, 60 per cent.; hemoglobin, 85 per cent.; erythrocytes, 5,000,000. Wassermann: strongly positive. Gonococcus fixation test: negative. Nonprotein nitrogen: 45 mg. per 100 c.c. Uric acid: 3 mg. per 100 c.c.

Roentgen-ray report: In the hand there is obliteration of intercarpal, carporadial, metacarpophalangeal and interphalangeal joint spaces with extreme bone atrophy. Examination of hip shows extensive bone atrophy without excrescence formation, also a diminution of the joint space. Knees, shoulders and elbows show a similar condition. There appears to have been in the joints an absorption of the cartilage and a fibrous ankylosis without bone destruction.

While in the hospital he had pain in many of the joints. Pain was most severe and constant in the metacarpophalangeal joints of the thumb which, he says, was the last joint to be affected. About a week after admission he first noted pain and tenderness over the two upper cervical vertebrae which had not been previously involved. At the time of his discharge, January 16, the pain was more severe but no stiffness had developed. His condition was otherwise unchanged.

Case 8.—Arthritis Deformans (many ankyloses).

History.—Edward McK., a machinist, born in the United States, 28 years of age, was admitted Dec. 19, 1916, and discharged unimproved Jan. 16, 1917. In the spring of 1908, while skating, he fell on his right knee. The fall caused him only temporary discomfort. One month later, however, the knee became swollen, stiff and slightly painful. In spite of vigorous treatment during the next two years, the joint did not improve. It was thought at first that it might be tuberculous. In October, 1908, however, a specimen of the joint fluid was injected into a guinea-pig at Roosevelt Hospital with negative results. In 1910, he contracted gonorrhea which lasted three months but did not affect the knee. In 1911, the left knee was involved in a similar manner but with more pain. Four months later the left elbow was affected. During the last year his neck has been stiff and painful and both ankles have been involved. He has received competent local treatments, besides numerous vaccines. All the joints have been affected insidiously. There has never been marked inflammation. So far as the patient knows, he has never had fever.

Physical Examination.—His face was that of a fairly well nourished man. The body and extremities showed marked muscular wasting and moderate emaciation. He was of an unstable, emotional disposition and was overcome by his misfortunes. Two of the molar teeth were carious. There was slight pyorrhea about the incisors. The tonsils were small and red with very deep crypts. The left ear drum showed two large white patches, one posterior, the other anterior to the malleus. There were no signs of active inflammation. The right ear drum was normal. The lungs showed very poor expansion. Massage of the prostate caused no discharge. The shoulders were not affected. The left elbow allowed less than five degrees of motion; it was practically

ankylosed at 100 degrees. The right elbow was ankylosed at 180 degrees. Neither showed signs of active inflammation. The wrists were swollen and tender. The right showed ten degrees of motion; the left even less. The metacarpophalangeal joints of both thumbs and of the right index finger were swollen, tender and painful on motion. The cervical vertebral articulations were completely ankylosed. There was marked tenderness along the cords to the right of the upper three spinous processes. There was slight motion in the vertebral articulations of the dorsal spine and still more in the lumbar region. The hips were completely ankylosed in flexion of 110 degrees to the line of the trunk. The knees were ankylosed, causing the legs to form an angle of 90 degrees with the thighs. The tibia and fibula were subluxated backward and outward on the femur. There was swelling, some tenderness and great pain on

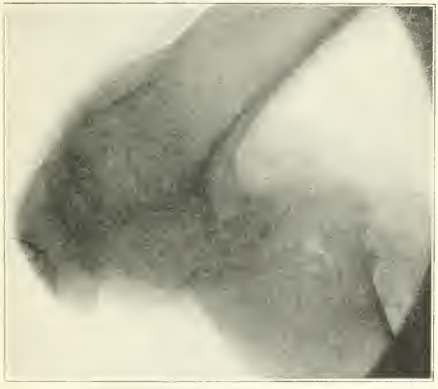

Fig. 6.—Edward McK (Case 81). Roentgenogram of right knee.

attempted motion in the left ankle which was practically ankylosed. Motion in the right ankle was limited to 30 degrees.

Laboratory Examination.—Urine: Negative. Blood: Leukocytes, 12,500; polymorphonuclears, 75 per cent.; erythrocytes, 4,700,000; hemoglobin, 90 per cent. Gonococcus fixation test: doubtful. Cultures from both tonsils showed an almost pure growth of *Staphylococcus aureus* with a few colonies of *Streptococcus viridans*. Nonprotein nitrogen: 24 mg. per 100 c.c. Uric acid: too low to estimate.

Roentgen-ray Report: Examination showed osteoarthritis deformans with excrescence formation. There was marked subluxation at the knee joint. The elbows and tarsal joints showed evidence of atrophy, diminution in the size of the joint space, but no bone destruction.

January 11 he developed herpes zoster along the course of the fourth and fifth intercostal nerves. Vesicles were numerous but pain was very slight. January 16 he was transferred to the Metropolitan Hospital unimproved.

Case 9.—Arthritis Deformans; scabies.

History.—Frank H., a proof-reader, born in the United States, 61 years of age, was admitted Nov. 4, 1916, and discharged unimproved Dec. 20, 1916. His wife died of "rheumatic gout" at the age of 41. He has led a sedentary life, is very moderate user of alcohol and tobacco. He has had gonorrhea five or six times, the last attack ten years ago. History of "hard chancre" twenty-five years ago; two soft chancres since then. No history of secondary syphilis.

Fig. 7.—Frank H., Case 9. Roentgenogram of right knee.

or of any specific treatment. He has never had tonsillitis or alveolar abscesses. He has not suffered from respiratory infections. No history of rheumatic fever or heart disease.

About seven years ago he developed a stiffness in the right knee which gradually became worse. Five years ago, the left knee began to get stiff. For the past two years he has noticed a gradually increasing stiffness and outward deflection of the fingers of both hands. The right knee has been painful at times, but there has never been much pain in the fingers, even on flexion. Recently there has been stiffness in both shoulders and in the spine. Patient thinks he had some urethral discharge at the beginning of his illness. He has lost some weight, but does not know how much.

Physical Examination.—Patient was a middle-aged man, poorly nourished and somewhat under-developed. Teeth: All molars missing, except two on

lower left side which were markedly carious; considerable pyorrhea present, particularly of lower incisors which were loose in sockets; no tenderness of gums. Throat: Tonsils red but not enlarged. Several posterior lymph nodes enlarged on both sides. Heart: Measured 8 cm. to left in fifth space; apex impulse not felt; right border of heart at right sternal margin; sounds faintly heard, faint systolic murmur at apex heard also over sternum; action slow and regular. Over the entire body, more marked on abdomen and arms, there were numerous small petechiae, apparently the result of scratching; also many small ecchymoses and scabs. Tendon reflexes all exaggerated. Joints: Spine straight. Considerable limitation of movement, especially in dorsal region when patient bends forward. Flexion was from the hips, the spine remaining rigid. Lateral motion was from the lumbar region. Shoulder joints: Arms could be elevated to an angle of only 45 degrees. Motion in shoulder joints considerably limited, especially in abduction and rotation. Flexion and extension good. Wrist joints showed some limitation of flexion and extension. There was moderate atrophy of infraspinatus and supraspinatus muscles. Metacarpals, phalanges and knuckles very prominent on both hands due, in part, to atrophy of the interossei muscles. There was considerable limitation of extension of all fingers on both hands (45 degrees). Flexion of fingers not limited. Moderate contraction of flexor tendons, more marked on left side. Hips: Limitation of abduction (30 degrees). Patient stood with legs bowed, knees prominent on account of a marked atrophy of the muscles, more marked on the left side. Right knee measured 33 cm., left the same. Flexion of knee joints, 90 degrees. No fluid in knee joints, ankles normal. Toe joints normal.

Laboratory Examination.—Urine: very faint trace of albumin: no casts. Phenolsulphonephthalein test: first hour, 42 per cent., second hour, 23 per cent. Sputum: Many streptococci: no tubercle bacilli.

Roentgen ray Report: In the chest the aortic shadow was somewhat broader than normal; otherwise, the findings were negative. The hands showed periarticular atrophy of the bones with narrowing of the joint spaces, and rarefaction of the articular borders. Roentgenogram of the right femur showed cortical thickening of the femur with bowing and rarefaction. The skull showed a similar rarefaction. The findings were those of an atrophic osteo-arthritis.

During the patient's stay in the hospital he suffered from a subacute bronchitis which at one time showed an acute exacerbation. The condition in his joints remained practically unchanged.

The four cases of arthritis deformans were all of severe type, of long duration, showing great deformities; in fact, two of the patients (Cases 6 and 7) were so crippled that it was difficult to collect twenty-four hour specimens of urine and almost impossible to make them end the period exactly on the minute according to the custom of the metabolism ward. Since each voiding was collected in a separate bottle, and the time of voiding recorded at once, it did not destroy the value of the observation if the urine secreted during one or two hours was lost. The last columns in Table 3 (Clinical data) show the exact time of all complete and incomplete specimens. The results of observations on the basal metabolism of these patients will be found in Tables 1 and 4. The effects of large carbohydrate and protein meals are represented in Figures 8 and 9.

DISCUSSION OF CHRONIC DEFORMING ARTHRITIS

By a majority of writers, chronic deforming arthritis has been considered a manifestation of infection from some septic focus within the body. By others, it is thought to be a disease of metabolism. In considering the results obtained from the study of these few cases, the two prevailing conceptions of etiology should be kept in mind.

The wasting and emaciation which accompany long standing infection have led often to the assumption that in such diseases there is an increase in basal metabolism and a toxic destruction of body protein. This assumption has never been properly confirmed. In the chronic infection of tuberculosis, several cases of which have been studied by McCann and Barr,[8] only slight toxic destruction of protein was found. The level of metabolism was in certain cases increased but the increase was usually accompanied by a considerable elevation of body temperature. Our knowledge of these factors in other chronic infections is fragmentary and incomplete. If one thinks of deforming arthritis as a chronic infection, facts concerning the level of basal metabolism and possible destruction of body protein are of considerable importance.

Basal Metabolism.—By referring to Table 6, it will be seen that two of the patients gave basal figures 7 per cent. above the average, in other words, within the limits of normal. One gave results 13 per cent. below the average but he was emaciated to nothing but skin, bones and ankylosed joints. One usually finds a low metabolism in such profound undernutrition. There is a most satisfactory agreement between the methods of direct and indirect calorimetry. The total in all experiments by the direct method was 1381.5 calories, by the indirect method 1376.5 calories, a difference of 0.3 per cent. The respiratory quotients were at all times normal and indicated no disturbance in the proportion of calories obtained from the different food constituents. In the study of these three cases, no disturbance of the normal basal metabolism has been detected.

Nitrogen Balance.—By referring to Table 3, it will be observed that nitrogenous equilibrium was maintained in all four cases, except when the nitrogen intake was cut to a very low figure. Even then the nitrogen excreted never exceeded the food nitrogen by more than a few grams. Furthermore, by reducing the nitrogen intake to a minimum it was possible to reduce the nitrogen excretion of these patients to as low a level as is possible with normal, healthy individuals. For instance, William B. for five consecutive days excreted less than 3.6 gm. nitrogen per day; Edward McK., less than 2.7 gm. for three days; Frank H., less than 3.6 gm. for five days. Edward R.

8. McCann, W. S., and Barr, D. P.: Clinical Calorimetry. Paper 29. The Metabolism in Tuberculosis. Arch. Int. Med. **26**:663 (Nov.) 1920.

averaged about 3 gm. for a considerable period, but his figures are somewhat uncertain since he lost a few specimens, as is indicated in the last column of this table. All of these results are within the normal limits found by Landergren, Kocher and others, and they indicate that there is no toxic destruction of protein in chronic arthritis.

If chronic deforming arthritis is a disease of metabolism, one may expect to find some evidence of diminished ability to metabolize one or more of the food stuffs. Pemberton's extensive studies have demonstrated practically nothing abnormal except a high glucose content of the blood following glucose ingestion. It must be said, that high sugar curves are also found in diabetes, hyperthyroidism, nephritis, severe infections and various other conditions. Even in supposedly normal individuals the curve of sugar in the blood after ingestion of glucose varies so much that conclusions drawn from apparently abnormal figures may be very misleading.

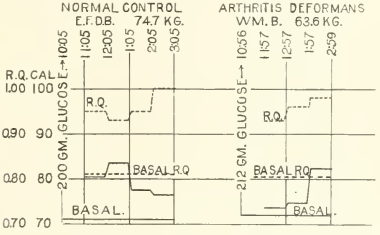

Fig. 8—Comparison of normal control and arthritis patient in their response to large carbohydrate meal. Solid lines—level of metabolism; dotted line, respiratory quotient.

Perhaps, a more direct way of securing evidence of the body's ability to handle food stuffs is by a study of the respiratory quotients and the specific dynamic action of the different classes of food following their ingestion. Experiments of this kind were done in two of the cases of chronic arthritis. December 8, William Bl. received 212 gm. dextrose one hour before going into the calorimeter. He remained in the calorimeter three hours. December 13, the same patient received 662 gm. chopped meat (24.3 gm. nitrogen) before going into the calorimeter. January 9, Edward R. was given 212 gm. glucose and was studied in the calorimeter. In Figures 8 and 9 the curves for heat production as determined by the indirect method and the respiratory quotients are compared with normal controls studied in Paper IV

of this series. The results are in no way conclusive, but there are no significant differences which would indicate an inability to oxidize either protein or carbohydrate.

The observations give no indication that arthritis deformans is a disease of metabolism. The patients studied were of the type usually considered to be the result of a chronic infective process. If this be

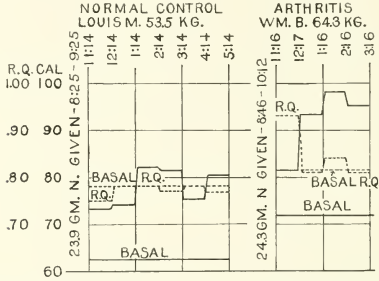

Fig. 9.—Comparison of normal control and arthritis patient in their response to a large protein meal. Solid lines—level of metabolism, dotted line, respiratory quotient.

the correct conception, one may say that the infection was unaccompanied by changes in the level of basal metabolism or by toxic destruction of protein.

SUMMARY AND CONCLUSIONS

1. Three cases of acute and subacute arthritis showed no variation from the normal basal metabolism. One case of acute arthritis observed during a continuous temperature of 38.4 C. showed a basal metabolism 26 per cent. above the average normal level. Other observations on the same patient during afebrile periods exhibited a metabolism practically within normal limits. In this case there was a marked loss of body nitrogen during a period when the energy requirement was more than covered by a liberal diet. This indicates a toxic destruction of body protein.

2. One case of gout showed little change in the level of basal metabolism.

3. Four cases of severe arthritis deformans on the Landergren diet, very low in protein but high in calories, excreted from 2.6 to 3.6 gm. nitrogen per day, figures which are well within the normal limits.

Three of these patients when tested in the calorimeter had a metabolism rate close to the average normal level. The respiratory quotients were normal, and there was no evidence of abnormal respiratory metabolism following the ingestion of large test meals of glucose and protein.

4. The observations on arthritis deformans do not indicate that it is a disease of metabolism. If infectious in origin, it may be said that the infection is not accompanied by increase in basal metabolism or by toxic destruction of body protein.

CLINICAL CALORIMETRY XXXII

TEMPERATURE REGULATION AFTER THE INTRAVENOUS INJECTION OF PROTEOSE AND TYPHOID VACCINE *

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During the last seven or eight years, many clinicians have been treating arthritic patients by means of intravenous injections of foreign protein. These produce chills which resemble malarial paroxysms and afford an ideal opportunity for studying in man the phenomena of temperature regulation. In 1917 the chills and fever in several cases of malaria were studied in the Sage calorimeter.[1] The present investigation was undertaken as a supplement to the work in malaria in order to study in more detail the mechanism of the rise and fall of body temperature.

The gaseous exchanges of patients have been studied by Kraus and Chvostek [2] after giving tuberculin, and in animals by Freund and Grafe,[3] Versar, who gave infusions of sodium chlorid,[4] and by Berrar,[5] who used aloin. In general, these animal experiments showed a rise in total oxidative processes accompanying the rise in temperature. Sometimes this increase amounted to 130 per cent.

The other phenomena which follow the intravenous injection of foreign protein have been studied in many clinics since the therapeutic application of this procedure was developed by Ichikawa, Kraus, Jobling and Petersen and others. Miller and Lusk [6] reported favorable results in arthritis and many others have tried their methods and have

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1. Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Paper 28, The Metabolism in Malarial Fever, Arch. Int. Med. **21**:627 (May) 1918.

2. Kraus, Fr., and Chvostek, F.: Ueber den respiratorischen Gaswechsel im Fieberanfall nach Injection der Koch'schen Flussigkeit, Wien. klin. Wchnschr. **4**:104, 1891.

3. Freund, H., & Schlagentweit, E.: Ueber die Waerme Regulation Kurarisierter Tiere, Arch. f. Exper. Path. u. Pharmakol. **69**:12, 1912.

4. Verzar, Fritz.: Die Wirkung intravenöser Kochsalzinfusionen auf den respiratorischen Gaswechsel, Biochem. Ztschr. **34**:41, 1911.

5. Berrar, M.: Die Wirkung des Aloins auf den Stoffwechsel, Biochem. Ztschr. **49**:426, 1913.

6. Miller, J. L., and Lusk, F. B.: The Treatment of Arthritis by Intravenous Injection of Foreign Protein, J. A. M. A. **66**:1756 (June 3) 1916; The Use of Foreign Protein in the Treatment of Arthritis, J. A. M. A. **67**:2010 (Dec. 30) 1916.

investigated the physiologic changes which accompany the paroxysm. Cecil [7] has made a clinical study of forty cases treated in this hospital, including in his series the cases published in this article. He obtained fairly satisfactory results but did not consider that treatment with foreign proteins was indicated until salicylates had been given a thorough trial. Snyder [8] used the same New York City Board of Health typhoid vaccine, starting with small doses.

Scully [9] made a careful study of the blood count, temperature and blood pressure after intravenous injections and published composite curves which are most instructive. He used typhoid vaccine in doses of from 37 to 75 million bacilli with patients suffering from acute articular rheumatism. The composite temperature curve reached a maximum of 103.6 F. four hours after the injection and fell gradually to normal in sixteen hours. The highest individual temperature was 106.6 F.; the lowest 102 F. The leukocytes showed first a fall and then a sharp rise. The average count was 14,000 at the time of injection. During the chill it dropped to 5,000 but rose to 40,000 about eight hours after the vaccine was given. The highest individual count was 77,200 at six hours; the lowest 13,600. The blood pressure probably rose during the chill but accurate measurements were impossible. After the chill, the composite curve showed a fall, reaching 92 mm. systolic and 60 mm. diastolic pressure six hours after the injection. Following this there was a gradual rise. The lowest individual reading was 60 mm. systolic and 40 mm. diastolic, the patient evidently suffering from marked shock. In addition to these phenomena, Scully examined the urine but found no marked changes.

Cowie and Calhoun [10] have emphasized the analogy between the nonspecific chill and the malarial paroxysm. They made numerous blood counts and found nucleated red cells and myelocytes and many atypical cell forms, particularly in the lymphocyte group. Jobling, Petersen and their co-workers [11] have studied in detail the ferments after the injection of foreign protein. They have found an instantaneous mobilization of a large amount of nonspecific proteose; decrease in antiferment; increase in noncoagulable nitrogen of the serum; increase in amino-acids; and a primary decrease in serum

7. Cecil, R. L.: A Report on Forty Cases of Acute Arthritis Treated by Intravenous Injections of Foreign Protein, Arch. Int. Med. **20**:951 (Dec.) 1917.

8. Snyder, R. G.: A Clinical Report of Nonspecific Protein Therapy in the Treatment of Arthritis, Arch. Int. Med. **22**:224 (Aug.) 1918.

9. Scully, F. J.: The Reaction after Intravenous Injections of Foreign Proteins, J. A. M. A. **69**:20 (July 7) 1917.

10. Cowie, D. M., and Calhoun, H.: Nonspecific Therapy in Arthritis and Infections, Arch. Int. Med. **29**:69 (Jan.) 1919.

11. Jobling, J. W.: Petersen, W., and Eggstein, A. A.: Studies on Ferment Action, J. Exper. M. **22**:401, 568, etc., 1915; Petersen, Wm. H.: Serum Changes Following Protein "Shock" Therapy, Arch. Int. Med. **20**:716 (Nov.) 1917.

proteoses. There is also an increased flow of lymph from the thoracic duct. Later there is a progressive increase in the noncoagulable nitrogen, in proteoses and serum lipase.

We must remember that while all these changes are taking place in the blood and cardiovascular system, the organism is being subjected to great variations in the degree of muscular activity, marked fluctuations in the respiratory activity, sudden demands for the mobilization of foodstuffs with increased products of katabolism, and also rapid changes in the temperature of the body cells. These metabolic and physical phenomena form the subject of the present investigation.

The apparatus used was the respiration calorimeter described in the previous papers of this series and the patients were kept under close observation in the metabolism ward. On account of the length of the observations, it was necessary to allow them some food shortly before the start of the experiment. All, with the exception of Albert G., were given a small "standard breakfast" four or five hours before the start of the observation. It has been shown in Paper 26 [12] of this series that this breakfast has no effect on the metabolism, except for two or three hours after it has been taken.

The subjects were five patients with various rheumatic affections, one comparatively well man with lumbar and sciatic pains and one normal control. Three of the patients were studied from the standpoint of possible changes in metabolism which might occur in chronic arthritis. The results of observations on their basal metabolism may be found in the accompanying article on arthritis. At the time of the observations there were in the general wards of the hospital a considerable number of patients being treated with intravenous injections of protein made according to the method of Jobling or with typhoid vaccine as prepared by the New York City Board of Health. The other two rheumatic subjects were intelligent men selected from among these patients. Both had previously given definite response to injections of foreign protein. In these, it seemed possible to calculate fairly closely the time interval between a given dose and the onset of a chill. This was a matter of importance since the technic of managing a calorimeter in short periods during a chill is extremely difficult. With one subject (Genaro A.), a rise in temperature followed the injection but the chill did not occur. Albert G., the normal control, and R. L. C., had never been given foreign protein before; yet, neither had the expected chill. All of the others reacted very much in the manner predicted.

12. Soderstrom, G. F.; Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Paper 26, The Effect of a Small Breakfast on Heat Production, Arch. Int. Med. **21**:613 (May) 1918.

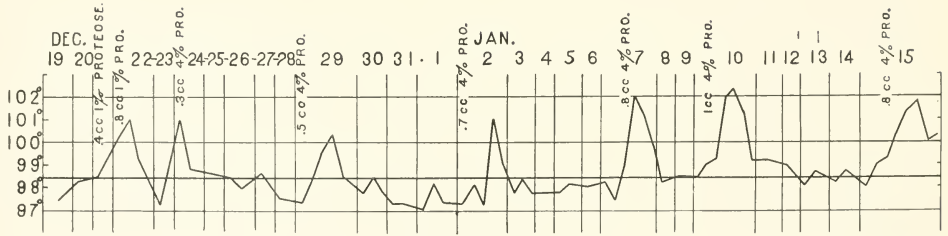

Fig. 1.—Temperature curve of William B.

Subject. Date. Weight. Surface Area, Linear Formula	Period	End of Period. Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
R. L. C.*.....	Prelim.	11:48	....	....	....	....	....	....	....
1/19 17, 62.3 Kg. (Ht.-Wt.) 1.77 Sq. M.	1	1:48	46.4	43.1	0.78	57.9	0.49	142.3	....
William B.	Prelim.	11:40	....	....	....	....	....	....	....
1 15 17 66.2 Kg. 1.80 Sq. M.	1	12:20	24.1	20.2	0.87	22.3	0.43	68.6	50 1
	2	12:50	39.0	32.6	0 87	26.4	0.43	111.2	49 4
	3	1:50	24.3	28.4	0.62	40.0	0.43	92.8‡	88 9
	4	2:50	28.6	26.8	0.78	39.5	0.43	88.8	92.5
Albert G.	Prelim.	1:07	....	....	....	....	....	....	....
1/13/15 66.8 Kg. 2.07 Sq. M. Meeh Formula	1	2:07	28.5	19.0	0.86	28.0	0 48	64.6	69.0
	2	3:07	26.7	21.2	0.92	29.7	0.42	72.5	74.1
	3	4:07	25.2	23.8	0.77	30 2	0 42	78 6	78.8
	4	5:07	25.0	22.7	0.80	31 2	0.42	75.4	73.2
John Br.	Prelim.	11:29	....	....	....	....	....	....	....
2/2/17 58.5 Kg. 1.75 Sq. M. (Ht.-Wt.)	1	12:19	54.8	44 7	0.89	29.0	0.68	152 8	70.6
	2	12:49	16.8	14.3	0.86	15.9	0.68	48.5	43.2
	3	1:19	15.6	13.8	0.82	15.6	0.68	46.4	44.1
	4	2:19	31.7	31 0	0.74	32.1	0 68	102.1	93.5
	5	3:19	31.4	28.8	0.79	46.9	0 68	96.1	112.2
Joseph McC.	Prelim.	11:09	....	....	....	....	....	....	....
2/7/17 51.4 Kg. 1.46 Sq. M.	1	12:09	20.9	18.6	0.82	27.8	0.27	62.4	61.5
	2	12:46	....	....	....	....	0.27	....	....
	3	1:15	8.8	10.1	0.79	13.4	0.27	58.2	27.8
	4	1:41	10.4	7.4		13.8	0.27		28.6
	5	2:41	29.6	27.0	0.80	32.6	0.27	90.3	66.1
	6	3:41	22.7	21.9	0.76	30.6	0.27	72.1	66.4
	Aver.	.....	....	....	....	....	....	....	....
Joseph McC.	Prelim.	9:28	....	....	....	....	....	....	....
2/15-12/17 53 6 Kg. 1 46 Sq. M.	1	9:58	10 7	8 9	0.87	9.8	0.16	30.3	26.3
	2	10:30	7.8	6.2	0.91	7.7	0.16	21.1	20.6
	3	11:00	28.1	22.4	0.92	17.6	0.16	77.1	44.0
	4	12:00	23.3	20 7	0.82	24 5	0.16	69.7	62 8
	5	1:00	27.1	23 4	0.84	27.2	0.16	79.3	68.7
	6	1:40	....	....	....	....	....	....	....
	7	2:40	22.4	19.7	0.83	26.3	0.16	66.5	69.3
	8	3:40	21 3	19 0	0.82	29.8	0.16	63.7	75.3
	9	4:40	20.7	18 2	0.83	26.7	0.16	61.3	68.8
	10	5:30	18.8	17.0	0.81	23.9	0.16	56.7	63.6
	11	6:00	10.7	9.1	0.85	13.9	0.16	30.8	34 0

* Direct lost because of leak in pipes of ice tank.
† Spirometer string broke in first and third periods.
‡ Calculated from R. Q. of 0.70.

Direct Calorimetry (Rectal Temp., Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder. Cm.	Nonprotein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per kg.	Per Sq. M. (Linear)	
...	38.6	..	..	....	..	..	..	....	....	Proteose 4% (Jobling) 0.5 c.c. at 10:05 a. m.
...	36.9	..	32	0.78	18	62	20	1.13	40.2	Quiet, no chill
....	37.3	..	..	....	..	..	..	....	....	Proteose 4% (Jobling) 0.8 c.c. at 9:18 a. m.
67.4	37.6	60	34	0.88	11	37	52	1.55	57.2	Shivering last 5 min.
104.0	38.6	..	21	0.87	20	26	54	3.36	123.5	Chill 12:30–12:40
115.4	39.1	79	14	0.60	..	..	..	1.40	....	Fairly quiet
62.6	38.6	76	14	0.77	13	48	39	1.34	49.3	Quiet
....	36.8	..	..	....	..	..	..	....	....	Typhoid vaccine 500 million subcutaneously at 10:07 a. m.
64.2	36.7	65	13	0.90	20	27	53	0.96	30.9	Meeb Quiet
90.5	37.0	60	28	0.94	15	17	68	1.09	35.0	Quiet
77.3	37.0	60	24	0.76	14	70	16	1.13	37.9	Rather restless
74.4	37.0	..	28	0.80	15	58	27	1.13	39.4	Rather restless
....	37.8	..	..	....	..	..	..	....	....	Typhoid vaccine 25 million intravenously at 10:36 a. m.
139.6	39.2	..	35	0.90	10	30	60	3.14	105.0	Chill, 30 min.
76.1	39.9	..	10	0.87	19	35	46	1.64	54.8	Quiet, voided
38.2	39.8	..	7	0.82	20	48	32	1.58	52.6	Quiet
87.6	39.7	..	20	0.73	18	76	6	1.73	57.7	Quiet
86.0	39.2	98	33	0.79	19	60	21	1.63	54.5	Somewhat restless
....	37.5	..	..	....	..	..	..	....	....	Basal
60.3	37.5	64	23	0.82	..	..	..	1.21	42.7	Very quiet
....	37.5	..	..	....	..	..	..	....	....	Removed from calorimeter, typhoid vaccine 40 million intravenously at 12:31 p. m.
20.4	37.3	58	12	0.79	..	..	..	1.24	40.7	Quiet
59.4	37.3	56	8							
152.0	38.4	..	12	0.79	..	..	..	1.76	57.9	Chill, 1:45–2:15 p. m
79.0	38.8	..	..	0.75	..	..	..	1.40	46.2	Very quiet
....	....	..	..	....	10	65	25			
....	37.2	..	..	....	..	..	..	....	....	Typhoid vaccine 50 million intravenously at 9:05 p. m.
18.0	37.1	72	8	0.88	7	37	56	1.18	41.5	Quiet
20.5	37.1	..	2	0.90	8	30	62	1.11	39.5	Very quiet
92.8	38.2	89	7	0.92	4	26	70	2.24	79.3	Chill, 10:21–10:53 p. m.
70.2	38.4	120	..	0.82	6	58	36	1.35	47.7	Quiet
78.3	38.3	..	20	0.84	5	52	43	1.53	54.3	Fairly quiet
....	38.5	..	..	....	..	..	..	....	....	Removed from calorimeter, given 240 c.c. water at 1:05 (37°)
57.4	38.2	79	9	0.83	6	56	38	1.29	45.5	Very quiet
62.2	37.9	..	7	0.82	7	57	36	1.23	43.6	Asleep
62.0	37.8	88	4	0.81	7	53	40	1.19	42.0	Very quiet
59.9	37.7	..	13	0.81	6	62	32	1.32	46.4	Very quiet
59.9	37.6	..	8	0.86	7	51	42	1.20	42.2	Restless last 5 min.

TABLE 1.—CALORIMETER—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Frank G.†.....	Prelim.	11:15	....	....	....	....	....	....	....
2/23/17									
56.7 Kg.	1	11:45	11.0	9.91	0.81	20.7	0.29	33.2	32.8
1.56 Sq. M.	2	12:45	40.9	35.6	0.84	37.7	0.29	120.1	68.6
	3	1:45	26.0	23.1‡	0.82	38.5	0.29	77.4	74.0
	4	2:45	25.2	24.4	0.75	51.0	0.29	80.3	90.6
	5	3:53	24.1	27.5	0.64	73.8	0.29	89.7	110.1
Genaro A.	Prelim.	11:15	....	....	....	....	....	....	....
3/2/17									
52.9 Kg.	1	11:45	12.1	9.9	0.89	12.9	0.68	33.3	32.1
1.56 Sq. M.	2	12:15	13.2	11.9	0.80	15.6	0.68	39.4	37.7
	3	1:15	25.9	23.5	0.80	32.3	0.68	77.7	68.7
	4	2:15	26.2	25.0	0.76	33.8	0.68	82.0	71.1
	5	3:15	27.2	26.2	0.76	36.5	0.68	85.8	78.7

* Direct lost because of leak in pipes of ice tank.
† Spirometer string broke in first and third periods.
‡ Calculated from R. Q. of 0.76.

CASE HISTORIES

CASE 1.—R. L. C., a physician, born in the United States, 35 years of age, has never been seriously ill, has had no attacks of tonsillitis or of articular rheumatism. During the winter of the past three or four years he has had lumbar and sciatic pains, which, at times, have entirely incapacitated him. At the time of the observation he was in the midst of a particularly uncomfortable attack.

Physical Examination.—Nothing abnormal. Tonsils are small and healthy in appearance. The teeth are in good condition. No areas of tenderness are found in the back or in the region of the sciatic nerve.

Jan. 19, 1917, he was given intravenously 0.5 c.c. of a 4 per cent. solution of Jobling's proteose. No rise in temperature or disagreeable symptoms followed the injection. No improvement of pain or stiffness resulted.

The calorimeter observation was unsatisfactory because there was no chill. A leak in the pipe made it impossible to use the method of direct calorimetry in this experiment.

CASE 2.—William B., arthritis deformans (gonorrheal?), a traveling salesman, born in the United States, 50 years of age, was admitted Oct. 16, 1916, and discharged improved Jan. 17, 1917. In 1899 he had gonorrhea followed by epididymitis. The discharge lasted for two weeks. He had had occasional sore throat but no previous attacks of joint pain.

July 21, 1916, he was seized with pain in the left arm and wrist and in the right ankle. Two days later he went to St. Vincent's Hospital where he was treated until Oct. 16.

Physical Examination.—He is a poorly nourished, well developed rather apathetic man. He has no temperature and is not toxic. The right elbow is ankylosed and is very painful. All of the muscles of the right arm and forearm are flabby and wasted. The fingers of the right hand are stiff from disuse. The right shoulder, left elbow and right ankle are very moderately involved. There is superficial edema of the feet and ankles.

—Data (Continued)

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Libbard)	
....	37.5	..	..	....	..	..	..	....	....	Typhoid vaccine 35 million intravenously at 10:51 a. m.
29.8	37.4	84	7	0.81	10	58	32	1.18	42.6	Quiet, asleep
150.7	39.1	96	..	0.84	6	51	43	2.12	77.0	Chill, 11:28 a. m. - 12:23 p. m.; drank 240 c.c. water (3: C.) 12:37 p.m.
76.5	39.2	96	19	0.82	10	54	36	1.37	49.6	Restless for 30 min.
73.2	38.9	..	6	0.75	10	77	13	1.42	51.5	Restless last 10 min.
93.0	38.6	..	18	0.62	..	..	..	1.58	57.5	
.. ..	37.6	..	..	....	..	..	..	....	....	Typhoid vaccine 20 million intravenously at 10:56 a. m.
92.0	37.6	66	1	0.92	37	20	53	1.20	42.7	Very quiet
40.4	37.7	..	5	0.80	23	44	33	1.50	50.5	Almost motionless
85.0	38.1	..	3	0.80	23	52	25	1.47	49.8	Almost motionless
80.5	38.3	74	3	0.75	12	68	10	1.55	52.6	Almost motionless
76.5	38.3	..	2	0.74	21	70	9	1.62	55.0	Almost motionless

November 27 he had an acute attack of follicular tonsillitis from which he recovered rapidly. From December 19 to January 15 he received at rather irregular intervals eight doses of Jobling's proteose intravenously. From the first dose he had no reaction. Both the first and second injections were of a 1 per cent. solution; the others were of a 4 per cent. solution, varying in dose from 0.3 c.c. to 1.0 c.c.

January 10 and January 15 he was observed in the calorimeter following proteose injections. Owing to technical errors, the observation of January 10 was lost. That taken on the fifteenth is here presented. No marked change in symptoms was noted after any of the proteose injections. The joint condition improved very gradually. With constant baking and massage he regained motion in the fingers of the right hand. The elbow was still ankylosed at the time of discharge, January 17.

Case 3.—Albert G., a normal control to whom typhoid vaccine was given subcutaneously, a laborer born in Italy, 24 years of age, was admitted Dec. 14, 1914, and discharged Jan. 14, 1915. His health was excellent. He was out of work and was admitted to the hospital to act as a normal control for other observations which were being carried on at the time. He was short, with large muscles and very little subcutaneous fat. He was neurasthenic, continually fearing that he would become ill.

January 13, at 10:07 a. m., he was given 500 million dead typhoid bacilli (New York City Board of Health vaccine) subcutaneously into the arm. The usual reaction occurred with moderate swelling and tenderness of the arm.[13]

Case 4.—John Br., acute arthritis, gonorrheal (rheumatic?), a clerk born in the United States, 19 years of age, was admitted Jan. 25, 1917, and discharged

13. For details of previous observations on this man, consult Soderstrom, G. F.; Meyer, A. L., and Du Bois, E. F.: Clinical Calorimetry, Paper 11, A Comparison of the Metabolism of Men Flat in Bed and Sitting in a Steamer Chair, Arch. Int. Med. **17**:872 (July) 1916; Gephart, F. C., and Du Bois, E. F.: Clinical Calorimetry, Paper 13, The Basal Metabolism of Normal Adults with Special Reference to Surface Area, Arch. Int. Med. **17**:902 (June) 1916.

improved March 23, 1917. January 7 he began to have a urethral discharge. Six days later he was seized with pain in the right knee, right foot, left foot and right thumb.

Physical Examination.—Patient was a well developed, somewhat emaciated boy, acutely ill, rather toxic. The tongue was slightly dry, with a brown coat. The left knee joint is distended with fluid, hot, slightly tender and held in semiflexion. The right knee, both ankles and some of the small joints of the hands and feet show swelling and moderate tenderness. There is a urethral discharge containing gonococci in large numbers.

January 29 and January 31 he was observed in the calorimeter, February 2 he was given intravenously a 25 million dose of New York City Board of Health typhoid vaccine and was observed in the calorimeter. On the fourth and again on the fourteenth he received typhoid vaccine. On March 1 he was discharged to the general ward, very slightly improved by the vaccine therapy. He was later given gonococcus vaccine intravenously. Following this his improvement was rapid. He was discharged from the hospital March 23 with slight swelling in his right knee joint but with no other symptoms.

Case 5.—Joseph McC., subacute gonorrheal arthritis, an elevator operator, born in the United States, 27 years of age, was admitted Jan. 24, 1917, and discharged unimproved. In 1910 he had an attack of gonorrheal urethritis followed by epididymitis. Since then he has had a urethral discharge several times, the last time being in November, 1916. In 1912 he had an acute arthritis involving all the joints and he was ill for nine weeks. A second attack of the same character, in 1914, lasted two months. He has never had sore throat, chorea or other manifestations of acute rheumatic fever.

Jan. 3, 1917, he began to have a dull pain in the lower end of the spine and in the lumbosacral muscles which radiated down the right thigh. His right heel became so painful that he could not walk. About the same time the urethral discharge recommenced.

Physical Examination.—This shows an under developed, poorly nourished man. He holds himself very stiffly because of pain in the back. There is pain on pressure over the sacrococcygeal joint and marked tenderness over the spine of the ninth dorsal vertebra. The under surface of the right heel is exquisitely tender. There is considerable watery purulent urethral discharge, a smear of which shows gonococci. The prostate is moderately enlarged. The right seminal vesicle is palpable.

Urine from both anterior and posterior urethra contains pus but no albumin or casts. Gonococcus fixation test is negative. Wassermann reaction is negative. Roentgen ray shows periosteal exostosis of the os calcis of both heels.

His symptoms remained unchanged during the first seven days in the hospital. February 1 he was given intravenously 40 million of the New York City Board of Health typhoid vaccine. On the third, the fifth and the seventh similar doses were given. The character of the reactions following the injections appears on the temperature chart. The chills began from thirty to seventy-five minutes after the injection. On the thirteenth a dose of 50 million was given. On the seventh and thirteenth the patient was observed in the calorimeter. No noticeable improvement resulted from the vaccine therapy. On the first day following each injection he was more stiff and uncomfortable. On the second day the condition returned to that which obtained before the vaccine was given. He was discharged improved.

Case 6.—Frank G., chronic gonococcus arthritis, a barber, born in the United States, 42 years of age, a widower, was admitted Feb. 13, 1917, to the service of Dr. C. E. Nammack, transferred to the Metabolism Ward and discharged unimproved May 8, 1917. He says he has had gonorrhea seven times, the first attack being at the age of 15. He has had three distinct attacks of arthritis, all of which had occurred during or immediately following an acute arthritis,

During the past year the joint pains have been almost constant. Since January, 1917, he has had a urethral discharge and more severe joint involvement. He has always used alcohol to excess. (During the past month he has consumed as much as a quart of whisky a day). February 16, in another ward, he received intravenously a 20 million dose of New York City Board of Health typhoid vaccine. February 19 he received 30 million. The joint condition was not improved but the urethral discharge, which had been profuse, was checked. He is a poorly nourished, fairly well developed, very dissipated looking man. He has no temperature elevation and does not appear to be toxic. His throat is congested. The tonsils are normal in appearance and his teeth are in fair condition. His spleen is felt two finger breadths below the costal margin. He has moderate pain, tenderness and swelling in the right wrist, right hand and right knee. His prostate is enlarged. Massage of this organ causes the discharge of a drop or two of thin, purulent material which contains large numbers of gonococci.

His gonococcus fixation test is strongly positive. Wassermann is negative. February 27 he was transferred to the general service. March 10 the urethral discharge again became profuse. March 27 he developed a severe gonorrheal conjunctivitis. He had entirely recovered from this at the time of his discharge May 8. The joint condition, however, was unimproved.

Case 7.—Genaro, A., acute rheumatic fever, a munition factory worker, born in Cuba, 22 years of age, was admitted to the hospital Feb. 25, 1917, and discharged improved March 16, 1917. He says that he has never been ill before. He denies gonorrhea and syphilis.

Since February he has had pain in both knees, wrists, shoulders, elbows and ankles. With it, he has had a slight sore throat, some headache, and at the onset of the illness several nose bleeds. March 26 he received intravenously in another ward a 60 million dose of New York City Board of Health typhoid vaccine; March 27, 50 million; and March 28, 50 million. He had severe reactions in each case. After the first injection there was considerable clinical improvement. The other doses had little or no effect.

Physical Examination.—He is a well nourished and developed Cuban boy of remarkably sanguine disposition in spite of considerable pain. He is not toxic. The tongue is moist. His tonsils are small and not inflamed. The teeth show many fillings and gold crowns. At the time of admission his heart was normal but later there developed a soft, blowing, systolic murmur, maximum at the apex and transmitted outward into the axilla. The spleen is felt one fingerbreadth below the costal margin. The left wrist, elbow and shoulder are painful on motion.

March 2, after receiving a 20 million dose of typhoid vaccine, he was observed in the calorimeter. He had no chill. On the third, fourth and sixth he received a dose of 40 millions. Each time he had a chill with severe reaction. The joint pains gradually improved. Improvement, however, seemed to bear no definite relation to treatment. After the last injection his temperature reached normal and remained so until his discharge March 16. At that time all joint pain and swelling had disappeared but the heart murmur persisted.

In all, eight observations were made, lasting from two to eight and a half hours. When changes in the metabolism were expected the periods were made as short as possible. One period of only twenty-two minutes was obtained. It would have been interesting to subdivide the period of chill but no experimental period can be ended unless the subject has been quiet for six or seven minutes. Short periods are not as accurate as long ones since a small error in determining the

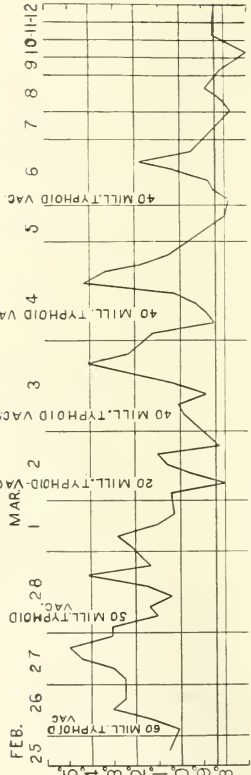

Fig. 2.—Temperature curve of Genaro A.

residual carbon dioxid or oxygen will cause a larger percentage change in the shorter period. This error will, of course, be compensated for in the next period.

The time of the chill never corresponds exactly to the experimental period in which it is observed. It is possible, however, to calculate with fair accuracy the heat production occurring during the chill itself. We may consider that the metabolism during the few minutes before the chill is at the same level as that of the preceding period. Similarly the metabolism in the short interval after the paroxysm approximates the level of the following period. The heat thus calculated for the interval before and after the chill is subtracted from the total heat produced during the entire experimental period. In this manner, the heat production during a twenty minute chill can be estimated even though the experimental period be forty minutes long.

The data of the calorimetric experiments are given in Table 1. Figure 3 shows graphically the results of the calorimeter observation on John B. Figures 4 and 5 show the results on Joseph McC. (Case 5). Figure 6 on Frank G. (Case 6); Figure 7 on William B. (Case 2); Figure 8 on Genaro A. (Case 7).

DISCUSSION OF RESULTS

The phenomena observed after the intravenous injection of foreign protein are almost identical with those observed in malaria.[1] For convenience of discussion the malarial paroxysm was divided into six periods: (a) a basal period before the chill; (b) a prodromal phase immediately before the chill; (c) the chill itself; (d) a period of rising temperature after the cessation of shivering; (e) a period of high continuous temperature corresponding to the clinical stage of heat, and, finally, (f) a period of falling temperature. In considering the reactions to foreign proteins, this same division is useful.

In the chills of malaria, the respiratory quotients were found to be high. The same thing is observed during the chill following the injection of vaccines, which indicates a rapid combustion of the glycogen stores of the body. In most of the experiments, the quotient falls steadily after the chill.

Four main questions of the mechanism of the rise and fall of body temperature will be considered.

1. The relation of heat production to heat elimination as factors in the rise and fall of temperature.

2. The divergence of the rectal temperature from the average body temperature.

3. The relation of heat lost in the vaporization of water to the total heat elimination and to the heat production.

4. The influence of body temperature on heat production.

The data on which the discussion is based are presented in Table 2.

TABLE 2.—Summary of Data on Heat Regulation

Name; Date; Surface Area	Condition of Patient	Length of Period	Rectal Temperature, C.	R. Q.	Heat		Per Cent. Divergence of Direct from Indirect, Cal.	Change in Rectal Temperature	Change in Average Body Temperature	Per Cent. Total Heat Elim. Lost in Vap. of Water	Per Cent. Total Heat Produced Lost in Vap. of Water	Calories per Square Meter per Hour	Per Cent Rise Above Normal Basal for Age
					Produced Ind. Cal.	Eliminated							
John B....	Chill.....	50 minutes	37.8-39.3	0.89	152.5	70.6	— 8.5	+1.4	+1.09	24.1	11.1	105.0	+ 156
7/2/17	Rising temperature after chill.	50 minutes	39.2-39.9	0.86	48.1	43.2	+58.0	+0.7	+0.10	21.6	19.4	54.8	+ 54
1.75 Sq. M.	High continuous temperature.	90 minutes	39.9-39.7	0.78	147.5	137.6	—14.7	—0.2	+0.20	20.4	19.2	55.2	+ 55
	Falling temperature.....	60 minutes	39.7-39.2	0.79	95.4	112.2	— 9.8	—0.5	—0.25	24.5	28.8	54.5	+ 68
Joseph Mc.	Afebrile before vaccine.....	60 minutes	37.5-37.5	0.82	62.4	61.5	— 3.4	±0.0	+0.02	26.5	26.1	42.7	+ 8
L.	Arebrile after vaccine but before chill.....	55 minutes	37.5-37.3	0.79	58.2	56.4	—14.4	—0.2	+0.04	28.3	27.4	40.7	+ 30
1.46 Sq. M.	Chill.....	60 minutes	37.3-38.4	0.80	90.3	66.1	+24.0	+1.1	+0.57	28.9	24.9	57.9	+ 49
	Rising temperature after chill..	60 minutes	38.4-38.8	0.76	72.1	66.4	+ 9.0	+0.4	+0.13	27.0	19.0	46.2	+ 14
Joseph Mc.	Afebrile before chill.....	52 minutes	37.2-37.4	0.89	51.4	46.9	— 5.7	—0.1	+0.10	21.9	20.1	40.5	+ 3
9/12/17	Chill.....	40 minutes	37.4-38.2	0.92	77.1	41.6	+30.0	+1.1	+0.78	23.2	13.4	70.3	+ 101
1.46 Sq. M.	Rising temperature after chill..	2 hours	38.2-38.6	0.83	149.0	131.5	— 6.5	+0.4	+0.40	23.3	20.5	51.0	+ 29
	Falling temperature.....	4 hrs. 20 m.	38.5-37.6	0.87	274.0	304.0	— 2.4	—0.9	—0.58	23.4	25.1	43.9	+ 11
Genaro A...	Afebrile.....	30 minutes	37.6-37.6	0.89	33.3	32.1	— 3.9	±0.0	+0.03	23.5	22.7	42.7	+ 8
3/2/17	Rising temperature without chill.....	2 hrs. 30 m.	37.6-38.3	0.79	199.1	177.5	+ 3.0	+0.7	+0.49	26.5	23.9	51.5	+ 31
1.56 Sq. M.	High continuous temperature..	60 minutes	38.3-38.3	0.76	85.8	78.7	—10.8	±0.0	+0.17	27.2	24.9	55.0	+ 50
William B.	Rising temperature before chill	40 minutes	37.3-37.6	0.87	68.6	50.1	— 1.7	+0.3	+0.34	26.1	19.1	57.2	+ 55
1/15/17	Chill.....	30 minutes	37.6-38.6	0.87	111.2	49.4	— 6.5	+1.0	+1.13	32.1	14.2	123.5	+ 229
1.80 Sq. M.	Falling temperature.....	60 minutes	39.1-38.6	0.78	88.8	92.5	—29.5	—0.5	—0.07	24.8	26.0	49.3	+ 31
Frank G....	Afebrile before chill.....	30 minutes	37.5-37.4	0.81	33.2	32.8	—10.2	—0.1	+0.01	37.0	36.5	42.6	+ 11
2/23/17	Chill.....	60 minutes	37.4-39.1	0.84	120.1	68.6	+26.0	+1.7	+1.09	32.2	18.4	77.0	+ 100
	High continuous temperature..	60 m.inutes	39.1-39.2	0.82	77.4	74.0	— 1.2	+0.1	+0.07	30.5	29.2	49.6	+ 29
	Falling temperature.....	60 minutes	39.2-38.9	0.75	80.3	90.6	— 6.3	—0.3	—0.22	33.0	37.2	51.5	+ 34

Relation of Heat Production to Heat Elimination.—In malaria, it was found that during a chill the heat production was enormously increased while the heat elimination remained practically at its basal level. After injection of foreign protein, the same mechanism is observed. It would seem as if the temperature regulation were set at a higher level and that the body responded by producing heat sufficient to warm the tissues to the new temperature level. After

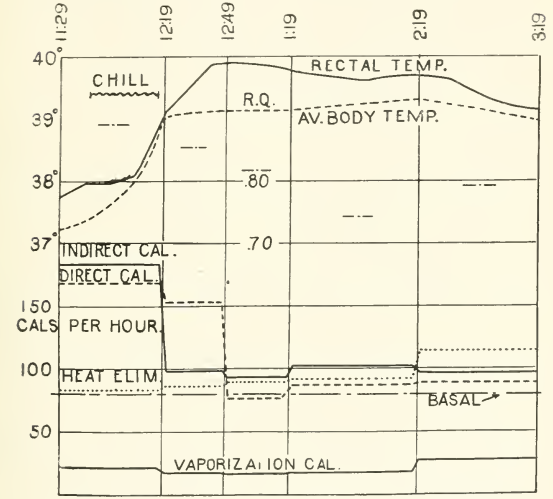

Fig. 3.—Calorimeter observation on John Br., February 2. At 10:50 a. m., 25 million typhoid bacilli were given intravenously. The chill lasted from 11:40 a. m. to 12:10 p. m. The upper curve shows the rectal temperature measured every four minutes; the dash line below shows the change in the average body temperature, as calculated from the difference between heat elimination and heat production as determined by the method of indirect calorimetry. This line is started arbitrarily 0.5 C. lower than the rectal temperature. While it is possible to determine the rise and fall of the average body temperature, it is absolutely impossible to fix the exact level at which these fluctuations take place. After the start at 11:29 a. m., the first satisfactory fixation of this line was at 12:49 p. m. Between these points the exact shape of the curve is not certain. The respiratory quotient (R. Q.) is indicated by short lines in each period. The line at 80.8 calories represents the basal heat production per hour as determined on January 31.

vaccine, the heat production is increased from 75 to 210 per cent. during the chill, while the amount of heat eliminated is scarcely increased above its former basal level. This, of course, results in the storage of large amounts of heat within the body. After the chill is over, the heat production drops sharply but still remains somewhat above the normal, as is usually the case during increased body temperature. The rectal temperature still continues to rise after the shivering ceases. The heat elimination is practically unchanged. During the

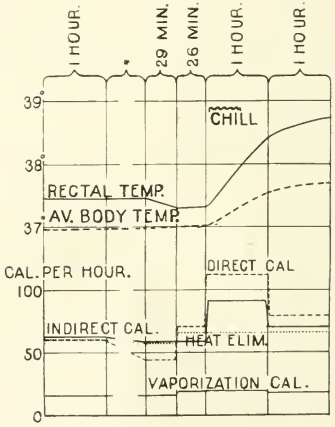

Fig. 4.—Calorimeter observations on Joseph McC., February 7. The first period from 11:09 a. m., to 12:09 p. m., was a basal determination. At 12:31 p. m. he was given an intravenous injection of 40 million typhoid bacilli. Two short periods were obtained before the chill, which lasted from 1:45 to 2:15 p. m. Note that the average body temperature rises more slowly than the rectal temperature.

stage of high continuous temperature the heat elimination increases until it is equal to the heat production; both, however, being at a level from 20 to 40 per cent. above the normal. During the fall in body temperature, the heat production drops gradually to the basal level and the heat elimination increases steadily.

Relation of Rectal to Average Body Temperature.—During the past ten years, more than 300 observations on patients with normal

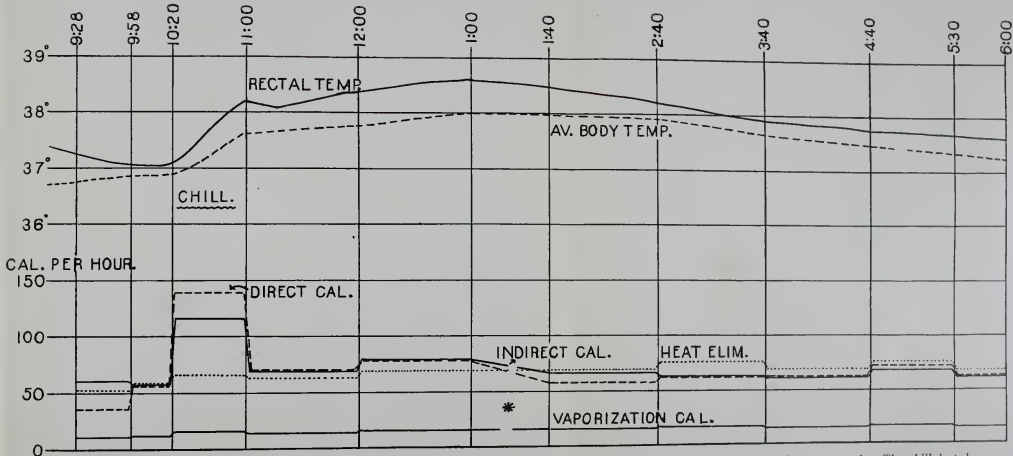

Fig. 5.—Calorimeter observation on Joseph McC., February 12 and 13. At 9:05 p. m. he was given 50 million typhoid bacilli intravenously. The chill lasted from 10:21 to 10:53 p. m. At 1:00 a. m. the calorimeter was opened to give the patient a drink of water. It was closed immediately and the next period started at 1:40 a. m. Note that the curve for the average body temperature lags behind that of the rectal temperature.

vaccine, the heat production is increased from 75 to 210 per cent.

past ten years, more than 300 observations on patients with normal

temperature have been made with the Sage calorimeter. They have shown a remarkably close agreement between the direct and indirect methods of measuring heat production. In patients with fever, however, and particularly in malaria, there has been a wide divergence between the two methods. This may be explained on the following basis. The measurement of heat production by direct calorimetry depends for one of its factors on the rectal temperature which in the

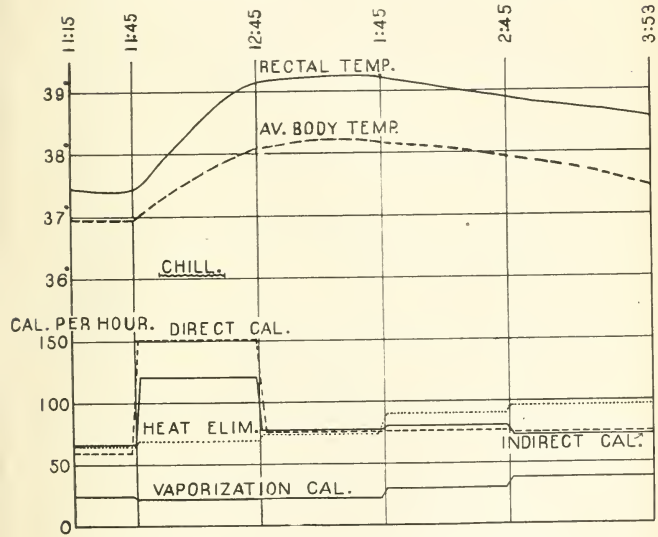

Fig. 6.—Calorimeter observation on Frank G., February 23. At 10:51 a. m. 35 million typhoid bacilli were given intravenously. The chill lasted from 11:58 a. m. to 12:25 p. m. The average body temperature rose less sharply than the rectal temperature.

calculation is assumed to represent accurately the average temperature of the body. During rapid production of heat, such as is seen during a shivering chill, the distribution of heat will not be immediately uniform, with the result that the temperature in the rectum may change more or less than that of the rest of the body.

Exact measurement of average body temperature appears impossible since we cannot have thermometers in all parts of the body. In the paper on malaria, however, an indirect method was devised which allows us to calculate this value. For a given interval the difference

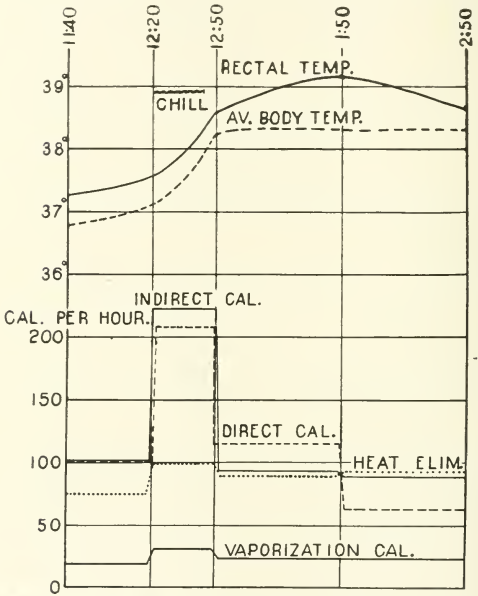

Fig 7.—Calorimeter observation on William B., January 15. At 9:40 a. m. he was given an intravenous injection of 0.8 c.c. of a 1 per cent. proteose solution. He shivered during the last five minutes of the first period and had a violent chill from 12:20 to 12:40 p. m. In this case the average body temperature seems to have risen more sharply than the rectal temperature.

is taken between the number of calories produced, as estimated by the chemical methods of indirect calorimetry and the calories eliminated as measured by the direct physical methods. This represents the heat lost or gained by the whole body. When this difference is divided

by the hydrothermal equivalent of the organism, the gain or loss in average body temperature is obtained. For example, heat production 100 calories, minus heat elimination 60 calories=heat stored 40 calories. In a man weighing 70 kg., the hydrothermal equivalent (heat necessary to raise the temperature of the whole body 1 C.)=58.1 calories.[14] The gain in average body temperature is, therefore, $\frac{40}{58.1}$ = 0.66 C. This may be compared with the change in rectal temperature which has been observed during the corresponding time interval.

In Figures 3 to 8, the average body temperature, as calculated by this method, is plotted with the rectal temperature. In about half of the cases, the two methods agree during the chill. In the others,

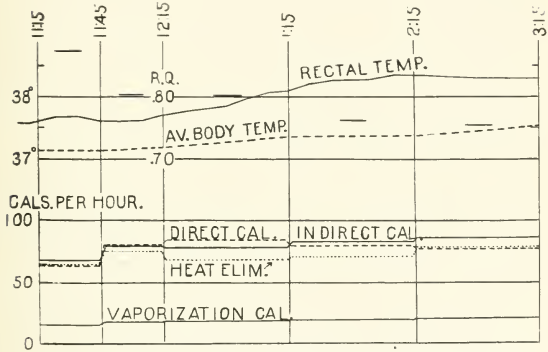

Fig. 8.—Calorimeter observation on Genaro A., March 2. This patient received a small dose of 20 million typhoid bacilli intravenously at 10:50 a. m. He did not have a chill. There was only a slight rise in rectal temperature and even less of a rise in the average body temperature.

the finding is similar to that observed in malaria. The rectal temperature rises more rapidly than the average body temperature. During the period of falling temperature, the heat measurements in the rectum represent with fair accuracy the conditions of the entire body. In the previous discussion of malaria, it was considered that the more rapid rise of rectal temperature indicated a storing of heat in the deeper portions of the body during the chill. In the light of these further observations, however, this cannot be regarded as a con-

14. This value is obtained by multiplying the weight in kg. by the factor 0.83 which is assumed to represent the specific heat of the body.

stant finding. We can only say that, during rapid variations in the production and elimination of heat, the distribution is not always uniform and that the rectal temperature is often an inaccurate index of the average temperature of the body.

The Relation of Heat Lost in the Vaporization of Water to the Total Heat Elimination and to the Heat Production.—Under the constant temperature conditions of the calorimeter, normal individuals accomplish about 25 per cent. of their total heat elimination through the vaporization of water. The same relationship was found in a large number of observations made in afebrile pathologic conditions. With continuous normal temperature, heat elimination and heat production are equal so the calories lost in the vaporization of water also constitutes 25 per cent. of the heat production. During the sharp rise in temperature accompanying chill, we have seen that the heat production is greatly increased while the elimination remains at its normal level. It is conceivable that the heat lost in vaporization might follow either one. In malarial fever, it was found to bear a fairly constant relation to heat elimination. It never followed the curve of rapid fluctuation in heat production. In the present experiments, the same relation is observed (Table 2). During the chill, the calories lost in vaporization constitute a very low per cent. of the heat production. During the fall in temperature, the percentage may be high. The relation to heat elimination, on the other hand, never deviates far from the limits of normal. This is well illustrated in the experiment on John Br. where the heat lost in the vaporization of water varies between 11 and 28.8 per cent. of the heat production while the relation to heat elimination varies only between 20.4 and 24.5 per cent.

The ability of the body to utilize water in heat elimination is of the greatest importance in the regulation of temperature. Because of its high specific heat and fluid character, it is capable of absorbing large amounts of heat from the cells and of distributing it to the surface of the body where it may be eliminated. The dry skin and concentrated urine of acute fevers has often given rise to the belief that the mechanism of heat loss is disturbed.

During exercise, in exophthalmic goiter and in other conditions in which the heat production is increased, the heat elimination increases correspondingly. Wolpert,[15] Benedict and Carpenter[16] and others have shown that during exercise, the heat lost in vaporization is increased not only absolutely but relatively to the total heat elimination.

15. Wolpert: Ueber den Einfluss der Lufttemperatur auf die im Zustand anstrengender körperlicher Arbeit ausgeschiedenen Mengen Kohlensäure und Wasserdampf beim Menschen. Arch. f. Hyg. **26**:32, 1916.

16. Benedict, F. G., and Carpenter, T. M.: The Metabolism and Energy Transformations of Healthy Man During Rest. Carnegie Institute of Washington, Pub. 126, 1910.

Thus, in severe work involving a heat elimination four times the normal amount Benedict and Carpenter found that the calories lost in vaporization constituted 47.6 per cent. of the total. Such findings have been compared with those occurring during fever in which a relative increase in the vaporization calories does not always occur. This is one of the factors which has led Balcar, Sansum and Woodyatt [17] to consider that fever may be due to an inability of the body to mobilize its water reserve for the elimination of heat. It has also been considered an argument for the supposed concentration of blood during fever.

It must be remembered that the rise in heat production involved in even light muscular work greatly exceeds the increase of heat production in fever. Except under conditions of chill, it is unusual to find the metabolism more than 50 or 60 per cent. above the normal

TABLE 3.—Comparison Between Exophthalmic Goiter and Typhoid Fever in the Percentage of Total Heat Elimination Lost in the Vaporization of Water

Subject	Diagnosis	Date	Heat Production, per Cent. Rise Above Average Normal Basal	Per Cent. Total Heat Elimination Lost in Vaporization of Water	Relative Humidity	
					Beginning	Ending
Morris S.	Typhoid.....	10/29/13	+41	24	49	49
Edwin T.	Goiter.....	3/10/15	+39	25	39	49
Charles F. ...	Typhoid.....	11/15/13	+37	23	37	47
Max W.	Goiter.....	4/24/14	+53	20	46	57
		3/28/14	+39	22	39	48
Edward B. ..	Typhoid.....	10/23/14	+28	23	41	38
Edwin T.	Goiter.....	3 6/15	+37	35	49	45

level during the course of a fever. It may be more in keeping, therefore, to compare water elimination in fever with some other conditions involving about the same increase in heat production. In Table 3 will be found a comparison of conditions in cases of exophthalmic goiter studied in Paper 14 [18] with those in cases of typhoid fever from Paper 7 [19] of this series. The temperature of the calorimeter was between 23 and 24 C. in all observations. Because the conditions or relative humidity were not always uniform the table is arranged in three groups of two each, showing respectively constant, rising and falling humidity.

17. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

18. Du Bois, E. F.: Clinical Calorimetry, Paper 14, Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**:915 (June) 1916.

19. Coleman, W., and Du Bois, E. F.: Clinical Calorimetry, Paper 7, Calorimetric Observations on the Metabolism of Typhoid Patients with and Without Food, Arch. Int. Med. **15**:887 (June) 1915.

It is to be noted that all percentages in both conditions are close to the average normal value. Max W. with a metabolism higher than any of the fevered typhoid patients lost only 20 per cent. of his calories in the heat of vaporization. The comparison is more striking when one remembers the notoriously moist skin of goiter patients.

In the study of typhoid fever, it was found[20] that during a rising temperature, the percentage of heat lost in vaporization of water was slightly lower than normal. The average was 22 per cent. which must be compared with the average normal of 24 per cent. The variations in the typhoid group, however, were great and the number of cases small. In spite of this, the finding has been considered by others as evidence of the body's inability to mobilize water and hence as a cause of fever. That this is not a constant finding during the rising temperature of fever can be shown in the case of George S., a malaria patient, whose record is shown in Table 4.

TABLE 4.—Relation of Heat Vaporization to Total Heat Elimination in George S., Malarial Fever

Condition	Per Cent. Rise in Heat Production Above Average Normal Basal	Per Cent. Total Heat Elimination Lost in Vaporization of Water
Rising temperature before chill	+ 24	28
Chill	+ 216	31
Rising temperature after chill	+ 76	21
High continuous temperature after chill	+ 65	29
Falling temperature, profuse sweating	+ 80	36+

It will be seen that the percentage of heat lost in vaporization is well above the average normal not only during the rising temperature but also during the chill and following periods. The same thing is shown even more strikingly in the case of Frank G in Table 2. Similar results were obtained in all observations in erysipelas.

Our data present no evidence that the rise of temperature is dependent on an inability of the body to mobilize its water reserve. It is true that the heat loss in vaporization of water is low when compared with the enormously increased heat production of a chill, but it never falls far below its average normal relation to the total elimination and as in the two cases just cited may rise considerably above it.

The Influence of Body Temperature on Heat Production.—In discussing the conditions in the period following a chill, it was emphasized that the heat production remained from 20 to 40 per cent. above the normal level after shivering had ceased. It was also remarked

20. Soderstrom, G. F., and Du Bois, E. F.: Clinical Calorimetry, Paper 25. The Water Elimination Through Skin and Respiratory Passages in Health and Disease, Arch. Int. Med. **19**:631 (June) 1917.

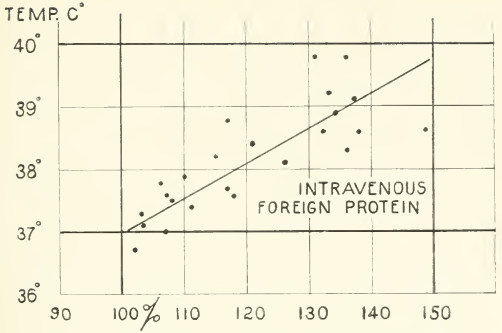

Fig. 9.—Relationship of basal metabolism to temperature in the fever following the injection of foreign protein. Ordinates represent rectal temperature in degrees centigrade, abscissae the metabolism expressed in percentages of the average normal. Each dot represents an experimental period in the calorimeter

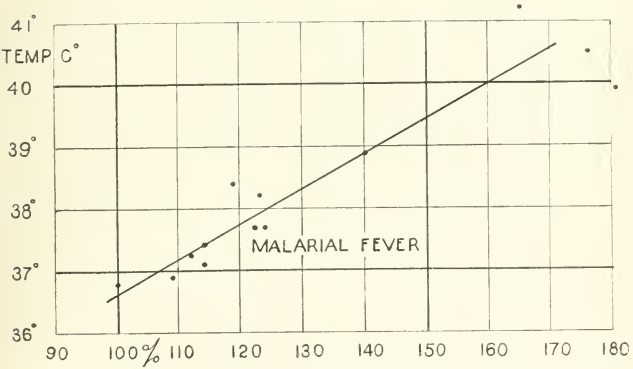

Fig. 10.—Relationship of basal metabolism to temperature in malarial fever.

that this was the usual finding in conditions of increased body temperature. Work on typhoid fever, tuberculosis and malaria has demonstrated that rise in body temperature is accompanied by increased heat production and that the increase corresponds to the degree of fever. Figure 9 shows the relation of heat production to the degree of body temperature after the injection of foreign protein expressed by the method utilized by McCann and Barr [21] in tuberculosis. The ordinates show the rectal temperature in degrees Centigrade. The abscissae show the level of the metabolism in percentage of the average normal. The line 90 means 10 per cent. below the average; 150 means 50 per cent. above the average. Each dot represents a calorimetric observation. Of course, it is necessary to leave out the shivering periods. It is possible that some of the results in the very high temperature following the chill are slightly affected by previous severe muscular exercise. Figure 10 demonstrates the relationships during the fever of malaria. In Figure 11 are grouped in one chart all of the fevers studied. The continued diagonal line is drawn from statistical calculations and the dotted lines are placed to represent divergencies of 10 per cent. in this average. Out of the total of 137 experiments in various fevers, 82 per cent. come within 10 per cent. of the average. In other words, the percentage variations in the metabolism for a given temperature are slightly greater than a similar group of normal individuals.

Most of the patients whose metabolism is very high for the degree of temperature were typhoid or malaria patients with a high level of protein metabolism. Most of those with low basal metabolism were cases of tuberculosis with a normal protein metabolism. We know that protein increases the metabolism through its specific dynamic action and this may explain the difference between the groups of patients. The ingestion of a large protein meal does not increase the heat production in typhoid where the protein metabolism is already high, but it does cause a striking increase in tuberculosis where the protein metabolism is at a much lower level. While the increased protein metabolism seems to be a factor in explaining differences between the various fevers we believe that it is outweighed by another and simpler factor.

The surprising uniformity of results expressed in Figure 11, suggests that we are dealing with a law of the velocity of chemical reactions enunciated by van't Hoff.[22] For ordinary temperatures the van't Hoff law can be expressed as follows: "With a rise in

21. McCann, W. S., and Barr, D. P.: Clinical Calorimetry, Paper 29. The Metabolism in Tuberculosis. Arch. Int. Med. **26**:663 (Nov.) 1920.

22. van't Hoff, J. H.: Studies in Chemical Dynamics. Revised by E. Cohen. Translated by T. Ewan. Easton, Pa. Chemical Publishing Co., 1896.

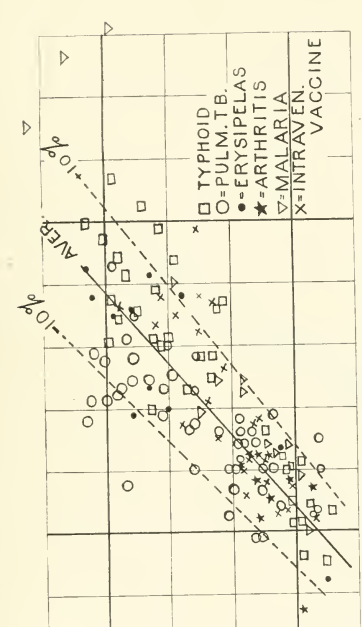

Fig. 11.—Relation of basal metabolism to temperature in six different fevers. The continuous line shows the average and the dotted lines are drawn to represent metabolism 10 per cent. above and 10 per cent. below the average.

temperature of 10 C. the velocity of chemical reactions increases between two and three times." In other words, the temperature coefficient is usually between 2 and 3. This means an increase of from 30 to 60 per cent. for the three degree rise from 37 C. to 40 C. Virtually all of the fever experiments are within these limits and the average line shows a temperature coefficient of 2.3.

Van't Hoff and Kanitz [23] give the temperature coefficients which show the rate of increase in a number of chemical reactions with an equal rise in temperature. If we plot these in exactly the style of the

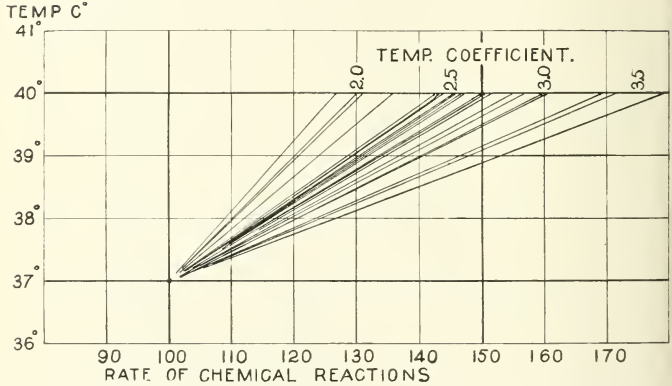

Fig. 12.—The lines in this chart represent a number of typical chemical reactions taken from van't Hoff and Kanitz. The slope of the lines shows the increase in the rate of the reactions as the temperature is raised. Note that the lines correspond closely to those which represent the total oxidations in the human body.

fever patients (Fig. 12) we note that the lines have approximately the same slope. In other words, the reactions in a fever patient respond to a rise in temperature in a manner which resembles closely the chemical reactions in the test tube suspended in a water bath.

There is a tremendous gap between the simple reactions in the test tube and the complex oxidations in the diseased human body and we should hesitate to compare them were it not for the large number

23. Kantiz, A.: Temperatur und Lebensvorgänge in Biochemie in Einzeldarstellungen: Heft 1. Gebrüder Bornträger, 1915, Berlin.

of biologic reactions which show temperature coefficients between 2 and 3. Van't Hoff calls attention to the rate of carbon dioxid elimination in plants which show a coefficient of 2.5. Kanitz gives a long list of similar coefficients for plant respiration, rate of isolated hearts, contraction of smooth muscle and the metabolism in cold blooded animals.

SUMMARY AND CONCLUSIONS

1. Eight calorimeter experiments have been made on subjects after the intravenous injection of proteose and of typhoid vaccine. In five of these it was possible to observe the phenomena of chills.

2. With the onset of a chill there is a sudden increase of from 75 to 200 per cent. in heat production due, in part, to the shivering. At the same time, there is almost no rise in the heat elimination. This discrepancy between production and elimination causes the storage of a large amount of heat within the body. After the chill there is a short period of level temperature when the heat production and heat elimination are equal and both are from 20 to 40 per cent. above the basal level. Following this, as the temperature falls, there is usually a steady decrease in heat production until it reaches the normal level. The heat elimination, on the other hand, increases still farther, thus getting rid of the stored heat. During the falling temperature there is never as large a discrepancy between elimination and production as during the chill.

3. The respiratory quotient tends to be high during the chill, indicating the rapid combustion of the glycogen stores of the body. After the chill, the quotient falls steadily.

4. By means of a comparison of the heat production and heat elimination, it is possible to determine the temperature changes of the body as a whole and compare them with the changes in rectal temperature. The rectal temperature indicates, in a general way, changes in average body temperature, but it is possible to have a rise in rectal temperature while there is a fall in the average body temperature. The opposite is also true.

5. The heat lost in the vaporization of water from the skin and lungs bears a fairly constant relationship to the total heat elimination but has no relationship to the heat production during rapid changes in temperature. Study of the water elimination in fever affords no evidence that the body is unable to mobilize water for heat elimination. Fever should not be attributed to failure in the function of water elimination.

6. Observations in this and in other fevers has demonstrated that rise in body temperature is accompanied by increased heat production the amount of which corresponds to the degree of fever. It is found

that this increase follows van't Hoff's law, which may be stated as follows: "With a rise in temperature of 10 C., the velocity of chemical reactions increases between two and three times."

7. The phenomena of the chill following intravenous injection of proteose or vaccine are strikingly similar to those of the malarial paroxysm, the method of temperature regulation being almost identical.

A CORRELATED STUDY OF THE INDICATIONS FOR TONSILLECTOMY AND OF THE PATHOLOGY AND BACTERIOLOGY OF THE EXCISED TONSILS*

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Careful studies of the flora of the tonsils and of the nasopharyngeal cavities have been made. The discovery of hemolytic streptococci is stressed as the most important bacteriologic finding. They are reported as present in approximately 50 per cent. of throats with extreme variations of from 10 to 100 per cent. In the nasopharynx they have been found less frequently and in smaller numbers. The importance of virulent hemolytic streptococci being the causative agent of many clinical conditions is well established. The rôle of these organisms as secondary invaders in postinfluenzal pneumonia, empyema, etc., is recognized. Also the ability of these bacteria to produce lesions in the stomach, gallbladder, appendix and endocardium; these lesions being secondary to primary foci of infection in the tonsils, teeth, etc., is stoutly affirmed by many. Therefore, the rôle played by streptococci in disease processes is an important one.

The steady progress that has been made in recent years in classifying the large and heterogeneous group of streptococci has given an added interest to the relation of the various strains of these organisms to clinical conditions. It has been demonstrated that several strains are homogeneous, that they have definite cultural characteristics, sugar reactions and agglutinin and precipitin properties. The association of certain strains with specific clinical conditions is now proved. Of the eight groups of hemolytic streptococci in Holman's classification,[1] four are known to be of frequent occurrence and closely related to septic disease processes and the remaining four are apparently nonpathogenic and of infrequent occurrence. Progress has also been made concerning the relation and the clinical significance of Holman's eight subgroups of nonhemolytic streptococci.

Likewise, the pathology of excised tonsils has been studied carefully and the changes which occur as the result of local infection are well known.

But while each phase of the relationship between the clinical indication for the removal of the tonsils, the pathology of the excised tonsils, and the predominating organism recovered, has been recorded

* From the Laboratories of the Santa Barbara Cottage Hospital.

1. Holman, W. L.: Classification of Streptococci, J. M. Research **28**:377, 1916.

many times by independent workers, the three phases have not been frequently worked out on the same material.

With this in mind we have tabulated the clinical indications for tonsillectomy in 218 patients. We have noted the pathologic changes in the excised tonsils. In studying the bacterial flora we have compared the results obtained by making cultures from the surface of the tonsil and, after cutting the tonsil with a sterile knife, with the cultures made from the depths of crypts. In tabulating the streptococci found, we have used the classification of Smith and Brown,[2] which divides these organisms into the hemolytic alpha, alpha prime, and beta groups and into the nonhemolytic gamma group. In deep colonies in poured blood agar plates which are not too thickly seeded the alpha group has a green area of discolored corpuscles immediately about the colony, outside of which there may or may not appear a partially hemolyzed zone. If the petri dish containing such colonies is placed in the icebox for twenty-four hours, the hemolyzed zone about the colony may become more clearly defined. Outside of this zone a second zone of greenish discoloration may develop, and beyond this another zone of hemolysis. If such a culture is alternately incubated and refrigerated as many as four zones may develop. Pneumococci resemble this group so closely that we have determined their solubility in bile, in order to accurately identify the colony. The alpha prime group of hemolytic streptococci have in deep cultures a faint haze immediately about the colony, due to incomplete hemolysis. The colonies of the beta group are surrounded by a sharply defined zone of complete hemolysis which varies from 1 to 5 mm. in diameter. The gamma group produces no hemolysis.

Method.—In order to obtain comparable results, we have followed the cultural methods suggested by Brown,[3] using beef extract and Digestive Ferments Co. peptone, the agar having a reaction of 0.5 per cent. normal acid to phenolphthalein. Twelve c.c. of this was mixed with 0.5 c.c. of human blood. Such a medium is very suitable for studying the various types of hemolysis. With a sterile loop material from the crypts was placed in about 2 c.c. of sterile physiologic solution of sodium chlorid from which emulsion the blood agar was inoculated, poured into Petri dishes and incubated. The plates were read at the end of twenty-four and forty-eight hours, then they were placed in the icebox for twenty-four hours and again read. The low power of the microscope was used in studying the type of hemolysis about the colony.

2. Smith, T., and Brown, J. H.: A Study of Streptococci Isolated from Certain Presumably Milk-Borne Epidemics of Tonsillitis Occurring in Massachusetts in 1913 and 1914, J. M. Research **31**:445, 1915.

3. Brown, J. H.: The Use of Blood Agar for the Study of Streptococci. Monograph, Rockefeller Inst. M. Research, No. 9, p. 40.

Single colonies were fished from Petri dishes, streaked on blood agar slants and the latter incubated. On obtaining a pure culture, the bile solubility of the organism and its sugar reactions were determined in those instances in which it was necessary.

Results.—Of the patients in this group of 218, 60 per cent. were children, 40 per cent. adults. Sixty-three per cent. gave a history of repeated sore throat. Frequent colds, together with enlargement of the tonsils were recorded in 14 per cent. Eight per cent. complained of mouth breathing. Eight per cent. had a history of one or more attacks of rheumatism. Seven per cent. had otitis media, and tonsillectomy was done in an endeavor to improve this condition.

Microscopic study of the entire number of tonsils removed revealed definite pathologic changes in 93 per cent. Seven per cent. were regarded as normal. In classifying the type of change we have followed the plan used by Moore,[4] i. e., chronic lacunar tonsillitis, chronic interstitial tonsillitis, and chronic peritonsillitis. We have classified separately those instances that presented gross or microscopic abscesses and those in which lymphatic hyperplasia was the only change noted (Table 1).

TABLE 1.—Percentage of Instances in Which the Various Changes Were Noted

Pathologic Condition	Percentage
Chronic lacunar tonsillitis	42
Chronic interstitial tonsillitis	21
Chronic peritonsillitis	6
Abscesses	10
Lymphatic hyperplasia as the only change	14
Mucous glands in capsule	7
Cartilage in capsule	3

Forty-two per cent., or nearly one-half of the entire number, presented changes in the lining epithelium of the crypts and its immediate neighborhood. In many, these crypts were filled with debris. The epithelium itself was quite frequently necrotic and microscopic abscesses just beneath the crypt epithelium were common. In the 21 per cent. of instances in which chronic interstitial changes were noted, there was a marked increase in the connective tissue stroma of the tonsil, representing a chronic inflammatory reaction. In the five per cent. of tonsils that had peritonsillar involvement the changes as described about the crypts and the connective tissue frame work were usually present to some degree but the evidence of infection and of repeated inflammation were especially pronounced in the thickening and hyperplasia of the capsular tissue.

The tonsils of the patients with a history of many attacks of tonsillitis, or of rheumatism, or of frequent colds, of mouth breathing, of otitis media, presented certain pathologic changes.

4. Moore, J. J.: Chronic Tonsillar Infections, J. Lab. & Clin. Med. **3**:283, 1917.

In Table 2 it will be noted that in 53 per cent. of the patients who had attacks of tonsillitis, the pathologic changes in the tonsil were most marked about the crypts, that is, the so-called chronic lacunar tonsillitis. Fourteen and four tenths per cent. of these had an associated lymphatic hyperplasia. The next most frequent change in this type of tonsil was the chronic interstitial tonsillitis present in 17.7 per cent., while peritonsillitis and abscesses were present in 8 and 4 per cent., respectively. The tonsils of the patients with a rheumatic history presented chronic interstitial change in 66.6 per cent. and peritonsillar change in 33 per cent. In 16 per cent. of these tonsils abscesses were found. Of the patients complaining of frequent colds, 58 per cent. had a lymphatic hyperplasia, and of those complaining of mouth breathing 100 per cent. presented this change. In these patients the adenoid tissue was also increased in amount.

TABLE 2.—Pathologic Changes in Tonsils in Various Conditions

Pathology	Attacks of Tonsillitis, per Cent.	Rheumatism, per Cent.	Colds, per Cent.	Mouth Breathing, per Cent.	Otitis Media, per Cent.
Chronic lacunar tonsillitis	53.0	16.6	33.3	...	50
Chronic interstitial tonsillitis	17.7	66.6	16.6	...	..
Chronic peritonsillitis	8.0	33.0	....	...	..
Abscesses of tonsils	4.0	16.0	....	...	..
Lymphatic hyperplasia	14.4*	....	58.3	100	50

* In association with other changes.

The bacteriologic findings, using Smith and Brown's classification, are interesting from many standpoints. The results of other workers using either the streaked plate or the poured plate method are so variant that we have used both methods simultaneously. We have thus been able to contrast the findings and to judge fairly of the worth of each method (Table 3). Without specifically subdividing the hemolytic streptococci into alpha, alpha prime or beta groups we have the following:

TABLE 3.—Bacteriologic Findings

	Streaked Plate Method, per Cent.	Poured Method, per Cent.
Hemolytic streptococci, all types	45.0	96.1
Nonhemolytic streptococci	3.5	2.6
Staphylococcus	64.0	37.0
Pneumococcus	18.0	49.8
Bacilli	7.0	1.9

Comparing these tables the great diversity in the results obtained is apparent. Using poured plates, hemolytic streptococci and pneumococci were found twice as frequently, whereas staphylococci in reportable numbers were found less than one-half as frequently as in streaked plates. By the latter method certain rapidly growing organisms, such

as the staphylococcus, obscured other and often more important organisms. Hemolytic staphylococci prohibited the recognition of other hemolytic organisms. The various groups of hemolytic streptococci were recognized with difficulty and uncertainty by the streaked method and were frequently missed altogether. We have also noticed that on a streaked plate the hemolytic beta group often completely obliterated the alpha, the alpha prime, or the gamma type even when the latter are present in numbers.

The findings explain the wide difference in the percentage of various organisms in tonsil reports by other workers, some of whom used one method and some the other. To us it is sufficient evidence that for accurate results the poured plate must be used.

The hemolytic streptococci which were present in 96.1 per cent. of the 218 tonsil examinations were classified according to the type of hemolysis. Colonies of the alpha type were present in notable numbers in 25 per cent. of instances, alpha prime in 32 per cent. and beta in 86.1 per cent.; all three of them frequently occurring in a single culture from the same tonsil. The beta group was further subdivided into those of wide and of narrow zone of hemolysis. Those classified as of the narrow zone had a diameter of 1 mm.; the wide zone had an average diameter of 4 mm. Since most beta hemolytic streptococci fall into one of the two groups, the narrow zone group representing 36.8 per cent. and the wide zone 73.4 per cent., we attempted to demonstrate that this small or wide zone characteristic was a fixed thing and warranted a further subdivision of the beta group.

Both groups were found to be pathogenic for rabbits (1 c.c. of a twenty-four-hour bouillon culture). We then routinely inoculated the test sugars with wide and narrow zone cultures and fermentation has uniformly resulted as shown in Table 4.

TABLE 4.—Differentiation of Streptococci According to Zone Production in Culture

	Saccharine	Lactose	Raffinose	Salicin	Mannite	Inulin
Wide zone	+	+	0	+	0	0
Narrow zone	+	+	0	+	0	0

Since there had been no difference in the reactions of the sugars and since both were pathogenic for rabbits, the permanency of the characteristic of a wide or narrow zone of hemolysis became of special interest. Clawson found hemolysis constant in a series of 134 strains even after two years. Brown [5] recorded some loss of hemolytic activity for certain strains. This loss always took the form of slightly smaller

5. Brown, J. H.: The Use of Blood Agar for the Study of Streptococci, Monograph. Rockefeller Inst. M. Research, No. 9, p. 81.

zones after a period of from fourteen months to two years. He never noted a transition from the beta to the alpha types or vice versa and concluded that the permanence of the apparently minor characteristics of all the strains studied is surprising. Anthony [6] also found only a slight variability in the hemolytic power of streptococci. It being the consensus of opinion that hemolytic characteristics of streptococci are constant, we felt that very possibly beta hemolytic streptococci could be divided into wide and narrow zone groups. However, this characteristic of a wide or narrow zone of hemolysis was found to vary frequently on subculture. A culture from a single colony of a wide or a narrow zone organism often gave colonies with both wide and narrow zones of hemolysis. This occurred so frequently that we felt that the evidence was not at hand to warrant a subdivision of this group. It would seem that the variation in the extent of hemolysis has to do with an extra cellular streptolysin, a substance which has been demonstrated in cultures of hemolytic streptococci and which is a common property of the members of this group.[7] The amount of hemolysis apparently depends on the amount of streptolysin produced.[8]

A detailed study of the organisms isolated from the excised tonsils of patients with various complaints such as tonsillitis, rheumatism, etc., was made. The findings are recorded in Table 5.

TABLE 5.—Organisms Isolated from Excised Tonsils

	Alpha, per Cent.	Alpha Prime, per Cent.	Beta, per Cent.	All Types Hemolytic Streptococci, per Cent.	Gamma, per Cent.	Pneumococci, per Cent.	Staphylococci and Other Organisms, per Cent.
Tonsillitis	5.0	2.5	76.0	83.0	1.5	5.0	10.0
Mouth breathing	11.0	....	81.0	92.0	....	8.0	....
Frequent colds	8.0	10.0	61.0	79.0	...	10.0	11.0
Otitis media	....	....	100.0	100.0	....	....	....
Rheumatism	18.5	....	54.5	73.0	9.0	9.0	9.0
Pathologic tonsils	8.5	2.5	74.5	85.4	2.1	6.4	6.0
Normal tonsils	14.0	....	14.0	28.0	....	14.0	58.0

Following tonsillitis the predominating organism was a hemolytic streptococcus in 83 per cent., the pneumococcus in 5 per cent. and staphylococci and other heterogenous organisms in 10 per cent. Nonhemolytic organisms predominated in only 1.5 per cent. Of the hemolytic organisms, the beta group were present in 76.3 per cent., the alpha group in 5 per cent. and the alpha prime in 2.5 per cent. As a contrast, tonsils from patients with rheumatism had as the predominating organism beta hemolytic streptococci in only 54.5 per cent., the alpha or *Streptococcus viridans* group in 18.5 per cent. and non-

6. Anthony: Some Characteristics of the Streptococci Found in Scarlet Fever, J. Infect. Dis. **6**:332, 1909.

7. Ruediger, G. F.: The Production and Nature of Streptocolysin, J. A. M. A. **41**:962 (May 12) 1903.

8. Braun, H.: Ueber das Streptolysin, Centralbl. f. Bakteriol. **62**:383, 1912.

hemolytic streptococci, pneumococci and staphylococci in 9 per cent., each. The alpha or *Streptococcus viridans* group was present in a higher percentage in these tonsils than in any other. This coincides well with clinical findings, this type of organism having a close relationship to rheumatism. Patients with otitis media had beta streptococci as a predominating organism in 100 per cent. The ear discharge had the same organism. Mouth breathing patients whose tonsils presented lymphatic hyperplasia harbored hemolytic streptococci in 92 per cent. and pneumococci in 8 per cent. Patients complaining of frequent colds and whose tonsils also presented lymphatic hyperplasia, had as the predominating organism beta hemolytic streptococci in 61 per cent., alpha streptococci in 8 per cent., alpha prime in 10 per cent., pneumococci in 10 per cent. and staphylococcus and other incidental organisms in 11 per cent.

Taking all of the pathologic tonsils as a group, hemolytic streptococci were present in 96.1 per cent. In 85.4 per cent. they were present as the predominating organism. Taking the bacteriologic findings of the 7 per cent. of normal tonsils in this series hemolytic streptococci of all types were present in only 28 per cent., pneumococci in only 14 per cent. and staphylococci and heterogeneous organisms in 58 per cent. Granting that this is too small a number of normal tonsils on which to base conclusions, yet it is apparent that hemolytic streptococci are present in a higher percentage in pathologic tonsils. This high incidence of hemolytic streptococci is in keeping with the findings of Davis,[9] Pilot and Pearlman [10] and others, though it is considerably higher than many other investigators have recorded. The latter, however, in many instances did not use the poured plate method.

We have made cultures from the crypts of excised adenoid tissue in eighty-four instances. The bacteriologic findings followed so closely the findings of the tonsil culture in the same patient that a separate table did not seem warranted. As a rule, the number of organisms in the adenoid tissue was much smaller than in the tonsil.

SUMMARY

Of 218 persons said clinically to need a tonsillectomy, microscopic examination of these tonsils gave evidence of pathology in 93 per cent.; 7 per cent. were normal.

Of these 218 persons, 63 per cent. gave a history of repeated "sore throats," 14 per cent. of frequent colds and were told that they had enlarged tonsils, 8 per cent. complained of mouth breathing, 8 per cent. of rheumatism and 7 per cent. of otitis media.

9. Davis, D. J.: Hemolytic Streptococci, J. A. M. A. **72**:319 (Feb. 1) 1919

10. Pilot, I., and Pearlman, S. J.: Bacteriologic Studies of the Upper Respiratory Passages, J. Infect. Dis. **29**:47, 1921.

Chronic lacunar (crypt) tonsillitis was the most frequent pathologic condition found. It occurred in 42 per cent. Chronic interstitial tonsillitis was present in 21 per cent., chronic peritonsillitis in 6 per cent., gross or microscopic abscess in 10 per cent. and lymphatic hyperplasia as the only change in 14 per cent.

Following repeated attacks of tonsillitis, changes in the tonsils occurred most often about the crypts (42 per cent.). In tonsils from patients with a history of rheumatism, chronic interstitial tonsillitis was present in 66 per cent., chronic peritonsillitis in 33 per cent.

The organisms most frequently isolated from these tonsils were hemolytic streptococci. They were present in 96.1 per cent. of all tonsils and were the predominating organism in 85.4 per cent.

The hemolytic streptococci were further subdivided into alpha, alpha-prime, and beta groups and were present in 25 per cent., 32 per cent. and 86.1 per cent., respectively.

Hemolytic streptococci were present in a much higher percentage (96.1 per cent.) in the pathologic tonsils of our group than in the normal tonsils (28 per cent.).

In nearly every instance the same organisms were isolated from the adenoid tissue as from the tonsils of that patient.

Ring formation, as described by Brown, occurred only with the alpha group of hemolytic streptococci and in 5 per cent. of the total number of the alpha cultures.

Avirulent diphtheria bacilli were isolated but three times in the entire series.

By using both the streaked plate and the poured plate method of culture and comparing the results, we have found the latter much more accurate and satisfactory.

BLOOD PIGMENT METABOLISM AND ITS RELATION TO LIVER FUNCTION *

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The exact mechanism involved in the metabolism of the blood pigments, and the precise relation of the liver to these processes, are still but imperfectly understood. Certain theories, however, concerning blood pigment metabolism are very generally accepted. The pigments of the bile have long been believed to be derivatives, in part at least, of hemoglobin. The work of Eppinger and Charnas,[1] Wilbur and Addis,[2] Robertson,[3] Schneider,[4] Hansmann and Howard,[5] Giffin, Sanford and Szlapka,[6] and others has shown that excessive degrees of red cell destruction are accompanied by an increased elimination of bile pigments. Most observers agree that the liver is the main agent concerned in these metabolic changes. However, the lower bile pigments, principally urobilin and urobilinogen, have been supposed to be formed independently of the liver, by the action of bacteria in the lower intestine, on the bilirubin of the bile. The recent work of Hooper and Whipple [7] on dogs with biliary fistulae has made necessary a modification of previous theories. These investigators question the intestinal production of urobilinogen and urobilin, and the absorption of these pigments from the portal circulation. They suggest that the liver itself is capable of forming these substances. They also prove that bilirubin can be formed in various parts of the body without the intervention of the liver, and conclude that normally the liver may be only one of several agents in the process of hemoglobin metabolism.[8] Furthermore, they produce evidence that red cell destruction, with the consequent liberation of hemoglobin, is not the only factor in the production

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1. Eppinger and Charnas: Arch. f. klin. Med. **78**:387, 1913.
2. Wilbur and Addis: Arch. Int. Med. **13**:325 (March) 1914.
3. Robertson, O. W.: Arch. Int. Med. **15**:1072 (June) 1915.
4. Schneider, J. P.: Arch. Int. Med. **17**:32 (Jan.) 1916.
5. Hansmann and Howard: J. A. M. A. **73**:1262 (Oct. 25) 1919.
6. Giffin, Sanford and Szlapka: Am. J. M. Sc. **182**:562, 1918.
7. Hooper and Whipple: Am. J. Physiol. **40**:332, 1916.
8. Whipple and Hooper: J. Exper. M. **17**:612, 1913.

of bile pigments. Dietary changes[9] and various drugs[10] are able to cause marked alterations in the elimination of pigments in the bile.

The resynthesis of the bile pigments to hemoglobin is a further property usually attributed to the liver. At present it is generally believed that the liver is able in some way to build up the lower pigment fractions into the more complex molecule of hemoglobin. However, evidence is lacking on this point, as well as to the manner in which hemoglobin becomes incorporated in the red corpuscles.

It is the purpose of this paper to present certain evidence regarding the normal and abnormal physiology of blood pigment metabolism in man, and to demonstrate, if possible, a further relation between the liver and such processes.

METHOD

The introduction of "biliary drainage" by Lyon,[11] in 1919, has provided a method by means of which a more systematic clinical study of the duodenum and biliary tract is permitted than was previously possible. Lyon claims that a solution of magnesium sulphate introduced through the duodenal tube relaxes the sphincter of Oddi, and thus a free flow of bile into the duodenum is obtained. Furthermore, Lyon believes, following Meltzer's[12] theory of contrary innervation, that the magnesium sulphate causes a contraction of the gallbladder musculature, with a resulting flow of gallbladder contents into the duodenum. Following the flow of dark gallbladder bile Lyon obtains a flow of lighter colored bile which he believes is derived from the upper biliary radicles and liver. Lyon thus attempts, after the use of magnesium sulphate, to divide the bile drainage into three fractions, "A," "B" and "C," which are supposed to contain respectively bile from the common duct, gallbladder and liver. By a study of the gross color, certain other physical characteristics, the sediment and the bacteriology of these fractions, Lyon believes it possible to diagnose and localize pathology existing in the duodenum and various portions of the biliary tract.

Although Lyon presents clinical data which are quite consistent with his assumptions, nevertheless definite experimental proof that magnesium sulphate, when introduced into the duodenum, causes a contraction of the gallbladder is conspicuously lacking. The exact action of the salt in the duodenum has yet to be determined. There is a certain amount of evidence that the relaxation of the sphincter of the common bile duct may not be accompanied by contraction of the

9. Hooper and Whipple: J. Exper. M. **23**:137, 1916.
10. Bauer and Spiegel: Deutsch. Arch. f. klin. Med. **1**:129, 1919.
11. Lyon, B. B. V.: J. A. M. A. **73**:680 (Sept. 27) 1919.
12. Meltzer, S. J.: Am. J. M. Sc. **153**:469, 1917.

gallbladder walls. Chrohn, Reiss and Radin[13] were unable to prove experimentally the existence of such a contrary innervation, although they apparently believe that the so-called "B" bile contains gallbladder contents. Einhorn[14] claims that various salts produce a flow of "B" bile into the duodenum. This assumption is undoubtedly correct, although magnesium sulphate produces more constant and better results than other salts. Einhorn further concludes from his experiments that the flow of "B" bile is not due to a flow of bile from the gallbladder into the duodenum, but that it is due merely to stimulation of liver cells to increased activity, with a resulting excretion of bile pigment in increased concentration. This conclusion, however, is based on crude quantitative estimations of pigment values, and is probably incorrect. Careful determinations of the bile pigments in a series of fractions taken before and after the use of magnesium sulphate, in a number of cases in which there was known to be no flow of bile possible from the gallbladder, either on account of a previous obstruction of the cystic duct, or on account of a previous cholecystectomy, tend, by comparison with a series of normal cases, to disprove Einhorn's conclusions. Further reference will be made to these determinations in a later portion of this paper.

For practical consideration, in spite of the fact that experimental work is still lacking as to the exact source of the "B" bile, it seems expedient to assume that it is made up, in part, of bile from the gallbladder. It is highly probable that a solution of magnesium sulphate, when instilled into the duodenum, accomplishes two things. First, it relaxes the sphincter of the common bile duct and causes a free flow of bile into the duodenum. Second, it probably causes a slight contraction of the gallbladder musculature, with the result that some bile from that organ is mixed in with the bile proceeding down the common duct. The result is a mixture of duct, liver and gallbladder bile.

Bile pigments in the duodenal contents have received but slight attention. Schneider,[4] in 1916, and subsequently others, have made quantitative estimates of the bile pigments of the duodenal contents, using a spectroscopic method. These observers concluded that in those cases in which it is generally considered that increased blood destruction is taking place the excretion of bile pigments is also increased. Schneider attempted to show a definite relation between the level of the bile pigments in the duodenum and the actual degree of hemolysis obtaining in any given case. Eppinger, Wilbur and Addis, Robertson, and others had previously obtained high pigment value in similar instances, by making bile pigment determinations of the stools. Haus-

13. Crohn, Reiss and Radin: J. A. M. A. **76**:1567 (June 4) 1921.
14. Einhorn, M.: New York M. J. **113**:313, 1921.

mann and Howard compared the method of estimating the pigments in the stools with the estimations based on the duodenal contents. Figures obtained by either method gave relatively high pigment values in those cases in which increased hemolysis was apparently taking place. Their findings were confirmatory of results obtained by Wilbur and Addis, but Hansmann and Howard do not believe that estimates based on duodenal contents run exactly parallel to those obtained from stool examination. Hansmann and Howard, however, believe the stool method to be more correct. Examination of duodenal contents seems, nevertheless, the more logical method of study. Such a method allows a study of the bile before the pigments have become diminished or altered by action of the intestinal bacteria. Furthermore, analyses based on estimation of bile pigments in the duodenal contents are performed more easily than similar determinations on the stools and are not subject to errors due to such variable factors as constipation, diarrhea, etc.

Lyon's method of obtaining a continuous flow of bile offers a distinct advantage over the method employed by Schneider and others, in which determinations were based entirely on single specimens. Single specimens, in the present studies, were subject to the greatest variations, on account of the intermittent flow of bile from the common bile duct, and on account of various other factors such as salivary, gastric and pancreatic secretions, which introduced errors by causing a dilution of the pigment content in the duodenum.

The technic used in this series of cases consisted in the introduction of the duodenal tube, and the collection by siphonage of duodenal contents in six fractions. These six fractions were collected over fifteen minute intervals, two fractions being taken from the fasting duodenum prior to the introduction of a 33 per cent. solution of magnesium sulphate, and four immediately following the use of the salt. The entire collection of duodenal contents thus covered a period of about one hour and a half.

The duodenal tube was retained over a period of from two to three hours in the majority of cases, depending on the length of time necessary for the tip to reach the duodenum. The exact location of the tube in the duodenum was determined by fluoroscopic examination in the majority of cases. Atropin sulphate, given before the introduction of the tube, practically eliminated any undue flow of saliva. The use of magnesium sulphate provided a nearly continuous and concentrated flow of bile into the duodenum and minimized the errors caused by the flow of gastric and pancreatic secretions. The objection might be raised that atropin might of itself introduce an error, by causing individual variations in the output of bile. Atropin does cause a slight

diminution in the excretion of bile by the liver cells.[10] This diminution is, however, very slight and in the cases studied the administration of the drug caused no appreciable effect in the flow of bile into the duodenum.

Bile pigments were estimated by Wilbur and Addis' method of spectroscopic examination, for each of the six fractions. This method consists essentially in dissolving the urobilinogen, urobilin and other lower bile pigments in a saturated alcoholic solution of zinc acetate, and then determining the pigment content by the spectroscope. The number of dilutions necessary to cause the disappearance of the characteristic absorption bands of the individual pigment was taken as the reading for any particular fraction, and a curve was plotted from the values obtained. Values of urobilinogen and urobilin were added together, and the total taken as the pigment value of the fraction. An attempt was also made to quantitate the bilirubin values of the duodenal contents, by the method described by Hooper and Whipple in their work on dogs, but it was found impossible to obtain consistent readings on human bile owing to the conversion of bilirubin in some of the fractions into bilicyanin. The color obtained by this method, by treating the bile with acid alcohol, was in some instances the characteristic blue-green desired and could be read against a standard solution of copper sulphate as described by these authors. In the majority of cases, however, the color ranged from a decided green to a dark blue, and occasionally the entire series of fractions was intensely purple owing to the presence of bilicyanin. Similar observations on animals have been made recently by Rous and McMaster.[15] Bilirubin figures, when obtained, ran approximately parallel to those of urobilin and urobilinogen. The actual dilution figures obtained from spectroscopic examination were not multiplied by a constant, as done by Wilbur and Addis in their original work, and later by Schneider, as there seemed no advantage to be gained by this purely artificial procedure. The curves shown on the accompanying charts, therefore, represent actual dilution values of urobilinogen plus urobilin.

The method of fractional analysis, I believe, offers distinct advantages over the method of studying only a single specimen. It provides a free flow of bile into the duodenum over a considerable period of time, and permits the taking of an average figure as well as the value of individual fractions. In this way it is possible to make a comparative study of the different fractions, and to obtain a much more exact picture of the level of bile pigments than can be gained from any single observation. Even such a method, however, is open to error,

15. Rous and McMaster: J. Exper. M. **34**:47, 1921.

and I wish only to point out its advantages and to emphasize its relative accuracy.

In addition to an estimation of the bile pigment in the duodenal contents, Blankenhorn's [16] method for studying the bilirubin content of the blood plasma was employed. This method consists essentially in a comparison of the yellow color of oxalated plasma with distilled water. Dilutions of the plasma with water are made until the yellow color has disappeared. The number of dilutions necessary to remove the yellow color of the plasma are taken as the approximate bilirubin content of the specimen. Normally between fifteen and twenty dilutions give the desired end-point.

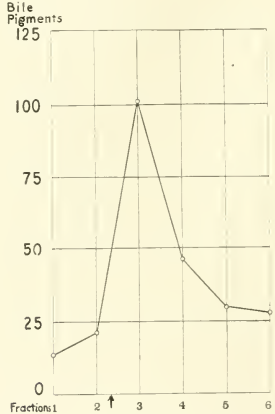

Chart 1.—Duodenal pigments in normal individuals. In this, and subsequent charts, points along the ordinates represent dilution values of the bile pigments, urobilin and urobilinogen. Points on the abscissae represent separate fractions of duodenal contents collected over fifteen minute intervals. The above curve is identical with the "normal" curves given in Charts 2, 3, 4 and 5, although in each case the scale varies. The arrow indicates the administration of 50 c.c. of a 33 per cent. solution of magnesium sulphate.

Bile Pigments in the Duodenal Contents in Normals.—As a basis for comparison with pathologic cases, observations on the pigment values in the duodenal contents of eight normal individuals were made

16. Blankenhorn, M. S.: Arch. Int. Med. **19**:344 (March) 1917.

and an average curve drawn from the results obtained. As shown in Chart 1, the average reading of all the six fractions in this series of normal cases was forty dilution units, with a maximum variation from this figure of ten units. The peak of the curve came shortly after the administration of magnesium sulphate and represents Lyon's "B" bile. The average pigment value of the peak of the curve was one hundred dilution units, with an individual variation up to fifty units. It will be seen that the variation from the average figures is a wide one, both in individual fractions and in the case of the general averages obtained from the total fractional estimations. These variations occurred in spite of the fact that duodenal contents in all cases were taken under similar conditions as regards the fasting state, the time at which the duodenal contents were collected and general freedom from symptoms. This point should be emphasized, inasmuch as previous investigators have inferred that the individual variation among normal persons is only a slight one. Furthermore, it is noticeable that there was a wide variation between individual fractions in the same normal person, even before the administration of magnesium sulphate. Bauer and Spiegel [14] have noticed similar variations in normal individuals in estimating the bilirubin content of the blood plasma. A further discrepancy may be observed between the pigment values in normals as given by Schneider and the values obtained before the use of magnesium sulphate in this series of determinations. My figures for normal individuals are relatively higher than those of Schneider. His average normal figure is about five dilution units. The results obtained from my series of normals, in the fractions that are comparable to his analyses, average about 8.5 dilution units. The difference between the two figures may be explained (1) by individual differences in obtaining end-points by spectroscopic examination, or (2) by the fact that specimens of duodenal contents were taken in this series after waiting a relatively long time following the introduction of the tube. Such a wait would insure a better flow of bile. In either event the differences are purely relative, and conclusions based on examinations of similar cases in both series are in the main identical.

In cases such as gastric ulcer, and so forth, in which there was no apparent cause for abnormal pigment values, there was essentially no deviation from the normal range.

Evidence of a Flow of Gallbladder Bile Following the Use of Magnesium Sulphate.—Following the establishment of the normal figures a series of cases was studied in which there was absolute obstruction of the cystic duct, as proved at operation, or in which the gallbladder had previously been removed. Obviously, there could be no flow of gallbladder or "B" bile in these cases and a comparison of results

obtained in these cases with the normal figures already given showed no characteristic peak after the administration of magnesium sulphate. On the other hand, there was only a moderate rise in pigment values after giving the salt, as shown in Chart 2. This rise can be explained entirely by a relaxation of the sphincter of Oddi, with a resulting free flow of undiluted bile into the duodenum.

In another series of cases in which there was definite gallbladder pathology without obstruction, the fractions taken immediately after the administration of magnesium sulphate, or in other words, those fractions taken at a time corresponding to the peak of the pigment curve, were the only ones to show certain cellular and crystalline ele-

Chart 2.—Duodenal pigments in normal individuals as compared with pigments in patients with no flow of gallbladder bile. Normal pigment values o—o—o—o. Values with no gallbladder flow • — • — • — •

ments believed to be characteristic of gallbladder contents. The similarity of the sediments in these fractions to those actually obtained from the gallbladders at the time of operation was striking. The close correspondence between these sediment findings, their occurrence coincident with the peak of the pigment curves, and the absence of a characteristic pigment curve in cases where there was known to be no flow of bile from the gallbladders all confirm the assumption that the so-called "B" bile consists, at least in part, of actual gallbladder contents. The importance of this assumption will be discussed in a later portion of the paper in a study of cases in which there was known gallbladder pathology.

Relation of Blood Destruction to Bile Pigment Elimination.—It was desirable to establish, if possible, further definite evidence that there was a distinct relation between the amount of hemolysis going on in the body, and the level of the bile pigments. Observations were made in two cases of paroxysmal hemoglobinuria which have been reported in a separate paper.[17] In these cases immersion of the extremities in icewater caused immediate and marked intravascular hemolysis. The plasma, duodenal contents and urine were examined for changes in pigment values during the course of the observations, which covered a period of about twenty-two hours. There was no important change in urinary pigments inasmuch as the attacks produced were not severe enough to cause any but the slightest traces of hemoglobin to appear in the urine. The hemoglobinemia was immediate and intense and was accompanied in one case by a drop in the red count of over 800,000 cells per c.mm. Subsequently the hemoglobin content of the plasma rapidly diminished, with an accompanying marked increase in the bilirubin content. This increase in bile pigment in the plasma continued until it reached its height at a point coinciding with the disappearance of hemoglobin from the plasma. It then gradually dropped, reaching normal at the end of about eighteen hours. Coincident with the peak of the bilirubin content of the plasma, the duodenal pigments rose rapidly, reaching a level about six to eight times the normal level in about three hours. These pigments did not return to the normal level until after eighteen to twenty hours. These results rather definitely confirmed the generally accepted theory that increased blood destruction is accompanied by increased elimination of bile pigments. Furthermore, it seemed safe to assume from the above observations that the bulk of the hemoglobin liberated into the circulation as a result of any hemolytic process is rapidly taken care of within the liver and broken down into lower bile pigments. Although other organs and tissues possess a similar property of carrying on the metabolism of blood pigments, under normal conditions the liver probably carries on the greater part of this important chemical process.

Bile Pigments in Various Types of Anemia.—With the clear recognition that increased blood destruction is accompanied by an increased elimination of bile pigments in the plasma and bile, as demonstrated by the above observations on paroxysmal hemoglobinuria, and as brought out by numerous investigators, a series of cases of various types of anemia was studied. This series included cases of anemia due to severe hemorrhage, lowered bone-marrow activity, pernicious anemia, hemolytic jaundice, malaria, and so forth. A somewhat similar series had been studied by Schneider, and later by Giffin, Sanford and Szlapka.

17. Jones, C. M., and Jones, B. B.: Arch. Int. Med. **29**:669 (May) 1922.

I wished, however, to obtain a comparative set of figures by the fractional method of duodenal analysis, and to attempt a more detailed study of the abnormal physiology occurring in these diseases. The cases studied fell roughly into two groups: (1) cases in which increased blood destruction is believed not to be present, or at least is not an important feature, and (2) cases in which it is generally believed that abnormal blood destruction is an important feature of the disease process.

As examples of the first type of cases a group of patients was studied in which the anemia was due entirely to blood loss. The anemia was due in two cases to hemorrhage from duodenal ulcers, in one to renal hemorrhage, in one to a series of attacks of paroxysmal hemoglobinuria, and in one to prolonged menorrhagia. The case of paroxysmal hemoglobinuria had been free from attacks for more than a week, so that there was no complicating factor of recent hemolysis. In none of these cases was there any evidence of abnormal red cell destruction. As was to be expected, the actual pigment values were all under the normal average (Table 1), indicating possibly an attempt

TABLE 1.—BILE PIGMENTS IN ANEMIA FROM BLOOD LOSS

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
20	28	35	12	65	4.0
21	7	12	11	23	2.6
22	36	72	10	28	2.5
23	21	30	9	80	3.7
24	13	20	18	50	3.2

on the part of the body to conserve hemoglobin. "Relative" figures, based on the actual pigment readings in the duodenal contents and the percentage of red cells in relation to normal, with one exception (Case 22), were also within or below the normal range. The single case referred to, with high "relative" figures, had a profound anemia, and the explanation for the high figures may lie in the fact that the liver was improperly functioning on account of the anemia itself.

"Relative" figures were obtained on the following assumption: The pigment values in the duodenal contents are in a sense absolute values, in that these values do not take into consideration the amount of circulating hemoglobin. Obviously, even if the pigment values in the duodenal contents are the same, there is greater relative blood destruction in a case with a low red count and hemoglobin than in a case with a normal red count and hemoglobin. It is interesting, therefore, to attempt roughly to correct these figures of pigment values to the same standard of circulating hemoglobin. Thus it is possible to ascertain the relative intensity of the blood destruction. It does not of

course necessarily follow that the same relative intensity of blood destruction would obtain if the red corpuscles and hemoglobin were at the normal level. Because it was simpler to carry out this correction on the basis of the numerical differences of red corpuscles, this procedure was adopted, rather than correction by utilization of hemoglobin variations, which theoretically is more logical. Relative figures were obtained by dividing the pigment values in the duodenal contents by the percentage of normal which the red count of the individual case showed, and then multiplying by 100. Thus, for example, a patient with a count of 3,000,000 red corpuscles per c.mm., and a pigment average of 100 units, other things being equal, would theoretically be destroying one-half the percentage of total red cells destroyed by a patient with a count of 1,500,000 red corpuscles per c.mm., and a pigment average also of 100 dilution units.

TABLE 2.—BILE PIGMENTS IN A CASE OF APLASTIC ANEMIA

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
25	28	108	11	26	1.3

A single case of true aplastic anemia (Table 2) was studied, which also showed actual bile pigment values well below the normal. However, the "relative" figures were high. Inasmuch as in this case also the anemia was extreme, the explanation of the high "relative" figures is possibly the same as that given for Case 22 of the preceding series, namely, the effect on liver function of the profound anemia. A more logical explanation may possibly be that, with an extremely low level of red corpuscles, and with practically no new blood formation, the few cells in the circulation undergo more rapid dissolution than normal on account of the undue work put on them.

TABLE 3.—BILE PIGMENTS IN A CASE OF POLYCYTHEMIA VERA

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
8	54	32	24	155	8.0

One case of polycythemia vera was studied. The patient had a red cell count of 8,000,000 cells per c.mm., and a hemoglobin content of 155 per cent. The actual pigment values averaged only slightly above normal (Table 3), but the "relative" figures were below the normal average. In spite of the enormous increase in the number of red cor-

puscles the process of blood destruction in this case was apparently normal, or even relatively below normal.

In contrast to the above cases, and as an instance of disease in which it is generally conceded that there exists an apparently high degree of blood destruction, a series of nineteen cases of pernicious anemia was studied. Other observers have pointed out that in pernicious anemia there is a marked increase in the bile pigments in the blood, duodenal contents, stools and urine.

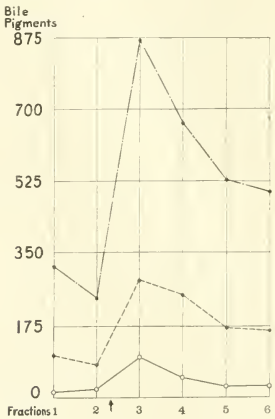

Chart 3.—Duodenal pigments in pernicious anemia. "Relative" pigment values —·—·—·—·—. Actual pigment values - - - - - - - -. Normal pigment values o-o-o-o-o-o.

Observations made in this series of cases entirely confirmed the results of previous investigators. There was a high level of bile pigments both in the blood plasma and in the duodenal contents. The average increase in duodenal pigments over normal was more than 500 per cent.; the highest averages were nine times, and the lowest twice the normal figures. Plasma bilirubin was, in the average, about four times normal; the highest figure was about eight times the normal, while the lowest was about twice normal. Based on average figures, therefore, the bile pigment content of the blood and duodenal contents ran about parallel, but in individual cases there was marked discrep-

ancy between the two values. This difference, in individual cases, between the pigment content of the plasma and the pigment values of the duodenal contents, is perhaps significant, and suggests some interference with liver function—a point that will be discussed later.

A question of considerable interest to be determined in studying these cases was whether the level of bile pigments in the duodenal contents corresponded with the actual clinical condition of the patients. Weakness, elevation of temperature, icterus, level of hemoglobin and red cells, etc., supply the clinician with evidence for comparison between individual patients. The condition of the individual patient theoretically depends, in large measure, on the relative severity of the hemolytic process and on the relative degree of blood-forming activity. Thus, a patient who is subjectively sick, and who presents the typical features of a relapse, usually gives evidence of a marked predominance of blood destruction over blood formation. A patient, one the other hand, with few subjective symptoms, a high hemoglobin content, usually shows evidence of little blood destruction and, on the contrary, a satisfactory blood formation. In spite of the theory that varying degrees of blood destruction are accompanied by corresponding variations in the level of the bile pigments, it is evident that changes in blood formation may modify the clinical picture to such an extent that the level of the bile pigments in the duodenal contents, although measuring the amount of blood destruction taking place, will not reflect the patient's clinical condition. High pigment values might, therefore, be obtained, even in the presence of a severe degree of blood destruction, without correspondingly severe clinical symptoms. Furthermore, any alteration of liver activity should modify the bile pigment excretion, both in the bile and in the blood plasma.

These theoretical considerations were well sustained by the findings. Examination of the figures obtained in the nineteen cases of pernicious anemia showed that the actual pigment values corresponded only in a very rough way to the clinical condition of the patient. Patients whose duodenal pigments were very high frequently were clinically less sick than those who showed relatively low bile pigment estimations, and vice versa. A second set of figures, however, did correspond closely to the condition of the individual patient, both as regarded his clinical condition and as concerned the actual physiologic processes taking place. These second figures are the "relative" figures already referred to, and were obtained by dividing the actual pigment readings by the percentage of red cells of the particular case. Such a modification of the actual pigment readings gave a close approximation to the clinical state of the patient, and in addition appeared to serve as a much clearer index of the relation of blood destruction to blood formation. Actually,

patients with high "relative" figures were sick, and presented the clinical findings of severe blood destruction—elevation of temperature, jaundice, etc., that are typical of a severe relapse. Those patients whose "relative" figures were only moderately high, on the contrary, were free from the more marked symptoms, while patients with "relative" pigment values at a still lower level were in a well marked remission. The average level of the "relative" figures, however, was about three times that of the actual readings, and indicates clearly the severity of the disease process. Furthermore, a comparison of the actual and "relative" values in any individual case provided a fair estimate of the balance between blood destruction and blood formation. When the two sets of figures were not far apart it would appear that the two processes were taking place at about equal rates; when the "relative"

TABLE 4.—Bile Pigments in Nineteen Cases of Pernicious Anemia

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
1	185	1,540	96	25	0.6
2	831	1,570	56	42	1.6
3	252	1,200	56	40	1.6
4	209	858	64	37	1.2
5	182	847	40	31	1.2
6	253	842	140	46	1.4
7	192	801	32	35	1.2
8	141	748	90	27	0.9
9	165	717	64	35	1.2
10	99	596	90	27	0.8
11	194	574	39	50	1.7
12	164	512	90	45	1.7
13	300	500	100	94	3.5
14	77	496	32	75	3.6
15	173	295	65	45	2.7
16	133	242	30	70	2.5
17	122	200	50	55	2.2
18	117	278	32	60	2.1
19	83	112	80	85	3.7
Average	194	682	66	48	1.8

figure was much higher than the actual reading it would seem that blood destruction was exceedingly active, and vice versa. Table 4 illustrates these points. The actual readings in the first column and the "relative" figures in the second column are both obtained by averaging the total pigment values of the six fractions obtained during duodenal drainage. The cases are arranged in order of magnitude of the "relative" figures and, as noted above, this order closely approximated the severity of the patient's clinical condition. Case 1, for example, was a patient in a very severe relapse, while Case 19 was a patient in a well marked remission with almost complete freedom from symptoms. Chart 3 illustrates the marked increase in big pigment elimination in these cases over the normal level, and further emphasizes the difference between the actual and "relative" findings.

Mention has already been made that in these cases of pernicious anemia the bile pigment in the plasma did not always exactly parallel the pigment content in the bile, although it was always well above normal, as previously shown by Blankenhorn. Such a finding suggests that this failure of the plasma bilirubin to parallel the bile pigments in the duodenal contents may be due to an alteration in hepatic function. It is pertinent, at this point, to call attention to a question only briefly noted in the literature. The average level of bile pigments in the duodenal contents in this series of cases of pernicious anemia is by actual reading 194 dilution units, or about five times the normal values.

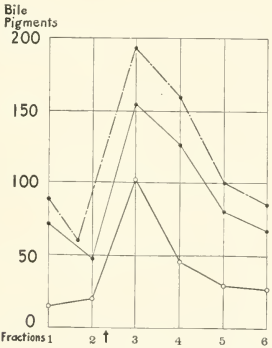

Chart 4.—Duodenal pigments in liver disease. "Relative" pigment values — — · — — · —. Actual pigment values ————. Normal pigment values o-o-o-o-o-o.

Individual cases went as high as eight to nine times the normal level. Such an increase over normal has previously been considered as due entirely to increased blood destruction, with excessive liberation of hemoglobin. Undoubtedly some part of the excess of bile pigments is due to the products of increased red cell destruction, but there is in addition a second factor which must be taken into account. Comparison with the observations on paroxysmal hemoglobinuria already mentioned makes this clear. One of the artificially produced attacks of hemoglobinemia was accompanied by a lowering of the red cell count by as much as 850,000 cells per c.mm. The hemoglobin liberated into the circulation was presumably derived solely from the destruction of

red cells, a destruction which approximated more than one-tenth of the total number of red cells, as measured by a routine red count. This excessive destruction of blood was followed shortly afterward by a rise in the bile pigments in the duodenum to a level of about 300 dilution units, or between six and eight times the normal figures. In paroxysmal hemoglobinuria there is no known evidence of any liver injury. Deranged liver function, therefore, need not be considered in paroxysmal hemoglobinuria, and any increase in bile pigments can safely be attributed essentially to increased blood destruction. In this example of pure hemolysis, uncomplicated by any other factors, a drop in the red cell count of 850,000 was accompanied by a rise in duodenal pigments to a level of about 300 dilution units. This level of bile pigments was well above the average of the entire series, and was but little under the level found in the most severe cases of pernicious anemia. It is difficult to conceive, even in the most severe cases of pernicious anemia, or in any other so-called hemolytic disease, that there is a constant rate

TABLE 5.—BILE PIGMENTS IN OTHER "HEMOLYTIC" DISEASES

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
Malaria:					
27	95	120	25	45	3.9
28	182	284	128	38	3.2
Hemolytic jaundice:					
29	228	251	120	70	4.6
30	129	139	109	30	1.5
31	152	225	65	40	1.2
32	108	99	45	70	5.5

of blood destruction going on so rapidly as to cause in a few minutes the dissolution of more than one-tenth of the total blood corpuscles in the body. A process causing such a degree of blood destruction, in the absence of a correspondingly rapid degree of blood formation, ought to result in complete exsanguination in a very short space of time. A second factor seems necessary to help explain the high level of bile pigments found in pernicious anemia. Ashby [18] has recently reached a somewhat similar conclusion. This second factor, I believe, lies in a marked impairment of liver function. Such an assumption, although suggested by Hooper and Whipple as a result of their work on dogs, has not been made as a result of observations in man.

In addition to the above cases of pernicious anemia, a number of cases were studied in which it is also usually agreed that there exists an abnormally high degree of blood destruction. This series contained two cases of malaria and four cases of acquired hemolytic jaundice. One of the latter had previously had his spleen removed. All of these

18. Ashby, W.: J. Exper. M. **34**:147, 1921.

cases showed high pigment values (Table 5) entirely comparable with those observed in pernicious anemia. As in the former cases, the "relative" figures gave the more accurate picture, and closely paralleled the clinical condition of the patients. In these cases, also, as in pernicious anemia, it seems reasonable to assume that there must be a second factor to account for the extremely high bile pigment values obtained. Blood destruction alone could hardly account for the increased bile pigment elimination. In two of the cases of acquired hemolytic jaundice in this series (Table 5, Cases 30 and 31) the liver enlargement was so marked indeed as to dominate the entire clinical

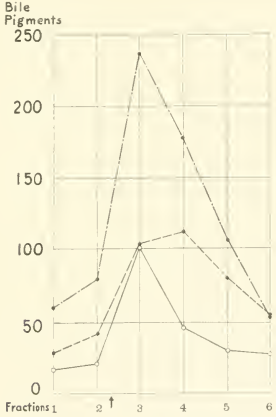

Chart 5.—Duodenal pigments in gallbladder disease. Pigment values in cholecystitis —·—·—·—. Pigment values in cholelithiasis - - - - - -. Normal pigment values o-o-o-o-o-o-o.

picture and to suggest definitely that a hemolytic process was not responsible for the entire condition. Impairment of liver function in these cases would also seem to be the logical additional factor to be considered, and such an assumption would seem to be even more logical in the cases of hemolytic jaundice than in the cases of pernicious anemia.

Bile Pigments and Impaired Liver Function.—In the type of cases already studied, in which the process of abnormal blood destruction

has been of long duration, it is well recognized that clinically, and at post-mortem examination, it is commonly possible to demonstrate liver pathology. Forty per cent of cases of pernicious anemia have during life palpable livers,[19] which at autopsy show a certain amount of fatty infiltration and deposits of iron containing pigment. Cases of hemolytic jaundice usually, and malaria not infrequently, present the clinical evidence of liver enlargement. The suggestion has already been made that in the above type of disease the abnormally high elimination of bile pigments may be due in part to an alteration of liver function. It is furthermore reasonable to assume, even in the absence of any clinical signs of liver derangement, that there exists a marked alteration in liver function, due merely to the presence of a severe anemia. Such an assumption finds support in the well-recognized fact that in cases of severe anemia the kidneys may show evidence of definite alteration of function by renal function tests and by the presence of albumin in the urine. With improvement in the anemia, the renal function also improves. It is, therefore, appropriate to turn from a consideration of the so-called hemolytic diseases, in which abnormal blood destruction and liver damage may be accompanying factors, to the study of a series of cases in which it is evident that the liver is the primary seat of disease, and in which there is considered to be little or no question of abnormal hemolysis.

A series of eighteen cases was examined, all of which presented clinical evidence of moderate to severe liver damage. This group included cases of carcinoma of the liver, cirrhosis, either alcoholic or syphilitic, hepatitis or cirrhosis due to a local or general infectious process, and Banti's disease. These types of cases are not usually considered to have any important degree of increased blood destruction, with the possible exception of Banti's disease. These cases, therefore, were of interest as a basis for studying the functional capacity of the liver, in terms of hemoglobin and bile pigment metabolism. The findings are tabulated and shown in Table 6 and Chart 4.

Six of the eighteen patients were clinically jaundiced, and nine more showed a "potential" jaundice. By the term "potential" jaundice is meant a condition in which the bilirubin content of the blood plasma is abnormally high but not sufficiently high to cause tissue icterus. As has been shown by Blankenhorn,[16] in certain chronic diseases in which there is a continual abnormal elimination of bilirubin, the concentration of this pigment in the blood plasma may be many times normal without causing tissue icterus. In spite of the presence of jaundice, either actual or "potential," in fifteen out of these eighteen cases the output of bile pigments into the duodenum was above normal. In the

19. Minot, G. R.: Oxford Medicine, **2**:623.

remaining three cases, the concentration of the bile pigments in the bile was within normal limits. Although some clinical abnormality in the liver was demonstrable, the abnormality may not have progressed far enough to overstep the large factor of safety present in this organ.

In fifteen out of eighteen cases, therefore, the liver, even when almost entirely invaded by foreign tissue, tended not to eliminate a decreased amount of bile pigment into the duodenum, but on the contrary to put out highly concentrated bile, as measured by pigment content. The actual pigment readings in the series of eighteen cases of liver disease showed an average curve (Chart 4), the values of which were over twice the normal level. From these facts alone, therefore, it is evident that the jaundice present in these cases was not at all obstructive in nature, at least in the usual interpretation, namely a diminished output of bile into the duodenum with accumulation of the residue in the blood and tissues.

Neither was the jaundice strictly hematogenous. The abnormal elimination of bile pigments, both in the bile and plasma, can not be said to be due to an increased amount of blood destruction. The average red cell count of the entire series was 3,900,000 corpuscles per c.mm., and one of the more severe of the cases, one of advanced carcinoma of the liver, showed a red count as high as 6,000,000 per c.mm. The red cells were markedly achromic, and the average hemoglobin content of the blood was approximately 60 per cent. The average color index of the cases was only 0.75, in contrast to the average index of 1.5 observed in the cases of pernicious anemia. In the stained smear the red cells showed only achromia, with slight variations in size and shape. There was lacking microscopic evidence of increased blood destruction; namely, the presence of microcytes or fragmentation of the red cells. Active blood formation, commonly present in the face of active blood destruction, was not seen, at least as represented by noteworthy changes in the number of young red cells. The usual conception of these types of liver disturbance, furthermore, does not associate them with increased blood destruction. Banti's disease, by some clinicians, is occasionally associated with abnormal destruction of the red corpuscles. The commonly accepted view, however, is that expressed by Krumbhaar,[20] who states that blood destruction is not the important element in this disease. It seems fair to assume, therefore, from the generally accepted views, that in these cases under discussion blood destruction was not importantly increased, and that the jaundice is not hematogenous in nature.

In the literature scant reference has been made to the bile pigment excretion in the above type of case. The general statement has usually

20. Krumbhaar, E. B.: Nelson's Loose Leaf Living Medicine, **4**:37.

been made that secondary anemias, in contrast to primary anemias, are accompanied by a diminished elimination of bile pigments. It is clearly evident, however, from the results charted in Table 6, that cases of anemia associated with liver disturbance are usually accompanied by increased bile pigment excretion. The so-called secondary anemias, if uncomplicated by liver disturbance, undoubtedly yield low pigment readings. When, however, in the course of such a secondary anemia the underlying cause affects the liver the entire picture of bile pigment excretion is changed, and instead of a low pigment elimination in the bile and plasma, there follows a complete reversion of the physiological processes involved, and the bile pigments reach a new and abnormally high level.

TABLE 6.—BILE PIGMENTS IN CASES OF LIVER DISEASE

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
Cancer:					
50.	173	144	40	85	6.0
51.	144	300	80	68	3.6
52.	98	213	15	25	2.3
53.	57	54	40	80	5.3
Cirrhosis (alcoholic):					
54*.	151	189	30	65	4.0
55.	64	60	30	80	5.3
56.	36	...	50	75	
Cirrhosis (syphilitic):					
57*.	77	96	140	65	3.9
58.	41	51	66	40	1.2
Hepatitis (infectious):					
60.	98	...	28	75	
61.	115	174	25	45	3.3
62*.	78	87	100	70	4.5
63 (typhoid).	81	96	10	..	4.2
64.	30	35	15	65	4.3
65*.	30	35	250	67	4.2
70*.	248	248	72	72	4.8
Hepatitis (toxic):					
66.	58	55	30	80	5.3
Banti's disease:					
67*.	220	280	150	65	4.1
Average.	101	114	59	66	4.1

* Clinically jaundiced.

It has already been shown that the jaundice occurring in such cases is neither strictly obstructive nor hematogenous in nature, in spite of the fact that in all the cases the liver parenchyma was severely damaged. It is well known that the liver, like the other organs, has a large factor of safety, as regards all of its functions. Exact information as to the extent of this measure of safety has never been determined in man. McMaster and Rous [21] have recently shown that the bile ducts from three-quarters of the liver substance can be obstructed in dogs and monkeys without the development of any clinical evidence of pigment or cholate accumulation in the organism. They also

21. McMaster and Rous: J. Exper. M. **33**:731, 1921.

showed that in the dog nineteen-twentieths of the liver substance can be placed in a condition of stasis, without the occurrence of tissue icterus such as regularly follows total obstruction in this animal. In their experiments, they found that invariably a local obstruction resulted sooner or later in atrophy of the affected tissue, with compensatory hypertrophy elsewhere. Their conclusions are of particular interest in the present discussion: "the clinical jaundice encountered in association with local liver lesions should be viewed, not as the result of local bile absorption, but as due to a general injury to the hepatic parenchyma or ducts, or to blood destruction." Such injury with its resulting hypertrophy, would accordingly result in functional changes, and bile pigment excretion would accordingly be modified. The nature of the cause of this functional disturbance is apparently not specific. An examination of the accompanying table will show that in no particular group of liver conditions was there any predominance of high pigment values. Bile pigment excretion was apparently influenced neither by the nature of the process, nor by the amount of the anemia. The mechanism is probably similar in all the cases, and the degree of derangement of hepatic function is solely dependent on the extent and rapidity of the disease process.

There remains, then, to discuss the actual nature of this alteration in liver function. As already noted, there was a marked increase in the actual amount of bile pigments eliminated by the liver. In the absence of any abnormal process of blood destruction the source of the excessive amounts of bile pigments is still to be determined. Changes in diet, according to Hooper and Whipple,[9] can cause marked alterations in bile pigment elimination in animals. Such a factor, however, can readily be excluded in the present series. The most logical explanation seems to be the following: Under normal conditions the liver is the principal agent in the metabolism of hemoglobin set free during the normal processes of red cell destruction. This pigment metabolism involves the breakdown into less complex molecules, through bilirubin and biliverdin, to the lower derivatives, urobilinogen and urobilin. The formation of bilirubin from hemoglobin may take place in the blood vessels and tissues without any intervention on the part of the liver, and similarly, urobilin is undoubtedly formed in the intestine by the action of bacteria on bilirubin. It is highly probable, however, that the liver itself is capable of breaking down the bilirubin into urobilin, without the intervention of the intestine. The observations already mentioned made on cases of paroxysmal hemoglobinuria suggest such a possibility. Furthermore, the liver has long been thought capable of resynthesizing hemoglobin from the lower bile pigments by building them up to more complex molecules and combining them with the iron

known to be retained by the liver. Such a process of resynthesis is entirely analagous to the general physiologic properties of all human cells and is not necessarily much more complicated than the formation of urea or glycogen from lower chemical constituents. The process of breaking down hemoglobin into its lower derivatives is, however, probably a less difficult matter than the subsequent resynthesis of hemoglobin from bile pigments. The latter function would perhaps logically be the first to be altered or lost. With the failure of the normal resynthesis of hemoglobin from bile pigments the unaltered bile pigments would then form an excess and would be eliminated as such in the bile.

The findings in this group of cases seem to confirm this supposition. The loss of resynthesizing power in a damaged liver would, of course, be only partial. The lowered formation of hemoglobin ought eventually to be reflected in a diminished hemoglobin content of the red cells with resulting low color index and achromia. In all these cases marked achromia of the red cells and a low color index occurred. The hemoglobin averaged 66 per cent., and the red count averaged 4,100,000 per c.mm. This slight diminution was possibly the result of a gradual slowing up of bone marrow activity. Such findings may be regarded as probable evidence of a diminished production of hemoglobin. That portion of the bile pigments not resynthesized into hemoglobin would be excreted as such, and would account for the increased elimination of bile pigments, even in the face of normal blood destruction. That such a theory further corresponds with the actual findings in the individual cases is attested by the fact that in the majority of cases showing the greatest reduction of hemoglobin content there was a proportionally high level of bile pigments in the duodenum. One case, for example, with a hemoglobin content of 40 per cent. and a color index of 0.35, showed a bile pigment elimination in the bile of over four times the normal.

The above theory would satisfactorily account for the appearance of jaundice and lowered hemoglobin content so frequently noticed in the course of acute infections such as pneumonia, typhoid, scarlet fever, septicemias, etc. In such conditions the infection, or the accompaning toxemia, may be assumed to cause a temporary alteration of the liver function, with resulting alterations in hemoglobin metabolism. The icterus frequently accompanying severely decompensated heart disease may also be explained on the basis of altered liver function.

In a severely damaged liver not only should there be an increase in the actual amount of bile pigments eliminated, but the relation of the various pigment elements in the bile should be distinctly altered. Those pigments most easily formed ought to be excreted at once instead of

being completely broken down to the lower forms. In confirmation is the frequent occurrence of excessive amounts of intermediate bile pigments—cholecyanin and urobilinogen—found in the duodenal contents in this series of cases of excessive red cell destruction, and those with liver disease. Schneider and others have already noted the presence of large amounts of urobilinogen in the duodenal contents in severe cases of blood destruction. This excess of urobilinogen was noted, not only in the present series of cases with liver disease, but also in those cases in which there was pathologic blood destruction. In addition, in those cases of severe anemia, the presence of cholecyanin was observed, frequently in large amounts. This latter pigment, as well as urobilinogen, is intermediate between bilirubin and urobilin, and its presence would seem to indicate very rapid and incomplete metabolism of hemoglobin derivatives by the liver. The presence, therefore, of these intermediate pigments in excess in cases of pernicious anemia would seem further evidence of liver damage in this disease.

It is therefore, tempting to assume that a disturbed function of the liver in the disease pernicious anemia is a considerable factor in creating abnormal pigment values in the plasma and in the bile. It is not as easy, however, to apply this explanation to pernicious anemia as to the other anemias in which abnormal pigment values are found. In pernicious anemia there is a relative increase in hemoglobin and iron pigment is found in various organs. The irregular and biazarre course of pernicious anemia, the attractive assumption that the red corpuscles in pernicious anemia are not only abnormal but different from the red corpuscles in other conditions, may account in part for the seeming discrepancy. The existence of difference between the red corpuscles in pernicious anemia and in other conditions has been indicated by work recently done on various types of anemia by Buckman [22] at the Boston City Hospital. In any event, while a part of the increase in bile pigment elimination in pernicious anemia may be attributed to excessive blood destruction, the remainder may perhaps be laid to a damaged liver. Inasmuch as continued attacks of hemolysis per se cause liver damage, the two factors are really related.

Furthermore, as pointed out by Brulé,[23] the proper conception of such a disease as catarrhal jaundice should locate the primary pathology not in the biliary passages but in the hepatic cell itself. Such a disease is primarily an infection of the liver parenchyma, and the pathology and abnormal physiology should be centered in the degree of actual parenchymal damage and disturbance of liver function. Such a conception of catarrhal jaundice offers the logical explanation of the

22. Buckman, T. E.: Personal communication.
23. Brulé, M.: Bull. méd. **8**:279, 1920.

diminished hemoglobin frequently found after an attack of even moderate severity, and accounts for the increased amounts of bile pigment eliminated in the bile after the flow is reestablished.

Findings in Cases of Gallbladder Disease.—In view of the frequent association of liver disturbance with chronic disease of the gallbladder it is pertinent at this point to examine briefly the results obtained in a series of cases of cholelithiasis and cholecystitis. Observations were made on ten patients suffering from typical gallstone attacks and on six patients with typical symptoms of chronic cholecystitis. In a majority of the cases the preliminary diagnosis was confirmed by subsequent operation. The pigment curves, as shown in Chart 5, are easily explained. They did not vary from the normal curve in their general contour. The actual level of the bile pigments, however, was distinctly higher than normal. (This series, of course, did not include cases of cystic or common duct obstruction.) The point of interest in these cases is that there was a distinct difference between the pigment values obtained from patients with stones and those obtained from patients with only cholecystitis. Those patients with cholelithiasis gave an average pigment curve approximately 75 per cent. above the normal level, although in individual cases the average figure was as high as three times normal. The cases of cholecystitis, on the contrary, gave a distinctly higher average. The average pigment values in this group were nearly twice those observed in cases with stone formation, and and were three times the normal figure. Individual cases of this group went as high as eight times normal. Furthermore, the peak of the pigment cure representing the greatest concentration of gallbladder bile was on the average more than twice that found in the group of cases with stones. According to the present conception of gallbladder disease, blood destruction does not play an important part in the disease process. The high pigment values, therefore, were due either to abnormal stasis or to liver pathology. The work of Rous and of McMaster,[24] recently published, indicates that in stasis the gallbladder has a great power of concentration, with the result that any bile contained in it, even for short periods of time, becomes abnormally high in pigment and other constituents. They show that this power of concentration diminishes in the face of a pathological process such as the presence of stone formation with partial or complete obstruction to the normal entrance of bile into the gallbladder. The high pigment content in cases of cholecystitis may thus be partially explained as well as the difference between those cases with stone formation and those with only low grade gallbladder inflammation leading merely to stasis. It is of especial interest in this consideration to note the findings reported

24. Rous and McMaster: J. Exper. M. **34**:47, 75, 1921.

in a personal communication from Fitz [25] from the Mayo Clinic. He reports finding highly pigmented bile in most cases in which operation was performed for cholecystitis, whereas the bile in those cases showing calculus formation was also dark but less highly pigmented. Furthermore, he was able to demonstrate that the specific gravity and the nitrogenous content of those cases with only cholecystitis tended to be much higher than in cases of cholelithiasis. Such findings are strongly confirmatory of the concentrating ability of the gallbladder in cholecystitis and help to explain the pigment values found in this group of cases.

While the high pigment values in these cases are undoubtedly due in part to gallbladder concentration, it is also highly probable that they may be due in part to an accompanying cholangeitis and hepatitis. The recent paper by Judd,[26] emphasizing the common association of gallbladder and liver infection, is also confirmatory. Such a conception would also explain the low hemoglobin content frequently found in connection with long standing cases of cholecystitis, and occasionally persisting even after cholecystectomy. The high pigment values in such cases are probably due both to abnormal gallbladder concentration and to an alteration in liver function.

CONCLUSIONS

1. Increased blood destruction is accompanied by an increase of the bile pigments in the blood plasma and bile.

2. Alterations in liver function, due to infection, new growth, cirrhosis, or even a profound anemia per se, are also accompanied by marked increases in bile pigment, both in the bile and plasma.

3. Jaundice, in cases with liver damage, may be entirely due to an alteration in bile pigment metabolism, without the necessity of any accompanying obstructive process or increase in the normal process of blood destruction.

4. The high level of the bile pigment in pernicious anemia can not be due solely to a process of increased blood destruction. A second factor is necessary to explain the increased pigment elimination. This second factor may well be an alteration in hepatic function.

5. In gallbladder disease the bile pigments in the duodenal contents are abnormally high, especially in those fractions containing the greatest concentration of bile from the gallbladder.

6. Cases of uncomplicated cholecystitis show a greater concentration of bile pigments than cases of cholelithiasis.

25. Fitz, R.: Personal communication.
26. Judd, E. S.: J. A. M. A. **77**:197 (July 16) 1921.

7. A presumable functional incapacity of the liver properly to metabolize hemoglobin, due to any cause resulting in liver damage, is accompanied by a lowered hemoglobin content of the blood. Such cases also show high bile pigment values in the plasma and bile.

8. Owing to the frequent association of hepatitis with cholecystitis it is probable that the frequent accompaniment of a low hemoglobin content and an apparent anemia in chronic gallbladder diseases is due to an alteration in liver function.

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A STUDY OF HEMOGLOBIN METABOLISM IN PAROXYSMAL HEMOGLOBINURIA

WITH OBSERVATIONS ON THE EXTRAHEPATIC FORMATION OF BILE PIGMENTS IN MAN *

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The close relationship of the coloring matter of the red blood corpuscles to the pigments of the bile is now generally accepted. Proofs for the existence of this relationship are numerous, and have been obtained by many investigators. Hematoidin, chemically isomeric with bilirubin, has long been known to occur in old extravasations of blood. Stadelmann,[1] working on dogs with biliary fistulas, showed that free hemoglobin in the plasma, produced by the artificial destruction of red cells, or by the injection of hemoglobin into the circulation, caused an increase in the quantity of bilirubin in the bile. Stadelmann and Gorodecki,[2] by injecting a solution of hemoglobin either subcutaneously or intraperitoneally, also caused in dogs a marked and prolonged rise in bile pigment in the fistula bile. The work of Brusch and Yoshimoto,[3] on dogs with biliary fistulas and ligated bile ducts, showed that intravenous injections of hematin caused increased amounts of bilirubin and urobilin to appear in the bile. In man the excretion of bile pigments in various so-called hemolytic conditions has been studied by numerous investigators. These conditions are found in pernicious anemia, hemolytic jaundice, malaria, etc. Hoppe-Seyler,[4] Gerhardt and von Müller,[5] Eppinger and Charnas,[6] de Jonge,[7] Simpson,[8] Robertson,[9]

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1. Stadelmann: Der Icterus und seine verschiedene Formen. Stuttgart, 1891.
2. Stadelmann and Gorodecki: Ibid.
3. Brusch and Yoshimoto: Ztschr. f. exper. Path. u. Therap. **8**:639, 1910.
4. Hoppe-Seyler: Virchows Arch. f. path. Anat. **30**:124, 1891.
5. Gerhardt and von Müller: Ztschr. f. klin. Med. **32**:303, 1897.
6. Eppinger and Charnas: Arch. f. klin. Med. **78**:387, 1913.
7. de Jonge: Geneesk. Tijdschr. v. Nederl. Ind. **44**:435, 1904.
8. Simpson, G. C. E.: Biochem. J. **5**:378, 1911.
9. Robertson, O.: Arch. Int. Med. **15**:1072 (June) 1915.

Wilbur and Addis,[10] and others have investigated the urine and feces for urobilin in human beings in normal and diseased conditions. In cases in which there was apparently a rapid rate of blood destruction these observers consistently noted abnormally large amounts of urobilin in the feces, and usually in the urine. Simpson reported one case of malaria which showed hematoporphyrin, as well as large amounts of urobilin in the stool examinations. Schneider,[11] Giffin, Sanford and Szlapka,[12] and Jones [13] and subsequent workers have demonstrated abnormally large amounts of bilirubin, urobilin and urobilinogen in the duodenal contents, particularly in cases of pernicious anemia, and other conditions in which blood destruction is considered to be excessive. The bilirubin content of the blood plasma has been shown by Blankenhorn,[14] among others, to be definitely increased in diseases in which it is usually considered that pathologic blood destruction is taking place.

From the literature it is clear that a large amount of evidence has been obtained as proof of the close relationship between liberated hemoglobin and the bile pigments in the blood, bile and excreta. It is true, however, that the relationship between the amount of hemoglobin liberated during the process of blood destruction at any given time and the bile pigments in the blood and bile, as measured by present laboratory methods, may not be strictly a quantitative one. On the contrary, although the level of bile pigments in the blood and bile undoubtedly may serve as an index or measure of blood destruction, it is, nevertheless, only a relative measure of hemolysis, and may be influenced by various factors. Hooper and Whipple,[15] have shown in dogs, that mere changes in diet can produce large variations in bile pigment excretion. In dogs with biliary fistulas, a high carbohydrate intake resulted, and in some cases an increase in fistula bilirubin as high as 100 per cent. above normal, while a meat diet alone gave a slight decrease in pigment values. These observers also showed that the functional capacity of the liver, in dogs, in large measure influenced the output of bile pigments. Dogs with Eck fistulas, and accordingly with damaged livers, showed a marked diminution in bile pigment elimination. On the contrary, Jones [13] was able to demonstrate, in a series of patients suffering from various types of liver disease, a marked increase in the output of the bile pigments, both in the blood and the bile. The use of certain drugs is also known to modify bile pigment excretion.

10. Wilbur and Addis: Arch. Int. Med. **13**:325 (March) 1914.
11. Schneider, J. P.: Arch. Int. Med. **17**:32 (Jan.) 1916.
12. Giffin, Sanford, and Szlapka: Am. J. M. Sc. **182**:562, 1918.
13. Jones, C. M.: This issue, p. 643.
14. Blankenhorn, M. A.: Arch. Int. Med. **19**:344 (March) 1917.
15. Hooper and Whipple: Am. J. Physiol. **40**:332, 349, 1916.

It has also been shown by recent investigators that the early views regarding the mechanism of hemoglobin metabolism must be modified considerably. The liver, and to some extent the spleen, were originally held to be the sole agents concerned with the breakdown of hemoglobin. The liver alone was held responsible for the reconstruction of hemoglobin from iron and the lower pigment molecules. Recent work, however, has shown that, whereas the liver undoubtedly plays the most important rôle in hemoglobin metabolism under normal conditions, this function, in animals, can be assumed, in part, if not entirely, by other organs and tissues of the body. Hooper and Whipple [15] were able to show in dogs with bile fistulas that the bile pigments could be formed just as readily in animals in which the circulation of the liver was greatly diminished by an Eck fistula, or with such a fistula and the hepatic artery ligated, as in normal animals. Injection of hemolyzed red blood corpuscles into a head-thorax circulation resulted in the appearance of increased bile pigments in the blood. Bile pigments were also found in increased amounts in the blood when free hemoglobin was injected into the pleural or abdominal cavities. Van de Bergh [16] has also shown in man, in four cases subjected to operation, and in two necropsies, that the blood serum from the splenic vein contained much more bilirubin than did the peripheral blood. These patients had pernicious anemia, Banti's disease, hemolytic jaundice, etc. He concludes that the excess bilirubin in the splenic blood was formed by the spleen. The views recently expressed by Pearce, Krumbhaar and Frazier,[17] that the spleen is an important factor in the process of blood destruction, are very generally accepted. In fetal life the spleen has the power of extensive blood formation. In the adult the spleen may undergo, in the presence of an injury to the bone marrow, a myeloid metaplasia; i. e., it can regain its fetal function under pathologic conditions. Whether the spleen may exert this power of blood formation in adult life under normal conditions is doubtful, though it is still an open question.

It thus has been shown in animals that hemoglobin katabolism can take place without the intervention of the liver, and that the spleen, in man, may carry on this function. In addition, it has been shown by experimental work on animals, that there is a close relation between the excretion of the bile pigments and the liberation of hemoglobin in the blood. The investigations carried out in man in such diseases as pernicious anemia, hemolytic jaundice, malaria, etc., have produced fur-

16. van de Bergh, A. A. H.: Nederlandsch. Tijdschr. v. Geneesk. **1**:1160, 1915.

17. Pearce, Krumbhaar and Frazier: The Spleen in Anemia, Philadelphia, 1918.

ther evidence of the derivation of the bile pigments from the products of hemolysis. Experimental evidence in man, however, in which measurable hemolysis has been produced in the circulation, with an immediate and continuous examination of the bile and blood, is conspicuously lacking.

It is our purpose, in this paper, to present further evidence regarding the katabolism of hemoglobin in man. It will be shown, first, that there is a direct relation between the liberation of hemoglobin into the plasma and the excretion of the bile pigments; second, that the liver is stimulated to increased functional activity by abnormal intravascular hemolysis; and third, that hemoglobin can be broken down in the blood vessels, capillaries and tissue spaces without the intervention of the liver or other organs.

The experiments which form the basis of this paper were conducted on two patients suffering from paroxysmal hemoglobinuria. It will be pertinent to insert at this point the following definition of this rare disease: "Paroxysmal hemoglobinuria is a chronic disease, due to syphilitic infection, manifesting itself in recurrent paroxysms of hemoglobinuria, and in characteristic constitutional symptoms. The blood of patients who suffer with this disease contains in latent form a specific hemolysin which becomes active when the blood is chilled, and produces the attacks."[18] Chilling of the blood to a temperature below 15 C. causes this specific hemolysin to become attached to the red cells. During subsequent warming at body temperature (37.5 C.) the hemolysin becomes active through the influence of the complement normally present in the blood, and hemolysis ensues. The amount of hemolysis is readily measured by the amount of free hemoglobin in the plasma, and is dependent on the length and severity of the chilling to which the blood is exposed.

One of the two cases (G. L. T) exhibited all the characteristic features of this striking disease. The patient was a congenital syphilitic. He showed in his blood the presence of the specific hemolysin peculiar to the disease, and was subject to attacks of hemoglobinuria on exposure to chilling. Antisyphilitic treatment had modified the course of the disease process, but at the time of our experiments the treatment had not been sufficient to free the patient from attacks. The second patient (A. L.) was also a congenital syphilitic. His sister had paroxysmal hemoglobinuria. Unlike his sister, however, he had never had an attack at all suggestive of this disease. His blood, nevertheless, showed the presence of the characteristic hemolysin, and both in vivo and in vitro, it was possible, by exposure to chilling, to demonstrate

18. Jones, B. B., and Jones, C. M.: Nelson's Loose Leaf Living Medicine, Washington, 1920.

definite hemolysis. This second case may thus be classified as a "potential" case of paroxysmal hemoglobinuria. It is of interest to note in this connection, that, in the blood of forty-five syphilitic patients who had no clinical symptoms of paroxysmal hemoglobinuria, we were able to demonstrate a similar hemolysin definitely in 6.6 per cent., thus approximately confirming the observations of Donath and Landsteiner,[19] Kumagai and Inoue,[20] and others.

The experiments conducted on these two patients consisted in the production of attacks of hemoglobinemia, with a subsequent study of the pigments in the blood, duodenal contents and urine. The condition studied was thus essentially intravascular hemolysis in man, uncomplicated by any other factor, such as liver damage, trauma, or by the introduction of any foreign substance into the circulation. Attacks of hemoglobinemia were brought about by immersing one or both of the patient's hands in ice water for several minutes, and then warming the chilled members. In none of the experiments was the chilling severe enough to cause more than a trace of hemoglobin to appear in the urine, and in two of the experiments hemoglobinemia only was produced.

Blood for examination was taken from an arm vein, either into a small amount of potassium oxalate solution, to prevent clotting, or allowed to clot at body temperature over a water bath. Special care was taken to prevent the occurrence of mechanical hemolysis.

The presence and amount of free hemoglobin in the blood was determined by spectroscopic examination of the oxalated plasma. The The number of dilutions with distilled water necessary to cause the disappearance of the characteristic absorption bands of hemoglobin from the spectrum was taken as the amount of free hemoglobin present in any given specimen of plasma. Inasmuch as bilirubin gives no characteristic absorption band in the spectroscope, its concentration in the blood plasma was determined by the method described by Blankenhorn,[14] which consists merely in the dilution of the plasma or serum with distilled water until the yellow color disappears on comparison with a tube of distilled water. Here also the amount of bilirubin present was taken as the number of dilutions necessary to cause the disappearance of the yellow color. As a further test for bilirubin in the plasma, the Gmelin test with nitric acid was used. This test gives a positive reaction in the presence of relatively large amounts of bilirubin, but gives no characteristic color changes when hemoglobin alone is present. The Gmelin test, therefore, was used as a second method for determining the presence of abnormal amounts of bilirubin in the plasma or serum, especially when the characteristic yellow color was

19. Donath and Landsteiner: Ztschr. f. klin. Med. **58**:173, 1905.
20. Kumagai and Inoue: Münch. med. Wchnschr. **38**:361, 1912.

obscured by the additional presence of free hemoglobin. A positive Gmelin test is not obtained with specimens of normal blood. The presence of any quantity of free hemoglobin in the serum or plasma made it impossible to estimate accurately the amount of yellow pigment present. In such cases, when the yellow color was obscured by the presence of free hemoglobin, dilutions were carried out with distilled water until no color was left. A sample of the same plasma was also examined spectroscopically for free hemoglobin. Comparison between the amount of hemoglobin present, and the number of dilutions necessary to remove all traces of pigment, gave a rough estimation of the amount of bile pigment present. Inasmuch as the estimation of the amount of free hemoglobin and bilirubin in the plasma or serum were made by essentially different methods, it is obvious that any comparison between such estimations must be only an approximate one. The same holds true of any comparison made between the bilirubin and urobilin concentration in the duodenal contents, as will be pointed out. Other pigments than hemoglobin and bilirubin were not found in the blood.

The duodenal contents were obtained through an Einhorn tube, and were examined for the presence of the various bile pigments—bilirubin, urobilin, urobilinogen, cholecyanin, etc. Only the first three pigments were found. The position of the tip of the tube in the duodenum was confirmed by fluoroscope, and a free flow of bile was obtained by the use of a solution of magnesium sulphate, as described by Lyon.[21] Bilirubin values were obtained by a colorimetric method described by Hooper and Whipple [15] in their work on dogs with biliary fistulas. Briefly stated, their method consists in the treatment of the bile drainage with acid alcohol, and reading the resulting blue-green solution against a standard solution of copper sulphate and India ink in a Duboscq colorimeter. Urobilin and urobilinogen values were estimated by the method used by Wilbur and Addis, Schneider, and others. The method consists in treating a given quantity of duodenal contents (or feces) with an equal quantity of a saturated alcoholic solution of zinc acetate (Schlesinger's reagent), filtering, acidifying the filtrate with Erlich's solution (paradimethylaminobenzaldehydrochlorid), and after allowing this to stand in the dark for fifteen minutes, reading in the spectroscope. The number of dilutions with ethyl alcohol necessary to cause the disappearance of the characteristic absorption bands in the spectrum is taken as the value of the individual pigments. Urobilin and urobilinogen values were added together and expressed as one figure. As previously mentioned, the difference between the methods of estimating bilirubin and the other bile pig-

21. Lyon, B. B. V.: J. A. M. A. **73**:980 (Sept. 27) 1919.

ments made any comparison between the different estimates purely an approximate one. This method of studying the duodenal pigments is fully described in a separate paper.[13]

The presence of hemoglobin or urobilin in the urine was determined by the use of a spectroscope. Other bile pigments were tested for but none were found.

Measurement of the blood loss taking place following an attack of hemoglobinuria was determined by a series of red cell counts taken before and after the production of attacks. Such estimations were of course somewhat inaccurate, inasmuch as they did not take into account alterations in the peripheral circulation and the blood volume. For practical considerations, however, such determinations indicated the severity of an attack, as did the presence or absence of free hemoglobin in the urine.

Three separate experiments were performed on the two patients.

PROTOCOLS OF EXPERIMENTS

EXPERIMENT 1.—Patient G. L. T.

The results of this experiment are clearly shown in Chart 1. Samples of blood and urine were taken as normal controls before inducing an attack of hemoglobinemia. There was no free hemoglobin in either the blood or the urine, and the bilirubin content of the blood plasma was normal. Duodenal contents were taken at fifteen minute intervals for an hour and a half, in order to establish a normal pigment curve. The first peak shown in the chart came after the introduction of a 33 per cent. solution of magnesium sulphate into the duodenum, and was due partly to an increased flow of bile into the duodenum through the relaxed sphincter of Oddi, and partly to the addition of some of the concentrated bile in the gallbladder to the general flow. After the control figures had been obtained both the patient's arms were immersed in ice-water for five minutes, in order to produce intravascular hemolysis. Duodenal contents were then collected at intervals during the next three hours and a half. Samples of blood were also taken from an arm vein at varying intervals until there was no further hemoglobin in the plasma, and until the bilirubin contents of the plasma had practically returned to the normal level. Samples of urine taken at different times during the experiment failed to show any increase in bile pigment content, and at no time was there any evidence of hemoglobin.

Examination of Chart 1 shows clearly that there was an immediate and sharp rise in the hemoglobin content of the blood plasma, although prior to the attack there was no free hemoglobin present. Furthermore, before the attack there was a normal amount of bilirubin in the plasma as measured by its yellow color, and the Gmelin test was negative. The free hemoglobin observed shortly after the arm had been chilled indicated the immediate destruction of the patient's red cells within the blood vessels. The amount of free hemoglobin reached its peak within about four of five minutes after the attack had been produced. The plasma was bright red and no tests could be obtained for the presence of bilirubin. Twelve minutes after the patient's arms had been removed from the ice-water, a specimen of blood showed less than one-fourth the amount of free hemoglobin observed in the previous sample. The plasma was only slightly red, and there was a positive reaction to the Gmelin test for bile pigment. Furthermore, the color dilution of the plasma was increased over the previous specimen by over 50 per cent. Blood taken forty-five minutes after the attack showed a still further reduction in free

hemoglobin content, and the plasma was deep golden in color. The Gmelin test was strongly positive, and color dilution values were more than four times the original normal figure. From this point the pigments in the blood gradually returned to normal, so that in one hour and twenty minutes after the production of the attack of hemoglobinemia there was no free hemoglobin in the plasma. The bilirubin content had returned so near to normal that the Gmelin test was negative.

A study of the pigments in the duodenal contents showed no increase over the peak of the normal curve, obtained prior to the attack, until one hour after the production of the attack. At this time there was a marked rise in the bilirubin values. It will be noticed that this rise in bilirubin content of the bile

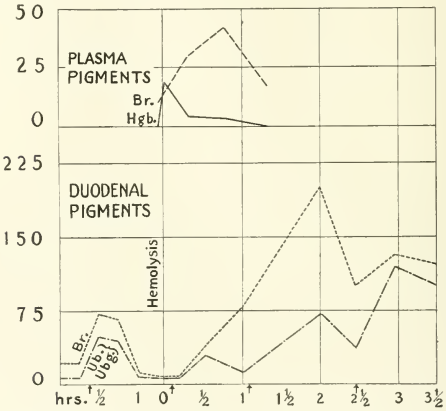

Chart 1.—The above curves of plasma and duodenal pigments are superimposed and have identical time relations. Points along the ordinates represent values of bilirubin (Br.), free hemoglobin (Hgb.), and combined urobilin and urobilinogen (Ub., Ubg.). Points along the abscissae represent specimens of plasma or duodenal contents obtained at the time intervals indicated. An attack of hemoglobinemia was produced at the point marked "Hemolysis." Magnesium sulphate solution (33 per cent.) was given at various times as indicated by arrows.

started at the time when the free hemoglobin had entirely disappeared from the blood, and when the bilirubin content of the plasma had already begun to return to the normal level. The bilirubin content of the bile continued to increase until it reached its highest concentration at a point two hours following the attack. From this point it gradually diminished in amount, but three and one-half hours after hemolysis was produced the bilirubin concentration in the bile was still nearly twice the greatest amount obtained before hemoglobin was liberated into the circulation. Urobilin and urobilinogen values also

showed a marked increase, but the time of appearance of these pigments was later than that of bilirubin. At the end of two hours, when the bilirubin concentration had reached its peak, urobilin and urobilinogen values began to show a definite increase over the normal. From this point, however, they continued to increase until the greatest concentration of these pigments in the bile was reached about three hours after hemolysis had been produced. These pigments then gradually diminished in amount, although three and one-half hours after the induction of hemolysis their concentration in the bile was still about double the highest point reached in the control readings.

Repeated examinations of the urine revealed at no time the presence of any abnormal pigments.

Analysis of the above findings brings out the following points. An attack was produced in a patient, in which there was an immediate liberation of a large amount of hemoglobin into the circulation. Almost immediately following the attack the hemoglobin freed from the patient's red corpuscles reached its highest concentration in the circulation. At the end of twelve minutes the larger part of the free hemoglobin had been removed from the circulation and had been replaced by bilirubin, which appeared in amounts greatly increased over normal. As the hemoglobin diminished, the bilirubin content increased, until the latter reached its peak in about forty-five minutes. Both pigments gradually returned to normal, about one-half hour later, and as they approached normal the bilirubin content of the bile showed a marked increase. Accompanying this increase of bilirubin in the duodenal contents there was a similar rise in the lower bile pigments, urobilin and urobilinogen. This latter increase, however, proceeded at a much slower rate, and did not reach its peak until the bilirubin had already begun to return toward normal.

Here, then, is an orderly sequence of events, and the following deductions may reasonably be drawn. Following an uncomplicated attack of red cell destruction in man the hemoglobin liberated into the general circulation was rapidly changed to, or replaced by, an increased amount of bilirubin in the plasma. Inasmuch as there was no restriction on the circulation, it is evident that the liver, or any other organ, might have participated in this transformation of hemoglobin into bile pigments. As a matter of fact, however, there was no demonstrable response in the liver excretion until all the hemoglobin, and the greater part of the excess bilirubin had disappeared from the plasma. Such a finding seems to indicate that the change from hemoglobin to bilirubin might well have taken place merely in the blood vessels and capillaries. That there was a marked response on the part of the liver to the sudden excess of hemoglobin in the circulation is indicated by the elimination in the bile of a tremendous amount of bilirubin. This increase amounted to as much as three times the normal concentration of this pigment in the bile, and is clear evidence of a definite relation between the liberation of hemoglobin into the circulation and the excretion of bilirubin in the bile. Such an increase is also definite evidence of a stimulation of the liver to increased activity by the products of red cell destruction. The accompanying rise in concentration of urobilin and urobilinogen in the bile following the production of an attack of hemolysis indicates the close relation of these pigments to bilirubin, and thus indirectly to hemoglobin.

After a careful examination of the time relation between the appearance of an excess of bilirubin in the bile and the subsequent increase of urobilin and urobilinogen another point of interest is brought out concerning the origin of these last two pigments.[22] It will be noticed on Chart 1 that the peak of a bilirubin curve in the duodenal contents came approximately one hour before urobilin and urobilinogen were found in their greatest concentration. Furthermore, the peak of the latter pigments came within three hours of the beginning of the experiment. This rise in urobilin and urobilinogen values was clearly the result of a liberation of hemoglobin into the general circulation, and followed the increase of bilirubin in the bile by a definite but relatively short interval. The time interval elapsing between the appearance of excess bilirubin was obviously too short to allow of intestinal action upon the bilirubin excreted in the bile, and subsequent reabsorption of pigment via the portal circulation. Bacterial action, especially on protein molecules, is not marked until the lower portion of the small intestine and the upper portion of the large intestine is reached. In this experiment it is obvious that bacterial reduction of the excess bilirubin in the intestine could in no way account for the increased amounts of urobilin and urobilinogen in the bile, and is direct evidence against the early theory of the intestinal formation of urobilin and urobilinogen. The time element alone appears to exclude such a possibility. The logical assumption is, therefore, that these lower pigments were formed by the liver directly from the bilirubin which was a result of increased hemoglobin katabolism. The power of the liver to form not only bilirubin, but urobilin and urobilinogen, is clearly indicated. The results suggest that the formation of bilirubin may take place outside of the liver, but do not prove this conclusively, inasmuch as the blood determinations were all taken from the general circulation, from which the liver and other organs could not be excluded. With these considerations in view a second experiment was tried with two main objects: (1) to check the results of the first experiment, and (2) to produce evidence of the extrahepatic formation of bile pigment.

Experiment 2.—Patient, G. L. T.

The results of this experiment are shown in Chart 2. Control specimens of blood, duodenal contents, and urine were taken and examined as outlined in Experiment 1. An attack of hemoglobinemia was produced this time by immersing only the patient's left arm in ice-water. In order to study the changes taking place in the blood vessels, without the intervention of the liver or other organs, a tourniquet was applied above the elbow of the left arm before immersion, and was kept on this arm for twenty-five minutes. In this way the blood in the vessels, capillaries and tissue spaces in the lower

22. Urobilinogen, although present in increased amounts, was at no time found in great concentration.

left arm could be subjected to chilling and subsequent warming without mingling with the general circulation. Samples of blood were taken from the left arm several times before the removal of the tourniquet, in order to observe any changes taking place in the pigments while the local circulation was thus isolated. Specimens of blood were also taken from the right arm at similar intervals in order to ascertain whether there was any leakage of blood from the immersed arm past the tourniquet into the general circulation. Unfortunately, the tourniquet pressure was not sufficient to prevent some leakage, and the results, while more suggestive than in the first experiment, were still not conclusive. The chart showed a similar curve for the pigments in the blood plasma to that obtained in the previous experiment. It will be noted, however, that both the free hemoglobin and the bilirubin contents of the plasma reached a greater concentration than that obtained before. It also required a much longer period for these pigments to return to their original concentration in the blood. The higher values may be readily accounted for by the fact that the attack of hemolysis produced in this experiment was more severe than

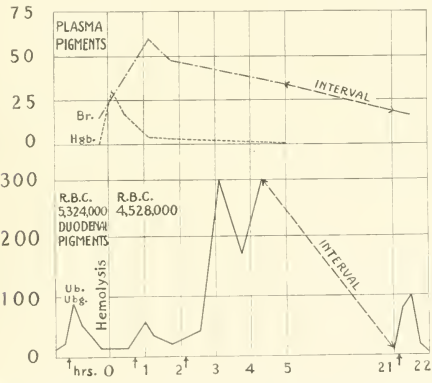

Chart 2.—Constructed in the same manner as Chart 1. The significance of the various pigments and the method of their determination is fully outlined in the text.

the previous one, as evidenced by the finding of traces of free hemoglobin in the first specimen of urine voided after the attack. Furthermore a large amount of the free hemoglobin in the vessels of the left arm was not released into the general circulation until the removal of the tourniquet, some twenty-five minutes after the attack of hemolysis was produced. Such a delay would naturally retard the complete katabolism of the various pigments. In this case the bilirubin content of the plasma did not return to normal until about twenty-one hours later.

As a means of determining the relative amount of blood destruction produced in this experiment duplicate red counts were taken from the peripheral

and general circulation before the immersion of the arm in ice-water, and shortly after the removal of the tourniquet. Before hemolysis was produced the red cell count was 5,394,000 per c. mm. Similar counts made almost immediately after the tourniquet had been removed averaged 4,528,000 per c. mm. In other words, the number of red corpuscles destroyed was roughly about 850,000 per c. mm. Such a figure does not take into account changes in the peripheral circulation or in blood volume, but permits at least a rough estimate of the severity of the attack.

The duodenal contents were collected as before, and determinations of urobilin and urobilinogen were made. The curve of bilirubin elimination was not estimated. This time, however, specimens were collected for four hours after the initiation of hemoglobinemia. The duodenal tube was then removed, but was reintroduced the following morning in order to determine approximately the length of time necessary for the duodenal pigments to return to a normal level. Blood examinations were made at the same time. Estimations of the duodenal pigments showed that they reached their peak in about three hours, but that they did not return to normal until about some twenty-one hours.

The results of this experiment confirmed the findings and conclusions of the first. In addition they afforded a rough estimate of the amount of blood destruction necessary to produce a given level of pigment values, both in the blood plasma and in the bile. In an attack of hemoglobinemia just sufficient to produce a trace of hemoglobin in the urine it apparently takes about twenty hours for the bile pigments in the plasma and bile to return to their former normal level. The experiment failed to give conclusive evidence of the extrahepatic formation of bile pigment.

Experiment 3.—Patient A. L.

The results are shown in the accompanying table. The purpose of the experiment was to obtain conclusive evidence that the bile pigments, or at least bilirubin, could be formed in the peripheral blood vessels and other tissues that occur in an extremity, without the intervention of the liver. Such a probability was suggested in both the previous experiments, but failure properly to isolate the peripheral arm circulation from the general circulation made any evidence obtained inconclusive. In this experiment the rubber arm band of a sphygmomanometer was applied to the patient's left arm above the bend of the elbow, and was used as a tourniquet. The systolic blood pressure of this patient was 118. Throughout the experiment the pressure on the arm was maintained above this systolic pressure with the result that the blood below the tourniquet was completely isolated from the rest of the general circulation. After a specimen of blood had been obtained as a normal control, the patient's left arm, with the tourniquet applied, was immersed in ice-water (temperature, 5 C.). In order to cause only a moderate amount of hemolysis the arm was kept in the water for a period of only two and one-half minutes. It was then withdrawn and covered with a warm blanket to supply the deficiency of body heat caused by the stasis of the peripheral blood. Specimens of blood were withdrawn from the arm circulation at intervals of three, twenty and thirty-three minutes after hemolysis had been produced. A specimen was then taken from the gneeral circulation before the removal of the tourniquet in order to prove that there had been no communication between the arm and the general circulation. The tourniquet was then removed and the blood from the arm circulation allowed to mingle with that of the general circulation. A final specimen was taken from the general circulation twenty minutes after the removal of the tourniquet.

The first specimen of blood taken after immersion of the arm (Specimen 2) showed a definite trace of free hemoglobin. The next sample of blood, taken twenty minutes after the beginning of the experiment, showed a large amount of free hemoglobin, so that the plasma was reddish yellow in color. The Gmelin test was negative. The delay in the appearance of the hemoglobin may be explained by the fact that, owing to the complete isolation of the arm from the general circulation, the temperature after immersion was well below that of the rest of the body. Inasmuch as the hemolytic reaction in paroxysmal hemoglobinuria takes place completely only after the blood has been returned to body temperature, it becomes evident that the slow return of the arm to body temperature greatly delayed the process of hemolysis. Specimen 4 was taken thirteen minutes later. The plasma was dark yellow in color, instead of having the strong reddish tinge observed in the previous specimen. Simple color dilution showed the same pigment content as in Specimen 3. The hemoglobin content, however, was less than half that observed in the previous sample. Furthermore, there was a definite positive Gmelin test. The tourniquet was then removed as the arm was very cold and cyanotic. Specimen 5, taken from the general circulation just before the tourniquet was removed, showed that no hemoglobin had entered the general circulation from the left arm. Specimen 6, taken from the general circulation about an hour after the attack of hemolysis was produced, and twenty minutes after Specimen 5, showed a trace of free hemoglobin, and in addition gave a doubtful Gmelin reaction.

The above findings may be summed up as follows: Intravascular hemolysis was produced in a very restricted portion of the circulation. Thus the products of hemolysis were completely isolated from the influence of the general circulation, or of any of the organs of the body. Free hemoglobin was liberated and reached its greatest concentration in the plasma in twenty minutes. Although still completely isolated, the free hemoglobin rapidly diminished in concentration. Accompanying this reduction in hemoglobin concentration there was a marked increase in the bilirubin content of the plasma, as indicated by a positive Gmelin test, and by a change in color of the plasma from a reddish yellow to a dark golden yellow. Inasmuch as no bile pigment had been introduced into the blood of the isolated arm circulation at any time it is evident that the free hemoglobin had undergone a transformation in the bilirubin in the local blood vessels, capillaries and tissue spaces. The absence of any trace of free hemoglobin in the general circulation before the removal of the tourniquet indicates that there was no communication between the process taking place in the arm and the rest of the body.

It will be noticed in the table that the hemoglobin content of the plasma in Specimen 6, taken from the general circulation twenty minutes after removal of the tourniquet from the left arm, is still about one-half the concentration in Specimen 4. Obviously the liberation of the free hemoglobin contained in the lower left arm into the blood of the general circulation, other things being equal, should result in a much greater dilution than that observed. A similar discrepancy

may also be noticed in a careful comparison of Charts 1 and 2. In Experiment 1 the free hemoglobin of the plasma obtained from the general circulation shortly after hemoglobinemia was induced was twenty-two dilutions. In Experiment 2 the hemoglobin concentration in the blood plasma taken from an almost completely isolated lower arm circulation, following a more severe attack of hemolysis, and resulting in the appearance of traces of hemoglobin in the urine, was only thirty dilutions. Such an apparent discrepancy between the amount of free hemoglobin observed in the general circulation and that noted in a restricted part of the circulation may be readily explained by a consideration of the mechanism taking place in paroxysmal hemoglobinuria. As has already been explained, complete hemolysis occurs only when the temperature of the chilled blood has returned to 37 C. In Experiments 2 and 3 the temperature of the arm in which the local circulation had been restricted by the application of the tourniquet did not return to normal for a considerable length of time. In Experiment 3, for example, the arm temperature, thirty-five minutes

EVIDENCE OF THE EXTRAHEPATIC FORMATION OF BILE PIGMENTS *

Specimen of Plasma	Time Interval After Attack	Color of Plasma	Color Dilutions	Gmelin Test	Hemoglobin Dilutions
1	Control	Straw	12	0	0
2	3 minutes	Pink straw	20	0	2
3	20 minutes	Reddish yellow	45	0	9
4	35 minutes	Dark yellow	45	+	5
5	25 minutes	Straw	12	0	0
6	55 minutes	Pink yellow	35	±	2.5

* Explanation: Intravascular hemolysis was produced in the vessels of the lower left arm following the taking of Specimen 1. Specimens 1 to 4 inclusive were taken from the left arm, where the blood was cut off from the general circulation by the maintenance of a tourniquet with a pressure constantly above systolic blood pressure. Specimen 5 was taken from the general circulation before the tourniquet was removed from the left arm. Specimen 6 was taken from the general circulation twenty minutes after the tourniquet had been taken off the left arm.

after the induction of hemolysis, was still well below normal. As a result complete hemolysis did not occur in either Experiment 2 or 3 as long as the blood in the arm was isolated from the rest of the circulation. Only when the blood contained in the arm vessels was allowed to enter into the general circulation did the hemolytic complex become completely activated. Thus hemoglobin determinations in specimens of blood taken from the local arm circulation were relatively low, while those specimens taken from the general circulation after removing the tourniquet continued to show a relatively high hemoglobin concentration in the plasma because of a continuation of the hemolytic process.

Definite evidence is thus presented of the extrahepatic formation of bilirubin from hemoglobin in man. The process in this instance took place solely in the blood vessels, capillaries, and tissue spaces of the patient's left lower arm. Inasmuch as the process was entirely confined to these anatomic structures it seems logical to assume that the

principal if not the sole agents concerned in the transformation of hemoglobin into bilirubin were the cells of the vascular endothelium. Such a conclusion has already been made by Hooper and Whipple [15] in the case of animals. If such an assumption is true, it is logically suggested that the normal activity of the liver in the process of hemoglobin metabolism is due to the endothelial cells with which it is richly supplied, both in the blood vessels and sinuses, and in the so-called stellate cells of Kupffer. While undoubtedly the transformation of bilirubin into the lower bile pigments is due to the activity of the parenchymal cells of the liver, it is evident that some, and possibly a large part of the first steps of hemoglobin katabolism may be carried on without the intervention of the hepatic parenchyma.

CONCLUSIONS

1. In the absence of complicating factors, varying degrees of blood destruction in man are accompanied by corresponding variations in the concentration of bile pigments in the blood plasma and bile.

2. In man, the liberation of excessive amounts of hemoglobin into the circulation results, first, in the rapid elimination of hemoglobin from the blood stream and its replacement by bilirubin; second, in the more gradual disappearance of excess bilirubin from the plasma; third, in the appearance of an increased amount of bilirubin in the bile; fourth, in subsequent diminution of bilirubin in the bile, and its replacement by increased amounts of the lower bile pigments, notably urobilinogen and urobolin; and fifth, in the gradual elimination from the bile of excessive amounts of the latter pigments. There is a definite time interval between each of these phenomena. The above process is probably only an exaggeration of the normal process involved in the metabolism of hemoglobin.

3. Experimental evidence in man suggests strongly that the bulk of this pigment elimination is normally carried on by the liver.

4. Under abnormal conditions, in man as well as in animals, free hemoglobin can be broken down, at least as far as the bile pigment bilirubin, in the blood vessels, capillaries, and tissue spaces, without the intervention of the liver or any other organ.

5. These experiments suggest that a large part of the transformation of hemoglobin into bilirubin could occur normally in the blood vessels. Possibly the greater portion of this change takes place in the blood vessels of the liver because of the vascularity of this organ.

6. The low bile pigments urobilin and urobilinogen can be formed in the liver, without the intervention of bacterial action in the intestine.

The writers wish to express their appreciation to Dr. Roger I. Lee and Dr. George R. Minot for extremely valuable criticisms and suggestions.

STUDIES OF THE CAUSE OF PAIN IN GASTRIC AND DUODENAL ULCERS II.

PERISTALSIS AS THE DIRECT CAUSE OF PAIN IN GASTRIC ULCERS WITH ACHYLIA AND IN DUODENAL ULCERS

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For many years clinicians have been aware of the fact that not infrequently the symptoms of infection of the gallbladder and appendix and of achylia gastrica of unknown etiology may simulate those of typical gastric or duodenal ulcer. Since reflex pain may be indistinguishable from the true pain in ulcer, to what should this gastric pain, brought on by extragastric lesions, be attributed? Is there direct damage to the stomach and duodenum through this reflex mechanism?

In the consideration of the cause of gastric pain from gastric and duodenal ulcers or reflexly from an infected gallbladder, appendix, or achylia gastrica, two factors are of importance. On the one hand, is the question of acidity or hyperacidity and hypersecretion, and, on the other hand, variations in tonicity, intragastric tension, and peristalsis of the stomach and duodenum. Clinicians generally have been satisfied with the plausible explanation of hyperacidity and hypersecretion being the most likely cause of pain. As proof they administer alkalies which stop the pain, and quite logically they conclude that control of the pain and subsequent healing of the ulcer are mainly questions of neutralization. This view has been substantiated by Cannon[1] in his classical work on the acid control of the pylorus. His theory does not explain the emptying of the stomach in gastric achylia, the rapid exit of water and egg albumin, nor the observations of Spencer, Meyer, Rehfuss and Hawk,[2] that a 1 per cent. solution of sodium bicarbonate hastens the discharge from the normal human stomach.

The experimental work of Luckhardt, Phillips and Carlson[3] indicates very conclusively that the pylorus opens for the ejection of chyme when it is reached by powerful advancing rings of contractions and when tonicity of the stomach musculature is greatly increased.

1. Cannon, W. B.: The Acid Control of the Pylorus, Am. J. Physiol. **20**: 283, 1907.

2. Spencer, W. H.; Meyer, G. P.; Rehfuss, M. E., and Hawk, P. B.: Gastro-Intestinal Studies. XII. Direct Evidence of Duodenal Regurgitation and Its Influence on the Chemistry and Function of the Normal Human Stomach, Am. J. Physiol. **39**: 459, 1915.

3. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Contributions to the Physiology of the Stomach. LI. The Control of the Pylorus. Am. J. Physiol. **1**: 57, 1919.

The gastric contents entering the duodenum are usually acid to phenolphthalein, but rarely show the presence of free acid to dimethylamidoazobenzaldehyd.

Carlson,[4] Ginsburg, Tumpowsky and Hamburger[5] and Hardt,[6] working independently, have demonstrated, by means of kymographic records, various types of contractions and peristalsis of the stomach, which they concluded are the main factors in the causation of the pain of ulcer. New light was thrown on the etiology of pain, not only from gastric or duodenal ulcers, but also from achylia gastrica.

INVESTIGATION

Method.—The relation of gastric motility to pain was studied in twenty-five patients by the kymographic method. All patients were given a standard meal, consisting of two soft boiled eggs, two pieces of toast, two glasses of milk, and the juice of a grapefruit. From one to two hours later, two tubes were swallowed, a Rehfuss tube and a small rubber tube with a fine rubber balloon attached at one end and a chloroform manometer to the end which projected from the mouth. The balloon, held as closely as possible to the cardiac end of the stomach, was blown full of air; it was compressed according to the various types of contractions of the stomach, and thus air forced into the manometer caused the rider to record the variations in tonicity and the contractions on a slowly moving kymograph. These tracings were continued for from one to three hours, and at intervals of one-half hour from 15 to 30 c.c. of stomach contents was aspirated to determine the presence or absence and percentage of free and total acids. The twenty-five patients were divided into two groups:

Group 1.—This group comprises twenty patients with duodenal ulcers, the majority of whom came to the clinic during a quiescent period in their trouble. The diagnosis was based on the clinical history and confirmed by roentgen-ray examination. All these patients were treated medically by the Sippy method at the completion of the kymographic record. None of the patients whose kymogram showed only Type I contractions (Fig. 1) experienced pain. All of these patients during the course of experiment revealed adequate free acids ranging from 20 to 90 (in terms of one-tenth normal hydrochloric acid). Six

4. Carlson, A. J.: Contributions to the Physiology of the Stomach, XLIV. The Origin of the Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **45**:81, 1918.

5. Ginsburg, H.; Tumpowsky, I., and Hamburger, W. W.: Contributions to the Physiology of the Stomach, XXXV. The Newer Interpretation of the Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916.

6. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum. Gastric and Duodenal Contractions as the Direct Cause, J. A. M. A. **70**:837 (March 23) 1918.

of the patients in whom contractions of Type III (Fig. 2) or Type IV (Fig. 3) were recorded, experienced burning or gnawing pain similar to pain in ulcer, in practically every instance synchronous with the peristalsis, but as long as Type I contractions were recorded they were without pain.

The degree of acidity seemed to have little bearing on the pain. The acidity on the whole was lower at the time of the pain and active peristalsis than during the absence of pain and slight peristalsis.

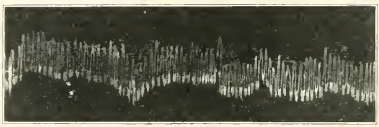

Fig. 1 (Case 147,732).—Type I contraction. Tonus variation or digestive peristalsis, without pain.

Group 2.—This group comprises five patients with achylia gastrica. Three patients were without pain and without any demonstrable pathologic condition, one patient had gastric ulcer and one had pain without any demonstrable pathologic condition. The three patients without pain had no definite epigastric distress other than a little bloating or a burning sensation. Two of them revealed only Type I contractions during the course of the experiment; but the third had definite

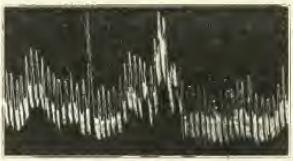

Fig. 2 (Case A351,625).—Type III contraction. Beginning hunger peristalsis, with pain.

Type II (Fig. 4) and Type III peristalsis. These three patients clearly show that normal tonus variations and peristalsis can be present in achylia gastrica. The patient with gastric ulcer (Case A147,732) had repeated gastric analyses which failed to reveal evidence of free acids. The typical epigastric pain of a gastric ulcer continued, pain coming on from two to three hours after eating, with relief by food, water, alkalis,

gastric lavage, and emesis. On several occasions during a period of distress, acid-free contents were washed out of the stomach and the patient obtained prompt relief. Kymographic tracings begun two hours after a test meal showed tonus variations without pain (Fig. 4); but gradually as the tonus variations were replaced by more active contractions of Type II and Type IV intermittent epigastric pain was complained of, which in almost every instance was synchronous with the peristalsis. The fifth patient (Case A254,365) had pain typical of ulcer, differing somewhat in that it continued for long periods without remission, but

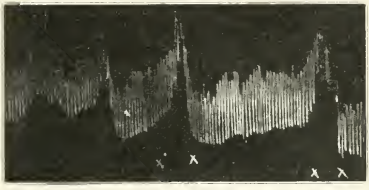

Fig. 3 (Case A356,604).—Type IV contraction. Vigorous hunger peristalsis, which is coincident with gnawing or burning pain.

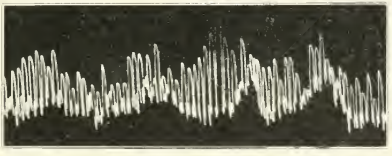

Fig. 4 (Case A254,365).—Type II contraction. Exaggeration of tonus variation which precedes the vigorous peristalsis; frequently associated with a moderate amount of pain.

no demonstrable pathologic condition. Several analyses of gastric contents failed to reveal any evidence of free acidity. At the time the patient experienced pain the kymograph recorded Type II (Fig. 4) and Type III (Fig. 2) contractions, the pain being absent during the period of slight tonus variations (Fig. 1).

REPORT OF CASES

Case 1 (A47,732).—*History.*—S. A. M., aged 49 years, first came to the Clinic, Dec. 11, 1915, complaining of epigastric pain three to four hours after meals. The attacks occurred in spells lasting from a few weeks to a month and remissions lasted from three to five months. Belching, drinking hot water,

milk, or cream had usually given relief. For three months beginning August, 1915, he had vomited nearly every night between 1 and 3 a. m.

Operation (Dec. 20, 1915).—This revealed a perforating duodenal ulcer extending into the pylorus, with adhesions to the head of the pancreas and with almost complete closure of the pylorus. Gastro-enterostomy and appendectomy were performed. Gastric analysis at this time revealed total acids 42 and free acids 30, with laboratory findings pointing to pyloric obstruction. The patient was free from symptoms for three months following operation.

Course.—From 1916 until the patient's second admission to the Clinic, June 19, 1921, he had frequent attacks of epigastric pain two to three hours after meals, which were relieved by emesis, food and alkalies. Roentgen-ray examination revealed a gastric ulcer.

At operation, June 27, 1921, scar tissue was found on the duodenum, but no ulcer within. An ulcer 1.5 cm. in diameter was located on the lesser curvature of the stomach, 3.75 cm. above the pylorus. The gastro-enterostomy was found to be patent and functioning. The ulcer was excised and the diagnosis confirmed by microscopic examination.

Case 2 (A254,365).—*History.*—M. T., aged 25 years, first came to the Clinic Dec. 26, 1918. He complained of epigastric distress of a burning character one hour after meals and at midnight. The pains were usually relieved by eating. In addition he complained of diarrhea which was closely associated with the epigastric distress. Gastric analysis failed to reveal any free acidity. *Endameba histolytica* was found in the stools. He was given emetin treatments for five days and sent home with advice as to treatment of diarrhea.

Dec. 26, 1919, the patient returned, still complaining of frequent attacks of burning pain in the epigastrium. The pain would be present for three or four days and then disappear for a week. The diarrhea had cleared up. He was given bromids three times daily after meals.

Dec. 27, 1920, the patient again returned with identical gastric complaints. The bromids had given relief for six months. This time he was given dilute hydrochloric acid, fifteen minutes after meals.

April 19, 1921, the patient returned with epigastric pain which had not been relieved by the previous treatment with hydrochloric acid.

The stomach had been examined with the roentgen ray on each admission but no evidence of gastric or duodenal ulcer had been obtained. Repeated gastric analysis had failed to reveal any free acids.

At the last visit kymographic records were taken which showed that the pains were intermittent and coincident with the active peristalsis. Alkalies and tincture of belladonna gave relief.

COMMENT

The two groups of patients substantiate the theory of variations in tonicity and peristalsis as the main factor in the cause of gastric pain; the acidity is considered a secondary and in some cases not even a necessary finding, as in the two cases of achylia gastrica. That the motility and tonicity of the stomach is quite independent of the acidity is indicated by the cases of achylia in which all the normal contractions were obtained in the absence of acidity. Furthermore, emptying of the stomach was not interfered with, since in none of these cases were there the slightest symptoms or signs of retention.

The quiescent period is probably the result of a diminution in the degree and extent of the inflammatory process, together with a decrease in the tonicity and contraction of the gastric and duodenal musculature. The administration of food, alkalies, water, emesis and gastric lavage

temporarily produces this quiescent state, mainly through the inhibition of the peristalsis which is replaced by the nonpainful digestive peristalsis, described by Rogers and Hardt.[7] The acid in all probability merely exaggerates to some extent the pain resulting from the more vigorous peristalsis and pyloroduodenal spasms.

The logical therapy in cases of gastric and duodenal ulcer should, it seems, tend primarily to inhibit peristalsis. About 85 per cent. of the patients treated surgically in the Mayo Clinic have been cured of the ulcer or satisfactorily improved. It might be assumed from these results that surgical procedures inhibit the vigorous peristalsis for a period long enough to promote healing of the ulcer, or at least a subsidence of the more acute inflammatory process. It is hoped that in the future this assumption can be demonstrated more conclusively by the kymographic method.

CONCLUSIONS

1. Gastric ulcer may be present in patients with achylia and may produce all the clinical symptoms characteristic of ulcer. The pain is primarily due to the peristalsis acting on an irritable focus. All the medical measures by which gastric acidity is neutralized and suppressed also inhibit the gastric peristalsis and thus relieve the pain.

2. Patients with gastric achylia in the absence of any demonstrable organic lesion may reveal the normal tonus variations and peristalsis.

3. Patients with uncomplicated duodenal ulcer do not experience pain during the period of digestive peristalsis, even in the presence of an adequate acidity. Active peristalsis of the "hunger type" (Types III and IV) is essential in the production of pain.

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7. Rogers, F. T., and Hardt, L. L. J.: Contributions to the Physiology of the Stomach. XXVI. The Relation Between the Digestion Contractions of the Filled, and the Hunger Contractions of the "Empty" Stomach. Am. J. Physiol. **38**:274, 1915.

THE SEAT OF THE EMETIC ACTION OF THE DIGITALIS BODIES *

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Emetics are divided commonly into two classes: (a) Those which irritate certain nerve endings in the gastric mucous membrane; (b) those which stimulate the vomiting center in the medulla directly.

Hatcher and Eggleston [1] showed that emesis follows the intravenous injection of any one of the several digitalis bodies in dogs, even after the removal of the gastro-intestinal tract, and while they considered it possible that vomiting is due to a reflex arising in some peripheral structure, such as the esophagus, they came to the conclusion that all the evidence available points to the vomiting center as the seat of the emetic action of all of the digitalis bodies.

The fact that these bodies differ so widely in their chemical composition directed our attention to the coincidence that every member of the group shows a greater or less parallelism between its cardiac and emetic activities, though the several members of the group differ widely one from another with reference to the intensity of both of these actions, suggesting a common seat, and we have sought to determine whether the vomiting which digitalis bodies induce is indeed of cardiac origin.

It is also of especial interest that emesis and cardiac standstill may be induced within a few seconds after the intravenous injection of a large dose of digitoxin but that neither of these effects can be induced nearly so quickly by the largest doses of ouabain.

We have used crystalline ouabain (sometimes called crystalline strophanthin) in the larger number of our experiments because it is a typical digitalis body of uniform purity, is readily soluble in water, and it lends itself to studies such as we planned. We have also used amorphous strophanthin, digitoxin, digitalein and tincture of digitalis in those experiments which we consider crucial.

The digitalis bodies leave the circulation rapidly after their intravenous injection,[2] and only traces of the poisons can be found in the

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* From the Laboratory of Pharmacology of Cornell University Medical College.

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1. Hatcher and Eggleston: The Emetic Action of the Digitalis Bodies, J. Pharmacol. & Exper. Therap. **4**:113 (Nov.) 1912.

2. Hatcher and Eggleston: Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, J. Pharmacol. & Exper. Therap. **13**:433, 1919.

blood after a few minutes, a fact of which we made use in the preliminary experiments of this investigation. In these experiments we tied or compressed the carotid and vertebral arteries, in order to diminish the circulation in the medulla, after which an amount of a digitalis body equal to a little more than the average emetic dose was injected intramuscularly or into the femoral vein. Emesis resulted in nearly every case though it is certain that less of the poison reached the vomiting center than could have reached it had there been no interference with the circulation.

Vomiting occurred in one experiment within two minutes after beginning the intravenous injection of ouabain and at the moment when an amount equal to about twice the average emetic dose had been injected, though emesis was delayed in the greater number of the experiments. This delay was almost certainly due in part to delayed absorption after intramuscular injection, and this in turn to the fact that the animals were somewhat depressed.

The cerebral circulation of the dog is said to become nearly normal soon after the carotid and vertebral arteries are tied, but this is not true of the cat. The animals usually slept or remained drowsy after the operation of tying the vessels, and further evidence that the circulation in the brain of the cat is greatly diminished by tying these arteries is afforded by the fact that the internal and external jugular veins were severed in one of these experiments without the loss of a drop of blood, and the blood escaped slowly when the carotid artery was cut across.

The results of these experiments are not conclusive because we cannot be absolutely certain that all of the poison had left the blood stream before emesis occurred and the delay in the onset of vomiting possibly may have permitted a fairly large amount to reach the medulla. The onset of emesis within two minutes after beginning the injection of ouabain in the first experiment, and at a time when the total amount injected was equal to only about twice the average emetic dose, affords strong evidence that vomiting was not due to a direct action on the medulla, because the interference with the circulation prevented the poison from reaching the medulla in an amount comparable to that which would reach it in the normal animal after an emetic dose.

An interval of twenty-four hours had been allowed to elapse after the operation and before the ouabain was injected in the first experiment, however, and it is possible that the circulation was partially reestablished during that interval, though the condition of the animal did not indicate that the circulation was normal. In the remaining experiments of this series the drugs were injected after the lapse of a

period which was considered necessary for complete recovery from the effects of the anesthetic. The protocols in brief of two experiments will be given.

PROTOCOLS OF EXPERIMENTS WITH OUABAIN

EXPERIMENT 1.—Female cat, weight 3.8 kg.; anesthetized with ether; the carotid arteries tied at a point about 3 cm. above the level of the sternum; the vertebral arteries tied near their origin; wound closed with sutures.

4:40 p. m.: Animal released; sleeps at once.
4:50 p. m.: Lifts head; wakens; soon sleeps; rapid respiration.
5:40 p. m.: Asleep but moves frequently.
Following day:
9:00 a. m.: Sits up; disturbed equilibrium.
3:25 p. m.: Femoral vein connected with buret for injection.
3:30 p. m.: Start injection of ouabain 1:10,000.
3:32 p. m.: Emesis; 0.13 mg. ouabain per kilogram of weight injected. Animal destroyed.

EXPERIMENT 2.—Male cat, weight 3.58 kg. Operation as in preceding experiment except that chloroform was used to induce anesthesia.

3:10 p. m.: Animal released.
3:35 p. m.: Sleeps quietly.
3:45 p. m.: 0.075 mg. ouabain per kg., 1:10,000, injected intramuscularly.
4:08 p. m.: Nausea followed almost at once by vomiting.
Following day: Animal in partial stupor; killed with chloroform; respiration markedly diminished; difficult to kill animal even with chloroform applied to nose on cloth.

Subsequent experiments were designed to compare the effect of permitting the drug to act on the vomiting center but not on the rest of the body, with that seen when the poison was allowed to enter the general circulation but not to reach the vomiting center.

In five experiments the carotid and vertebral arteries were tied or compressed, and the brain, with the vomiting center, was perfused for periods varying from five to fifteen minutes through the carotid arteries and jugular veins with defibrinated blood to which ouabain had been added in amounts varying from a small fraction of the average emetic dose to one that caused convulsions. In no case did vomiting occur nor were any symptoms of nausea observed after the animal was released.[3]

Five experiments were performed in the manner just described, except that the ouabain was injected into the femoral vein while the brain was being perfused with unpoisoned defibrinated and diluted blood, the perfusion being continued for periods of ten minutes, during which time all but traces of the poison left the circulation. The brain was perfused at a pressure greater than that of the general cir-

3. We employed a modified Langendorff apparatus; the temperature of the perfused fluid was kept at 37 C.; the pressure was regulated by means of compressed oxygen or air and a mercury valve.

culation, and we are fairly certain that no more than traces of the poison (if any) reached the medulla during the period of perfusion, though we could not measure the pressure in the circle of Willis at that time. Three of these five animals vomited; one showed unmistakable signs of nausea, and one showed some signs of nausea but these two did not vomit, because they were much depressed. The vertebral arteries were intact in two of these experiments but the results did not differ materially from those in two experiments in which they were tied.

Every one who has perfused the brain of the living animal appreciates the difficulties which are involved in the attempt to secure an approximately normal condition of the animal during the procedure, and we shall not enter into a discussion of the details of these experiments. We should be unwilling to base our conclusions concerning the seat of the emetic action of the digitalis bodies on the results of the perfusion experiments alone, but we can say that these results are in harmony with those obtained in other experiments which afford conclusive evidence that the digitalis bodies do not induce emesis through a direct action on the medulla. Those animals which were used in this series of experiments and which did not vomit after the injection of ouabain intramuscularly or into the femoral vein were so greatly depressed that emesis could not be expected to occur.

It is well known that Thumas [4] described an area measuring about 5 mm. in length and about 2 mm. in width, situated in the floor of the fourth ventricle and extending to a point about 2 mm. posterior to the calamus scriptorius, which he called the vomiting center. Thumas found that destruction of the tissue lying within this area inhibits vomiting, and that the application of apomorphin hydrochlorid to this area causes emesis in dogs. We have found that the application at this point of as little as 0.000,1 mg. apomorphin hydrochlorid for every kilogram of body weight causes emesis in dogs, and that larger doses cause vomiting within a few seconds.

The experiment is performed in the following way: The animal is anesthetized with chloroform and secured with the belly resting on the operating board; the base of the skull is exposed by incision; a button of bone is removed by means of a trephine having a diameter of six millimeters; the opening is enlarged slightly by chipping the bone; the dura mater is incised at the margin of the cerebellum; the wound is closed with a pledget of cotton soaked in phenol solution in oil and the animal is released. When the animal has recovered from

4. Thumas, L. J.: Ueber das Brechcentrum und über die Wirkung einiger pharmakologische Mittel auf dasselbe, Virchows. Arch. f. path. Anat. **123**: 44, 1891.

the effects of the anesthetic, it is replaced on the board (or, in some cases, it stands on the table); the tissues are pulled aside and any blood or spinal fluid is removed with a pledget of cotton; the solution to be tested is dropped onto the area from a syringe graduated to 0.01 c.c., or the solution is dropped onto a very small pointed camel's hair brush with which it is painted onto the surface. It is important that general anesthesia be avoided at this time, and the use of the phenol in oil, applied to the edges of the wound, prevents pain.

Cats and dogs usually bear the operation well and appear normal as soon as they recover from the effects of the anesthetic. Ether was used in one of our experiments in which the drug was applied on the day following the operation, but chloroform was used in the other experiments because it is much less prone to cause vomiting. None of our animals vomited from the effects of the operation or from those of the chloroform. Troublesome hemorrhage from the diplöic vessels commonly follows the use of a trephine of greater diameter than that mentioned. Some of our experiments were performed with practically no loss of blood. Physiologic solution of sodium chlorid was dropped onto this area in control experiments and was found to be without perceptible effect.

We have sought to determine whether the digitalis bodies induce vomiting after direct application to the vomiting center, and ouabain, amorphous strophanthin, digitoxin and digitalein were applied to this area, but in none of the experiments of this series were we able to induce nausea or vomiting in this way, though widely varying amounts of the poisons were used. When very large doses of these drugs are applied to the center, they cause death without inducing emesis, and the application of moderately large, but not fatal, doses also appears to cause depression of the vomiting center, for emesis cannot then be induced by the intramuscular injection of ouabain.

The direct application of small amounts of the digitalis bodies to this area does not have any perceptible effect on the vomiting reflex, and the intramuscular injection of ouabain then causes emesis precisely as it does in the normal animal. While we speak of the amounts thus applied as small, since they are far less than the amounts required by intravenous injection to cause vomiting in the normal animal, they are actually much larger than those which can come into contact with the tissues of this area after the intravenous injection of an emetic dose and before vomiting takes place. The tissue embraced within the area described by Thumas constitutes approximately 1/75,000 of the total weight of the dog, and since vomiting frequently follows the intravenous injection of ouabain or digitoxin within two or three

minutes, it is evident that only a minute fraction of the total amount injected can come into contact with the vomiting center before emesis takes place.

The protocols in brief of four experiments are given. The first of these shows that armorphous strophanthin is absorbed into the general circulation, for the effects were typical except for the absence of nausea and vomiting, and that it causes depression of the vomiting mechanism. The second experiment shows that digitoxin also induces depression of the vomiting mechanism, since the intramuscular injection of a fatal dose of ouabain then failed to cause emesis. The third experiment shows that the application of a small amount of ouabain is without influence on the vomiting reflex, and the fourth shows that the application to this area of a moderate amount of ouabain causes depression or paralysis of the vomiting mechanism, since the intramuscular injection of very large doses of ouabain then failed to induce emesis. The result in this experiment is of interest in that the animal lived thirty-six minutes after the first intramuscular injection of an amount of ouabain equal to nearly three times the average fatal dose, and that it lived twenty minutes after the second injection, made sixteen minutes after the first injection, having received a total of nearly eight times the average fatal dose. It would appear that the depression induced delays the absorption of the drug from the intramuscular tissues.

The results of these experiments in which the poison was applied directly to the vomiting center point almost conclusively to the fact that ouabain does not induce emesis through any direct action on the medulla, and the absorption of a fatal dose after its application to the floor of the fourth ventricle without the production of nausea is of especial interest.

PROTOCOLS OF EXPERIMENTS

Experiment showing absorption of amorphous strophanthin after its application to the floor of the fourth ventricle.—Male cat, weight, 2.3 kg. Chloroform administered for anesthesia.

11:08 a. m.: Operation completed, animal released.
1:30 p. m.: Animal ate meat.
2:30 p. m.: 0.5 mg. amorphous strophanthin per kg. in 20 parts of physiologic solution of sodium chlorid applied to the floor of the fourth ventricle; immediate depression; animal unable to stand.
2:40 p. m.: Respiration irregular.
3:05 p. m.: No nausea; death.

Experiment showing depression of the vomiting mechanism following the application of a moderate amount of digitoxin to the floor of the fourth ventricle.—Male cat, weight 4.4 kg.; chloroform administered for anesthesia.

11:45 a. m.: Operation completed.
2:25 p. m.: Water administered through a stomach tube.
2:31 p. m.: 0.002 mg. digitoxin per kg. in 1.000 parts mucilage applied to floor of fourth ventricle; animal released; condition excellent.

2:48 p. m.: No perceptible effect; 0.45 mg. ouabain per kg. of weight injected intramuscularly.
3:03 p. m.: No symptom of nausea; convulsions and death.

Experiment showing that the application of a small amount of ouabain to the floor of the fourth ventricle is without perceptible effect on the vomiting mechanism.—Female cat, weight, 2.24 kg.; chloroform administered for anesthesia.

2:10 p. m.: Operation completed.
2:30 p. m.: 0.005 mg. ouabain per kg. in 10,000 parts physiologic solution of sodium chlorid, applied to the floor of the fourth ventricle.
3:00 p. m.: No symptoms of nausea.
0.2 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
3:15 p. m.: Emesis, repeated.
3:20 p. m.: Convulsion and death.

Experiment showing the depressant action of a moderate amount of ouabain on the vomiting mechanism following its application to the floor of the fourth ventricle.—Female cat, weight, 2.9 kg.; chloroform administered for anesthesia; operation as preceding.

3:15 p. m.: Animal appears normal.
3:47 p. m.: 0.01 mg. ouabain per kg. in 500 parts physiologic solution of sodium applied to the floor of the fourth ventricle; respiration rapid.
4:30 p. m.: Respiration about normal.
4:49 p. m.: No symptom of nausea.
0.33 mg. ouabain per kg. intramuscularly.
5:05 p. m.: 0.66 mg. ouabain per kg. intramuscularly.
5:18 p. m.: Walks normally; diarrhea.
5:25 p. m.: No symptom of nausea; convulsion and death.

It is well known, of course, that the heart is supplied not only with nerve fibers from the vagus, but also with fibers from the sympathetic which pass through the stellate ganglia to the sympathetic chain of ganglia, and we found that cutting the cord above the level of the second thoracic vertebra (which prevents impulses from passing from the heart to the medulla by way of the sympathetic) usually prevents nausea and vomiting after the administration of digitalis bodies.

Section of the cord below the level of the fifth thoracic vertebra has no perceptible effect on the emetic action of the digitalis bodies. This operation does not interfere with afferent impulses from the heart, hence these results have a certain value only in connection with those in which the cord was cut at a higher level.

Since the emetic action of the digitalis bodies is sometimes abolished by section of the cord above the level at which the sympathetic fibers from the heart enter, and since atropin does not affect this action, we did not anticipate that vagotomy would influence it, nevertheless we undertook to determine the effect of this operation.

A cannula was placed in the trachea and the vagi were cut at the level of the sixth cervical vertebra, after which the injection of ouabain invariably caused vomiting in four experiments in the cat.

Removal of the stellate ganglia alone interfered with the emetic action of ouabain in some of these experiments, and removal of the ganglia together with cutting of the cardiac branches of the vagus prevented the appearance of symptoms of nausea almost invariably, after the administration of digitalis bodies, but mercuric chlorid still caused emesis promptly. In one experiment of this type, however, nausea followed the injection of digitalis, but a necropsy on the cat showed that the sympathetic cardiac nerve gave off three small branches to the sympathetic chain at a point between the heart and the stellate ganglion, consequently the removal of the ganglia did not prevent the passage of impulses from the heart through the sympathetic to the medulla in this experiment. The sympathetic nerve shows many irregularities in different individuals, and care is necessary in the interpretation of the results of experiments in which it is involved.

We believe that the results of these experiments justify the conclusion that when the nerve supply to the heart is intact the injection of a digitalis body causes emesis if the animal is in good general condition, but that the digitalis bodies are incapable of inducing nausea or vomiting when all of the nervous connections between the heart and the medulla are cut, though mercuric chlorid still causes vomiting exactly as it does in the normal animal.

This would indicate that the emetic impulses to which ouabain (or digitalis) gives rise do not traverse the same afferent path, or paths, which the afferent emetic impulses resulting from the action of mercuric chlorid traverse, or, to express it more accurately, mercuric chlorid appears to give rise to emetic impulses which reach the medulla through paths other than, or in addition to, those traveled by the emetic impulses which digitalis bodies induce.

Poisons are widely distributed in the vegetable kingdom, and it is evident that animals (as well as man) often take them with their food. We are so accustomed to seeing vomiting and diarrhea result from the irritant action of poisons (including under that term all harmful substances, such as indigestible food) that we are prone to lose sight of the fact that the stomach and intestine are not the only organs of the body which require protection from injury due to ingested poisons, and the heart, liver, lungs, kidneys and nervous system are attacked by certain poisons which have no injurious action on the stomach. The latter probably has developed a greater range of tolerance than any of the other organs, and it would be remarkable if Nature had provided such a complex reflex as that necessary for vomiting for the protection

5. The operation which we employed for the removal of the stellate ganglia is that described by E. Cyon* (6. E. Cyon: Methodik der physiologischen Experimente and Vivisectionen, Giessen, 1876, p. 174) which does not involve the opening of the chest.

of the stomach while leaving other, and more vital, organs having a similar innervation unprotected, and vomiting effectually protects the heart against the further absorption of poisons no less than it protects the stomach.

Impulses appear to pass upward from the heart to the medulla chiefly by way of the sympathetic, and to a less, though probably variable, extent, by way of the vagus. When the sympathetic alone is cut the administration of ouabain usually fails to induce nausea or vomiting. This may be due to the fact that the impulses passing upward by way of the vagus are usually insufficient to set up the vomiting reflex, or it may be that in those cases where vomiting is not elicited by the digitalis bodies after the sympathetic has been cut the vagus carries no fibers concerned with this vomiting reflex. It is significant, at any rate, that vagotomy alone does not prevent emesis after the injection of the digitalis bodies and that Eggleston [7] found that atropin does not interfere with emesis induced by digitalis, though it does inhibit that caused by pilocarpin.

In order to show that the cutting of the nerve paths from the heart, and not the disturbance due to the operative procedure, interfered with emesis, we conducted several experiments in which the celiac plexus was removed and the vagi were cut at the level of the diaphragm before the digitalis bodies were administered. This operation is more severe than that involved in the removal of the stellate ganglia and cutting the vagi in the neck, and some of the animals were so depressed that one could say with confidence that vomiting could not be induced by any digitalis body. Digitoxin was injected into two of these animals despite their being greatly depressed, because it seemed possible that the drug might induce emesis.

We repeated the experiment on seven cats which bore the operation with less depression, and all of these vomited or showed unmistakable signs of nausea, and we can say that the removal of the celiac plexus and cutting the vagi at the level of the diaphragm do not interfere with the emetic action of the digitalis bodies except in those cases in which the operation causes severe depression. With improved operative technic there was less depression and three of the last four animals of this series vomited while the fourth showed unmistakable signs of nausea.

Inasmuch as the animals in which the vagi were cut and those used in the last series of experiments behaved like normal animals (except for the depression) toward the digitalis bodies, there is no obvious need

7. Eggleston: The Antagonism between Atropin and Certain Central Emetics J. Pharmacol. & Exper. Therap. **9**:11 (Oct.) 1916.

of giving the protocols of the experiments, but condensed protocols of experiments of the other types are given.

The tabulated results of all experiments show that thirty-five of the animals which received digitalis bodies or mercuric chlorid vomited or gave unmistakable signs of nausea, and that the result in one of these was doubtful. Thirty of these actually vomited; four showed unmistakable signs of nausea but did not vomit after the severe operation for removal of the celiac plexus and vagotomy. One of these four, and the other one which failed to vomit, had only average emetic doses of ouabain, and such doses sometimes fail to induce emesis in normal animals. The typical signs of nausea—frequent chewing and swallowing of saliva—are as unmistakable as vomiting itself. When the animal licked its lips only infrequently, even though repeatedly, it was counted as doubtful. In none of the forty-four experiments in which the results are recorded as negative was there any symptom of nausea.

Protocols of experiments showing the effect of section of the cord on the emetic action of ouabain in the cat. 1. Female cat, weight, 1.7 kg.: chloroform administered for anesthesia.

2:20 p. m.: Spinal cord severed between the first and second thoracic vertebra; no interruption of respiration: fore legs normal, hind legs paralyzed.
2:30 p. m.: Condition fair.
4:15 p. m.: 0.15 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
4:36 p. m.: 0.1 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
5:20 p. m.: 0.05 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
5:25 p. m.: No evidence of nausea: convulsions and death.

2. Female cat, weight, 2.30 kg.: chloroform administered for anesthesia.

3:30 p. m.: Spinal cord severed between the sixth and seventh thoracic vertebra; slight hemorrhage.
4:10 p. m.: 0.2 mg. ouabain per kg. in 5,000 parts physiologic solution of sodium chlorid, injected intramuscularly.
4:20 p. m.: Vomiting.
4:25 p. m.: Convulsions and typical death.

Protocols of experiments showing effect of extirpation of the stellate ganglia and vagotomy. 1. Male cat, weight 1.12 kg.: chloroform administered for anesthesia.

12:10 p. m.: Operation for removal of both stellate ganglia; cannula into the trachea; vagi cut.
12:25 p. m.: 1.0 mg. digitoxin per kg. in 2,000 parts physiologic solution of sodium chlorid injected intramuscularly; rapidly developing depression.
1:34 p. m.: No symptoms of nausea have developed; convulsion.
1:36 p. m.: Death; necropsy shows complete extirpation of both ganglia.

2. Male cat, weight 1.64 kg.: chloroform administered for anesthesia.

3:10 p. m.: Completed operation as in preceding experiment.
3:18 p. m.: Condition excellent.

TABLE 1.—Showing the Effect of the Application of Digitalis Bodies to the Floor of the Fourth Ventricle (the Vomiting Center of Thumas) in the Cat

Substance Used	Amt. per Kg. in Fractions of a Mg.	Result
ouabain	0.01	great depression
ouabain	0.01	no perceptible effect
ouabain	0.01	depression of vomiting center *
ouabain	0.05	no perceptible effect
ouabain	0.1	no perceptible effect
ouabain	0.3	death
ouabain	0.005	no perceptible effect * *
ouabain	0.005	no perceptible effect * *
ouabain	0.005	no perceptible effect * *
ouabain	0.015	depression of vomiting center *
ouabain	0.001	no perceptible effect †
ouabain	0.0065	no perceptible effect
ouabain	0.45	death
am. strophanthin	0.000,67	no perceptible effect * *
am. strophanthin	0.01	no perceptible effect * *
am. strophanthin	0.5	death
digitoxin	0.01	depression of vomiting center *
digitoxin	0.002	depression of vomiting center *
digitalein	0.015	no perceptible effect * *

* The intramuscular injection of a digitalis body later failed to induce emesis, showing that the vomiting center was depressed.

* * The intramuscular injection of a digitalis body later induced emesis, showing that the vomiting center was not paralyzed.

† A dog was used in this experiment.

TABLE 2.—Showing the Effect of Extirpation of the Stellate Ganglia Alone, and with Vagotomy, on the Emetic Action of the Digitalis Bodies in the Cat

Substance Used	Am. per Kg. in Mg.	Mode of Administration	Nausea or Vomiting
EXTIRPATION OF THE STELLATE GANGLIA ALONE †			
ouabain	0.3	intramuscularly	—
ouabain	0.5	intramuscularly	—
digitoxin	1.5	intramuscularly	+
tinct. digitalis	1000.0	intravenously	—
mercuric chlorid	50.0	by stomach	+
tinct. digitalis	1000.0	intravenously	+
EXTIRPATION OF THE STELLATE GANGLIA WITH VAGOTOMY			
digitoxin	1.0	intramuscularly	—
digitoxin	1.2	intramuscularly	—
strophanthin	0.4	intramuscularly	—
strophanthin	0.5	intramuscularly	—
tinct. digitalis	1000.0	intravenously	—
mercuric chlorid	50.0	by stomach	+
mercuric chlorid	50.0	by stomach	+

* The + sign indicates that nausea or vomiting occurred; the — sign indicates that they were absent.

† There was incomplete extirpation of the stellate ganglia in three experiments, and in these nausea and vomiting occurred. They are not tabulated here but they are included in the table giving the summary of results of all of the experiments.

3:25 p. m. 50 mg. mercuric chlorid per kg. in 1,000 parts of water administered through stomach tube.

3:28 p. m. Retching.

3:46 p. m. Typical nausea and vomiting; animal destroyed; necropsy showed complete extirpation of both stellate ganglia.

Depression of the vomiting center could be determined only by the subsequent intramuscular or intravenous injection of an emetic dose of ouabain or other digitalis body. This test was not made in every experiment and it is probable that the vomiting center was depressed in several of those cases where no perceptible effect is recorded. General depression always tends to inhibit emesis.

TABLE 3.—Summary of the Results of Experiments Designed to Determine the Seat of the Emetic Action of the Digitalis Bodies

		Animal	Nausea or Vomiting	
			+	—
I.	*Carotid and Vertebral Arteries Tied:*			
	1. Ouabain injected	cat	5	0
	2. Digitoxin injected	cat	2	2*
	3. Controls; no poison used	cat	0	5
II.	*Perfusion of the Brain and Vomiting Center:*			
	1. Ouabain added to perfused fluid	cat	0	5
	2 Ouabain injected into femoral vein	cat	5	1?
	3. Controls; no poison used	cat	0	3
III.	*Digitalis Bodies Applied to Vomiting Center Directly:*			
	1. Ouabain	cat	0	8
	2. Ouabain	dog	0	2
	3. Digitoxin	cat	0	2
	4. Digitalein	cat	0	1
	5. Amorphous strophanthin	cat	0	3
IV.	*Section of the Cord:*			
	(a) above the level of the second thoracic vertebra:			
	1. Ouabain injected intramuscularly	cat	0	2
	2. Pilocarpin injected intramuscularly	cat	1?	1
	3. Mercuric chlorid by stomach (control)	cat	2	0
	(b) section below the level of the fifth thoracic vert.:			
	1. Ouabain injected intramuscularly	cat	2	0
V.	*Vagi Cut About the Level of the Sixth Cervical Vertebra:*			
	1. Ouabain injected	cat	4	0
	2. Mercuric chlorid by stomach (control)	cat	1	0
VI.	*Extirpation of the Stellate Ganglia:*			
	1. Ouabain injected	cat	0	2
	2. Digitoxin injected	cat	1	0
	3. Tincture digitalis intravenously	cat	3‡	1
	4. Mercuric chlorid by stomach (control)	cat	1	0
VII.	*Extirpation of the Stellate Ganglia and Vagotomy:*			
	1. Digitoxin intramuscularly	cat	0	2
	2. Amorphous strophanthin intramuscularly	cat	0	2
	3. Tincture digitalis intravenously	cat	1†	1
	4. Mercuric chlorid by stomach (control)	cat	1	0
VIII.	*Extirpation of the Celiac Ganglion with Vagotomy:*			
	1. Ouabain intramuscularly	cat	2	0
	2. Digitoxin intramuscularly	cat	5	2*

* These animals were much depressed.

‡ The extirpation was incomplete in two experiments.

† There was an abnormality of the sympathetic nerve.

While the present discussion is concerned primarily with the problem of the seat of the emetic action of the digitalis bodies, we wish to offer certain suggestions relating to the physiology of vomiting, and to state that we are now trying to secure evidence to determine whether our view is correct, for this problem is intimately concerned with that of the emetic action of the digitalis bodies.

We believe that the vomiting center described by Thumas bears the same relation to the act of vomiting (and possibly to other functions) which the spinal cord bears to the many normal reflexes in which it is known to be concerned. We believe that afferent impulses more or less constantly, or, at least, frequently, pass from various peripheral organs, including the stomach and the heart, through the sympathetic to the center in the medulla of the normal animal, but that these normal impulses are too feeble to set up the powerful reflex concerned in vomiting which is accompanied by violent, and even convulsive, contractions of the diaphragm and abdominal muscles.

It is well known, of course, that sensory impulses pass almost constantly from various parts of the body to the cord and give rise to slight reflex movements or none. If one scratches the skin gently there is no perceptible reflex, but a violent scratch induces a prompt reflex movement. It is also well known, of course, that strychnin acts on the cord in such a way that the passage of impulses is facilitated so that gentle scratching of the skin then induces typical convulsions.

We believe that the direct action of apomorphin on the vomiting center in the medulla is wholly analogous to that of strychnin on the cord, and that when the reflex excitability of the center is increased by apomorphin emesis results from normal afferent impulses.

We have recently obtained evidence which we believe lends some support to the view that the vomiting center of Thumas is merely a mechanism for the coordination of the reflexes concerned with nausea and vomiting (and possibly with other functions) and while we do not wish to enter into a discussion of the details of these experiments at this time we wish to say that we have induced nausea in cats and dogs, with actual vomiting in one, by applying strychnin to the vomiting center. It is significant also that morphin causes apomorphin-like emesis in dogs and strychnin-like convulsions in frogs.

Vomiting is known to be induced by the action of toxic substances or by injuries affecting many organs, including the stomach, intestines, liver, uterus, kidneys, testicles, and brain, and the results of our work point to the heart also as the seat of reflex vomiting.

Since the various reflex paths are always ready for instant service, even in individuals who have never vomited, it seems reasonable to suppose that the tone of these paths is maintained in health by means

of impulses which traverse them constantly or frequently; for example those from the stomach when it contains food, those from the heart when there is any minor disturbance or change in rate due to sudden exertion, and it is well known that violent or prolonged exertion frequently induces nausea of greater or less severity.[8]

If our views are correct, nausea and vomiting are of fundamental importance for the protection of various organs and tissues against poisoning (using that term in its broadest sense) and different organs have developed this protective mechanism independently of the irritant action which these substances exert on the gastric mucous membrane. It is especially interesting in this connection to observe that rodents, which are incapable of vomiting, have developed several different, and apparently independent, methods of protecting themselves against the toxic action of digitalis bodies on the heart, and also against the injurious actions of various other vegetable poisons.

SUMMARY

1. Several of the digitalis bodies, including ouabain, amorphous strophanthin, digitoxin, digitalein and tincture of digitalis, were used in about eighty experiments designed to determine the seat of their emetic action in the cat and dog.

2. In one series of experiments the carotid and vertebral arteries were tied, after which the intramuscular or intravenous injection of ouabain or digitoxin caused nausea or vomiting. Two animals failed to vomit owing to severe depression.

3. Nausea and vomiting could not be elicited in cats by perfusing the brain and medulla with diluted defibrinated blood to which ouabain had been added.

4. Nausea and vomiting were induced in cats by the injection of ouabain into the femoral vein in experiments in which the poison was prevented from reaching the medulla by perfusing that organ with unpoisoned diluted defibrinated blood for a period of ten minutes, during which all but traces of the poison left the circulation.

5. Nausea or vomiting could not be induced in any of the experiments on fourteen cats and one dog in which ouabain, amorphous strophanthin, digitoxin, and digitalein were applied to the floor of the fourth ventricle—the vomiting center of Thumas—in widely varying amounts.

6. The application of small amounts of digitalis bodies to the floor of the fourth ventricle—the vomiting center—is without influence on the vomiting reflex and the subsequent intramuscular injection of ouabain or other digitalis body causes emesis in the same way as it

8. One of us is frequently troubled with nausea following certain types of moderate exertion that induce some cardiac irregularity and rapid pulse.

does in the normal animal. Large doses applied to this area depress the center, and vomiting cannot then be elicited by the intramuscular or intravenous injection of a digitalis body.

7. Apomorphin hydrochlorid causes emesis in dogs when it is applied to the vomiting center in amounts corresponding to 0.0001 mg. per kilogram of body weight

8. Cutting the vagi at the level of the sixth cervical vetrebra (with tracheotomy) does not interfere with the emetic action of an intravenous injection of ouabain.

9. Section of the cord above the level at which the sympathetic cardiac fibers enter it, or removal of the stellate ganglia, usually prevents nausea and vomiting after the administration of digitalis bodies.

10. The severing of all nervous connections between the heart and the medulla always prevents nausea and vomiting after the injection of moderate doses of digitalis bodies.

11. Removal of the celiac plexus does not interfere with the emetic action of the digitalis bodies except in so far as the operation causes depression.

12. The administration of mercuric chlorid through a stomach tube in doses of 50 mg. per kilogram of weight causes emesis in cats in which the spinal cord has been cut at the level of the second thoracic vertebra and in those in which the stellate ganglia have been removed and the vagi have been cut.

CONCLUSIONS

Digitalis bodies cause reflex nausea and vomiting through their direct action on the heart.

The afferent impulses pass from the heart to the vomiting center in the medulla, by way of the sympathetic mainly, in part, by way of the vagus, probably.

Nausea and vomiting accompanying various circulatory disturbances, and more particularly those of cardiac origin, acquire a new interest for the clinician in the light of our results.

A theory relating to the physiology of nausea and vomiting is submitted.

THE ALKALI RESERVE IN PULMONARY TUBERCULOSIS *

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The question of acidosis in tuberculosis is still a debatable one. Pottenger [1] states that "there are probably many factors present in tuberculosis which have a tendency to increase acidosis, such as deficient intake of oxygen, deficient excretion of carbon dioxid, which occurs particularly in the disease, as a result of diminished pulmonary area, etc. Klebs [2] takes the opposite view, that "the gaseous metabolism in tuberculosis is but slightly, if at all, altered, the system accommodating itself to the lessened lung area, and, as is usual in the body, accomplishing the same amount of work with the decreased amount of tissue." A. Loewy, and Kraus and Chvostek [3] found a moderate increase in oxygen intake and carbon dioxid excretion in cases of pulmonary tuberculosis. It will be one of the objects of this work to show that in far advanced cases of pulmonary tuberculosis with considerable destruction of lung tissue by cavitation and caseous bronchopneumonia, there is only a slight decrease in the blood alkali reserve, at no time approaching a real acidosis.

The cases were carefully selected from 213 patients having every variety of lesion, the far-advanced type predominating. The method of Van Slyke [4] was used to determine the bicarbonate content of the blood plasma in terms of the percentage by volume of carbon dioxid. Using the precautions outlined by Van Slyke, 10 c.c. of blood was drawn from a median vein at the elbow, placed in a centrifuge tube containing 5 drops of a 20 per cent. solution of potassium oxalate, and covered with liquid petrolatum. The blood was centrifuged and the carbon dioxid combining power of the plasma determined within three hours in every instance. The temperature, pulse and respiration of each patient was taken from fifteen minutes to half an hour after the blood was drawn. The first specimen of urine passed by the patient following withdrawal of blood was examined for reaction, and at the same time tests for urochromogen and diazo substances were made. The reaction of the urine was determined by the use of a 0.2 per cent.

* From the Percy Shields Memorial Research Laboratory, Cincinnati Tuberculosis Sanatorium, and the Department of Bacteriology, University of Cincinnati.

1. Pottenger, F. M.: Clinical Tuberculosis, V. **1**:456, 1917.
2. Klebs, A. C.: Tuberculosis, 1909, p. 266.
3. Loewy, A., Kraus & Chvostek: quoted from Arnold Klebs.[2]
4. Van Slyke, D. D.: Method of determining carbon dioxid and carbonates in solution, J. Biol. Chem. **30**:347 (June) 1917.

solution of methyl red in alcohol. One drop of this reagent was added to 5 c.c. of clear urine in a test tube, the contents shaken and the color reading made by looking through the depth of the fluid. A distinct canary yellow color imparted to the urine was indicative of a urine alkaline to methyl red, i. e., having a hydrogen-ion concentration less than p_H 5; an orange color pointed to a urine neutral to methyl red; i. e., a hydrogen-ion concentration of p_H 5; while a red color showed a urine to be acid to methyl red or having a hydrogen-ion concentration greater than p_H 5.

An accurate check on the clinical conditions of the patients was kept, and the cases were classified in four groups as follows:

Condition 1.—"Up-patients," requiring only a minimum of rest hours. Clinically, these patients were in good condition, and usually did small chores in the ward kitchen or main dining room.

Condition 2.—Patients who were put to bed because they were coughing a little, running a slight afternoon fever denoting some active lung lesion. Clinically, these patients felt well and were kept in bed with difficulty. They were allowed toilet privileges only.

Condition 3.—These were bed-ridden patients, who ran a high afternoon temperature, i. e., over 100 F., coughed a good deal, produced considerable sputum daily, suffered with chills and sweats, and were slightly dyspnoeic at times. Clinically, these patients were manifestly ill.

Condition 4.—These patients suffered from an accentuation of symptoms outlined under Condition 3, and were considered in an immediately dangerous state. They would sometimes become slightly cyanotic with approaching death.

DATA AND RESULTS

The cases selected were males and females, white and colored, old and young, having every variety and severity of lesion. Sixty-seven determinations were made on sixty-one cases. In six cases, two determinations were made about a week apart in an endeavor to obtain records as close to death as possible.

A change for the worse in the clinical condition of the patient was always accompanied by a mild corresponding drop in the alkali reserve (Table 1).

In five of the six cases in which two determinations were made between five and sixteen days apart, a decrease of from two to eight points in the alkali reserve was noted (Table 2).

Comparison of the alkali reserve of the blood with the reaction of the urine in the bladder in a series of cases showed a tendency for the former to decrease, as the reaction of the urine passed from alkaline to acid (Table 3).

A comparison of the alkali reserve with the temperature of patients showed that an increase in temperature above 100 F. was usually accompanied by a drop in the alkali reserve (Table 4).

TABLE 1.—Blood Alkali Reserve of Sixty-One Patients *

Clinical Condition	1	2	3	4
Number of Determinations	22	23	13	9
Alkali Reserve Range	48-70	50-73	52-62	50-62
Average Alkali Reserve	61.1	59.9	56.4	54.4

* Normal blood alkali reserve 53-78.

TABLE 2.—Blood Alkali Reserve in Six Special Cases

Case Number	Date	Alkali Reserve	Clinical Condition
F-186	3/31/21	56	III
	4/7/21	58	III
F-30	3/31/21	54	III
	4/7/21	52	IV
F-67	4/2/21	58	III
	4/18/21	50	IV
F-70	4/2/21	62	IV
	4/7/21	58	IV
E-178	4/2/21	60	III
	4/17/21	52	IV
E-308	4/7/21	62	III
	4/18/21	59	IV

TABLE 3.—Comparison of Alkali Reserve with the Reaction of Bladder Urine

Reaction of Urine	* Alkaline	Neutral	Acid
Number of Determinations	19	23	18
Range of Alkali Reserve	52-73	50-68	48-70
Average Alkali Reserve	61.1	58.0	57.7

* Alkaline to methyl red; hydrogen ion concentration less than $p_H 5$. Neutral to methyl red; hydrogen ion concentration, $p_H 5$. Acid to methyl red; hydrogen ion concentration greater than $p_H 5$.

TABLE 4.—Comparison of Alkali Reserve with Temperature

Temperature	100 F and under	Over 100 F
Number of Determinations	37	27
Range of Alkali Reserve	48-73	50-69
Average Alkali Reserve	60.4	56.6

There was apparently no correlation between variations in the respiratory rate of patients and the blood alkali reserve. In fifteen cases with a respiratory rate over 25, the average alkali reserve was 58.0, as compared with an average alkali reserve of 57.3 in fifty-two

cases with a respiratory rate under 25. There was no correlation between variations in pulse rate and the blood alkali reserve. In seven cases where blood had been drawn one to sixteen days previous to death, the blood alkali reserve ranged between 50 and 58, the average being 52.7. Two cases of acute miliary tuberculosis, diagnosis verified at necropsy, had alkali reserves of 52 each. In one case the blood was examined forty-one days, in the other case seven days previous to death.

The existence of positive urochromogen or diazo substance in the urine was indicative of a tendency for the blood alkali reserve to diminish. Eleven cases giving positive reactions showed an average alkali reserve of 56.3. It will be noted in Table 1 that this figure is very close to the average found in patients designated Condition 3, this latter average being 56.4.

TABLE 5.—The Alkali Reserve in Cases with Extensive Lung Destruction Showing Number of Days Before Death Following the Last Alkali Reserve Determination

Case No.	Alkali reserve	No. of days before death that alkali reserve was done
F-107	55	1
F-70	58	9
F-30	52	16
F-186	58	8
F-165	52	11
F-107	50	46
F-178	52	56
F-141	55	45
F-118	52	90
F-191	66	102
F-172	60	90
F-161	63	90

A careful study of the lung necropsy findings was made in twelve cases by Dr. J. B. Rogers. Every case revealed extensive lung destruction with fibrosis, cavitations and caseous bronchopneumonia, and yet the alkali reserve ranged between 50 and 63, the average being 56.2

With the permission of Dr. J. B. Rogers a detailed account of the lung necropsy findings is given in the first three cases outlined in Table 5.

Case 1.—Alkali reserve 55, one day before death.

Right Lung.—Practically the entire upper lobe is occupied by active acute interlocular cavities surrounded by a caseous gelatinous pneumonia. The lower border of the middle lobe is occupied by caseous pneumonia, while the apex contains a cavity approximately one inch in diameter. The upper half of the lower lobe contains numerous cavities, while the lower half is infiltrated with caseous pneumonia.

Left Lung.—The outstanding feature is the presence of an empyema. A cavity is found rupturing into the pleural sac which contains approximately

500 c.c. pus. The entire lung is collapsed and compressed against the hilum. Both upper and lower lobes are excavated by multilocular cavities surrounded by fibrous tissue.

Case 2.—Alkali reserve 58, nine days before death.

Right Lung.—The upper lobe is honeycombed by large multilocular cavities surrounded by a limited amount of fibrous connective tissue. The middle lobe contains numerous small cavities, one-half inch in diameter. The lower lobe is completely consolidated as a result of confluent caseation and broncho-pneumonia.

Left Lung.—The upper one half of the upper lobe contains large multilocular cavities, while the lower one half is infiltrated with caseous broncho-pneumonia. The upper one half of the lower lobe contains confluent caseous broncho-pneumonia.

Case 3.—Alkali reserve 52, sixteen days previous to death.

Right Lung.—Practically the entire upper lobe is hollowed out by a cavity, which is surrounded by confluent caseous bronchopneumonia. The middle lobe is infiltrated with confluent caseous bronchopneumonia. The lower lobe contains scattered masses of caseous bronchopneumonia.

Left Lung.—At the apex there is a cavity about one inch in diameter, surrounded by caseous pneumonia. The remainder of the upper lobe is occupied by smaller cavities which are surrounded by caseous bronchopneumonia. The lower lobe contains patches of caseous bronchopneumonia.

The necropsy findings in the remainder of the cases are very similar to those described above, the alkali reserve of the blood being surprisingly high in some of the cases with extensive lung destruction. This state of affairs is in sharp contrast with that found in influenza and influenzal bronchopneumonia where the alkali reserve dropped as low as 24 in a severe case (Hachen and Isaacs[5]).

SUMMARY AND CONCLUSIONS

1. In tuberculosis there is a moderate depletion in the blood alkali reserve only after the lesion becomes far advanced and is accompanied by rather severe clinical symptoms, such as increased fever, chills and sweats, slight dyspnea and general malaise (Table 1).

2. The blood alkali reserve in an individual case continues to decrease slowly with approaching death until a minimum of 50 is reached (Table 2).

3. The blood alkali reserve was 3 points lower in cases where the urine as voided was neutral or acid to methyl red. An acid urine is, of course, not an indication that an "acidosis" exists (Table 3).

4. An increase in temperature above 100 F. was usually accompanied by a decrease in the alkali reserve (Table 4).

5. There was no correlation between the respiratory rate and the blood alkali reserve.

6. There was apparently no correlation between the pulse rate and the blood alkali reserve.

5. Hachen, D. S., and Isaacs, R.: The Alkali Reserve in Epidemic Influenza and Broncho Pneumonia, J. A. M. A. **75**:1624 (Dec. 11) 1920.

7. The alkali reserve was comparatively low (52) in two cases of acute miliary tuberculosis.

8. Urochromogen or diazo substance in urine was frequently found when the blood alkali reserve was relatively low.

9. In thirteen cases showing at necropsy extensive tuberculous involvement of all lobes, the average alkali reserve was 56.

10. Although there is a decrease in the alkali reserve as the case advances, at no time is there a marked "acidosis" in pulmonary tuberculosis.

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PIGMENT METABOLISM AND REGENERATION OF HEMOGLOBIN IN THE BODY *

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The words "pigment metabolism" should mean the general exchange and balance in the body of all pigment substances—the income of pigment forming material, the story of pigment building in the body, the disposition of recognized end products in the body and the elimination of certain pigment complexes.

Any junior medical student can relate the true story of pigment metabolism in the human body. The medical textbooks have long retold the story as illustrated in Figure 1; and it seemed to be one of the facts in physiology which stood firm in the midst of progress and newer investigations. Its very age gave it respectability and true academic security of tenure. The time honored story is as follows: Certain food elements and iron are constructed in the bone marrow into a complex substance, hemoglobin. When the red cells are worn out or destroyed, the hemoglobin appears as bile pigment in a quantitative ratio. This bile pigment secreted into the intestine is changed to stercobilin and in large part excreted in the feces. Some of it may be absorbed and re-excreted by the liver; but, given a liver abnormality, it may escape the portal blood stream and be excreted by the kidneys as urobilin.

A number of recent investigations have modified this picture somewhat, as illustrated by Figure 2. Wilbur and Addis [1] suggest that with the absorption of stercobilin the "pyrrol complex" may be split off and reconstructed into hemoglobin. This is a very interesting hypothesis and would be an example of a very pretty conservation on the part of the body, but we shall review experimental observations which we believe rule out this suggestion.

Our conception of body pigment metabolism may, perhaps, be expressed diagrammatically as shown in Figure 3. One point in particular deserves notice in that we no not accept as proved that

* From the George Williams Hooper Foundation for Medical Research, University of California, San Francisco; Harvey Society Lecture, Jan. 7, 1922.

1. Wilbur and Addis: Arch. Int. Med. **13**:235 (Feb.) 1914.

there is any absorption of stercobilin from the intestine. Granting that urobilin may be formed in the liver, there is not a shred of evidence, clinical or experimental, that stercobilin is ever absorbed from the intestine. Most observers admit that a times urobilin may be formed in the liver (Wilbur, Addis and many others), but forget this fact when absorbed in a discussion of the formation of stercobilin in the lumen of the intestine. We believe that stercobilin in the intestine is as little concerned with this question of pigment metabolism as is the stercobilin in the feces or the urobilin in the bladder urine. Therefore in Figure 3 we know of no evidence for a line between the circles indicating urobilin and stercobilin.

We have published (Whipple & Hooper[2]) evidence that bile pigment is not necessarily related directly to destruction of red cells and hemoglobin. This is indicated in Figure 3 by a direct line from "pigment complex" to "bile pigment" and illustrates the relation of

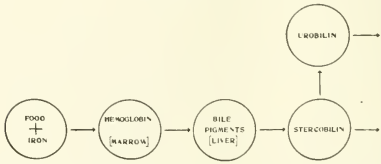

Fig. 1.—Pigment metabolism in the human body as formerly believed to occur.

bile pigment production to food and other factors which can modify pigment production quite apart from hemoglobin destruction. Granting that bile pigment production may be influenced by other factors than hemoglobin destruction, we see how absurd it is to draw conclusions unreservedly as to blood destruction from the analysis of stercobilin—for example, in pernicious anemia. The life cycle of the red cell has been established (Eppinger and Charnas[3]) on such flimsy evidence as the analysis of stercobilin.

That body protein as well as food factors are concerned in the production of bile pigment and hemoglobin is easily established by fasting experiments. Bile pigment excretion will continue during fasting periods, and, more than this, we have shown that hemoglobin will be formed in fasting periods not only sufficient for red cell maintenance but for actual increase above a moderate anemia level.[4] It is obvious

2. Whipple and Hooper: Am. J. Physiol. **40**:349, 1916.
3. Eppinger and Charnas: Int. of klin. Med., 1913, p. 78.
4. Whipple and Hooper: Am. J. Physiol. **45**:576, 1918.

that disintegration products of body cells are used in the upbuilding of hemoglobin and are related to the output of bile pigment, urobilin, stercobilin, and urochrome.

BILE PIGMENT

Much of the older work on the biliary pigments has been reviewed recently by Hooper and Whipple [5] and need not be discussed at this time. It has been claimed by some that hemoglobin introduced into the blood stream will be quantitatively excreted as bilirubin in the bile. Whipple and Hooper [6] have been able to show that no such quantitative relationship holds for hemoglobin and bile pigment. It seems very probable that much of the hemoglobin set free in the blood stream may be used in the body economy for a variety of purposes—among others the construction of hemoglobin for new red cells. For example,

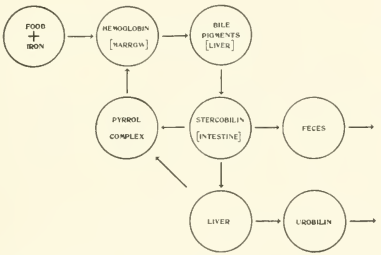

Fig. 2.—Pigment metabolism as modified by recent investigation.

it is sufficiently well established that intravenous injections of hemoglobin or the destruction of red cells in the body will aid in the recovery from simple anemia with consequent upbuilding of new hemoglobin.[7] It is very probable, however, that the hemoglobin in the blood stream is not used direct but only after being broken down to the unit structural factors—whatever these may be. This point is graphically illustrated by the double arrows between the "pigment complex" and "hemoglobin" in Figure 3.

It is now generally accepted that true bile pigment can be formed from hemoglobin within the body or by other than liver

5. Hooper and Whipple: Am. J. Physiol. **40**:332, 1916.
6. Whipple and Hooper: Am. J. Physiol. **43**:258, 1917.
7. Hooper, Robscheit and Whipple: Am. J. Physiol. **53**:263, 1920. Itami: Arch. f. exper. Path. u. Pharmakol. **62**:104, 1910. Itami and Pratt: Biochem. Ztg. **18**:302, 1909.

cells. Whipple and Hooper[8] showed that this transformation could be effected within two hours in the blood stream of the head and thorax with complete liver exclusion. The same workers[9] showed that hemoglobin can be transformed into bilirubin in the serous cavities within a period of twelve hours. McNee[10] has confirmed a part of this work. It is probable that the vessel endothelium and Kupffer cells are concerned in the vascular reaction. We believe that this reaction is not a physiologic curiosity but one of considerable importance in all conditions associated with escape of hemoglobin into the blood stream—for example, paroxysmal hemoglobinuria, malaria, toxic anemias, etc. Under such conditions we believe there is good evidence that much of the hemoglobin is changed to bile pigment and other substances quite apart from essential liver cell activity.

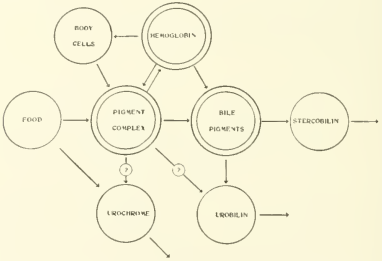

Fig. 3.—Conception of body pigment metabolism.

It is well established[2] that the bile pigment elimination in dogs can be increased by a change in diet—for example, a sudden change from a meat to a carbohydrate diet may increase the bile pigment elimination more than 50 per cent. This can be repeated time after time and it seems at least improbable that this reaction is dependent on blood destruction. We may explain this reaction, in part, as follows. The meat diet is normal for the dog. The increase in bile pigment excretion due to carbohydrate excess may represent an abnormal or alternative reaction—a deviation of pigment elements and construction into bile pigment for elimination. It is possible that some of these pigment elements concerned in this reaction might be

8. Whipple and Hooper: J. Exper. M. **17**:612, 1913.
9. Hooper and Whipple: J. Exper. M. **23**:137, 1916.
10. McNee: J. Path. & Bacteriol. **18**:325, 1913.

available under favorable conditions (anemia) for hemoglobin construction or under usual conditions (meat diet) for elimination elsewhere than in the bile. Urochrome is a possible end product of pigment elements and deserves much more study in normal and abnormal conditions.

The term "pigment complex" is used in this paper to indicate a group of substances which are essential parts of the mature body pigments. It is obvious that certain food factors contribute to this "pigment complex" as foods are directly concerned in the production of new hemoglobin and the formation of bile pigments and urochrome. It is equally clear that the body protein and cells contribute to this "pigment complex," as all body pigments are produced in measurable amounts in fasting periods. We believe that the evidence is sufficient to show that as hemoglobin disintegrates in the body it also contributes to the "pigment complex" and so influences, in a measure, the new formation of hemoglobin. It is probable that only a small amount of the destroyed hemoglobin is conserved in this fashion. The pyrrol nucleus seems to be one of the factors which must be concerned in this "pigment complex," and it is probable that all facts related to pyrrol metabolism will have a direct relation to the complicated body pigment metabolism. These points are illustrated graphically in Figure 3.

Bile pigments in the bile fistula animal are not increased by the feeding of fresh bile pigments or of fresh or cooked blood or of digestion products obtained from blood.[11] This might be assumed to be from lack of absorption. There is no evidence that bile pigment or stercobilin are absorbed from the intestine. However, it has been shown that the feeding of hemoglobin will influence the curve of new hemoglobin construction after anemias.[7] This indicates an absorption of substances which are concerned with the "pigment complex" but it is clear that these same factors do not influence the output of bile pigments in bile fistula dogs—at least under the conditions of our experiments. These experiments are much against the suggestion of Addis (Fig. 2) that there may be a conservation of bile pigment factors which are absorbed from the intestine and reconstructed into hemoglobin. Perhaps the strongest argument against the absorption of stercobilin and its utilization in body pigment construction (Fig. 2) is the fact that bile fistula dogs under observation continuously for two years or longer show no evidence of pigment lack, no anemia, no fall in pigment production and no reaction whatever to the feeding of bile pigments.

A study of the bile pigment output of the Eck fistula liver furnishes some interesting facts to consider at this time. Dogs with

11. Whipple and Hooper: Am. J. Physiol. **42**:256, 1917.

combined Eck and bile fistulas eliminate less bile pigment than controls—sometimes only from 30 to 50 per cent, of normal.[12] The Eck fistula liver is functionally inefficient and there is no direct contact with the portal blood. Both these facts may well contribute to this low pigment output, but the main point to emphasize is that the pigment output is influenced by liver function rather than by the amount of hemoglobin waste products formed in the body. We have ample evidence that various liver injuries will likewise depress bile pigment excretion—again, clear evidence that the liver has a constructive function in producing bile pigments rather than a simple passive eliminative function.

Bile fistula dogs with anemia give very interesting and complex reactions to hemoglobin injections.[6] In general, we may say that the elimination of bile pigments is not in any way parallel to the amount of hemoglobin injected. The same is true for control dogs with bile fistulas but no anemia. There is some evidence in these anemia experiments for conservation of certain of these pigment factors within the body. We may suspect a reconstruction of some of these factors into hemoglobin because of the anemia needs. There are some experimental data in favor of this explanation.

Certain of our bile fistula dogs have developed peculiar diseased conditions which may or may not be concerned directly with pigment metabolism. For example, certain dogs lose great amounts of inorganic salts from the bones, so much so that the ribs show very many "green stick fractures." These bones are reduced to mere elastic shells and the heavy long bones are likewise depleted of lime salts. There are many suggestive points in these experiments which are of peculiar interest at this time (diet and bony changes) but a discussion of this complex question must be postponed for the present.

Splenectomy in bile fistula dogs[13] gives reactions at times which are of the greatest interest to the hematologist. These dogs may show blood crises much like those observed in pernicious anemia. The color index may be very high for considerable periods—a most unusual condition in dogs. At times such dogs show maximum pigment production, which cannot be explained by destruction of red cells and hemoglobin. A specific experiment [Dogs 16-41, Table 69[13]] shows periods of great bile pigment increase—even six times normal per kilo body weight. To account for all this bile pigment as derived from hemoglobin we must postulate a complete destruction of all circulating hemoglobin every four or five days or less, or a daily red cell replacement of from 20 to 25 per cent. This is unthinkable in the light of

12. Whipple and Hooper: Am. J. Physiol. **42**:544, 1917.
13. Hooper and Whipple: Am. J. Physiol. **43**:275, 1917.

our knowledge of red blood cell regeneration in the dog, and we cannot imagine that all this pigment had been built up to hemoglobin before being broken down into bilirubin. Rather we wish to assume that the body is stimulated to a maximum production of pigment substances—in part, toward hemoglobin, in part, to bilirubin and, perhaps, to other pigment substances. The high color index indicates a maximum saturation of corpuscles with the pigment hemoglobin (refer to pernicious anemia below).

Study of the bile pigments present in human serum in health and disease has been reported by a number of investigators (Van den Bergh,[14] Brulé,[15] Blankenhorn[16] and many others). It is evident that there are various free and partially bound pigments in the blood plasma or serum. Some of these pigments may dialyze through a parchment membrane and others will not do so. The significance of these various types of pigments has been discussed at considerable length by the different workers, but as yet there does not seem to be complete accord as to interpretations. Much important information will undoubtedly come from this work but wherever possible a more extended study of the body, feces and urine pigments should be made simultaneously.

UROBILIN

In discussing the pigment substances in the urine we wish to use the term urobilin to include the closely related substance urobilinogen. We use the term stercobilin to indicate the same substances in the feces. It seems to be accepted generally that stercobilin is formed in the intestine due to bacterial action on bile pigments. It is assumed solely on indirect and incomplete evidence that stercobilin is, in part, absorbed from the intestine. We believe there is no evidence for this assumption and much against it. This absorption of stercobilin should be discredited until such time as some positive evidence of intestinal absorption is brought forward. It is admitted by most clinical observers that urobilin is present at times in human bile in the liver [1] or gall-bladder.[17] We have observed the presence of urobilin frequently in bile fistula dogs during fasting periods—in fact, this may seriously interfere with experimental work on bilirubin.[18] We believe that all evidence favors the production of urobilin in the liver and bile passages (cholangitis), its absorption at times into the blood stream from the liver and subsequent appearance in the urine. It is probable that

14. Van den Bergh: Der Gallenfarbstoff im Blute. 1918.
15. Brulé: Recherchés récentes sur les icterus, Paris, Masson et Cie, 1919.
16. Blankenhorn: Arch. Int. Med. **27**:131 (Jan.) 1921.
17. Straus and Hahn: München. med. Wchnschr. **67**:1286, 1920.
18. Whipple, Hooper and Robscheit: Am. J. Physiol. **53**:151, 167, 1920.

urobilin, like bilirubin, at times is produced in tissues other than the liver (blood extravasations, pneumonia, etc.).

We do not wish to deny the value of urobilin determination on the urine, feces and bile, but the deductions drawn from such observations should be made with a proper conception of the various reactions concerned; and absorption of stercobilin is not one of the factors to be accepted at present. Studies of urobilin in the urine may indicate certain liver abnormalities or pigment disturbances in other parts of the body. Analyses of stercobilin give figures of great interest but high figures may indicate overactivity of the liver in pigment production rather than excessive blood destruction with elimination through the liver of bile pigments or urobilin. The analysis of fresh human bile obtained by means of the duodenal tube will give facts of much value (Lyon and others [19]). It should be remembered that such samples are suitable only for qualitative analysis. The amount of dilution can never be determined but the ratio of bile pigments to bile acids may be of considerable significance, although difficulties in analysis are present. The presence of urobilin and abnormal elements in the duodenal bile may contribute facts of great value for a complete understanding of a complicated disease picture.

The various methods for determination of urobilin or stercobilin are admittedly unsatisfactory. Moreover, certain changes in the feces may make analysis inaccurate or quite impossible (constipation, diarrhea, etc.[1]). Attempts aimed toward accurate quantitative extraction are reported by Hausmann,[20] Goiffon,[21] Baumann [22] and others. When a simple and accurate quantitative method is at hand the work on these problems will be greatly facilitated. A method to give complete satisfaction in stercobilin estimations must give accurate figures not only for stercobilin but its various related substances which confuse the picture in simple complications like constipation and diarrhea.

UROCHROME

Urochrome is the stepchild of the pigment family. Numerous theories as to its origin have been advanced but it can safely be asserted that its parentage is doubtful. It has been suspected that urochrome was related to urobilin, to blood pigments, to urea and to food pigments. These views have recently been reviewed by Pelkan,[23] whose work indicates an important relationship of urochrome to food

19. Lyon: J. A. M. A. **73**:980 (Sept. 27) 1919.
20. Hausmann: Ztschr. f. exper. Path. u. Therap. **13**:373, 1913.
21. Goiffon: J. Pharmacol. Chem. **21**:286, 1920.
22. Baumann: Arch. Int. Med. **28**:475 (Oct.) 1921.
23. Pelkan: J. Biol. Chem. **43**:237, 1920.

protein. He brings evidence that carotin is not concerned in the urochrome excretion.

Urochrome contains the pyrrol group,[24] which is always of interest in any pigment work. There has been no extensive work done to study the appearance and relationship of this pigment with other important body pigments in health and disease. It is at least possible that urochrome forms one of the avenues of disposal of pigment elements ("pigment complex") even before such substances are built into hemoglobin or bile pigments. These possibilities do not preclude fluctuations of urochrome due to large intake of foods rich in pigment forming materials. This substance should be studied simultaneously with other pigments (blood and bile) in health and disease, in clinical and experimental conditions.

LIPOCHROME

Lipochrome is a peculiar pigment which is thought to have merely a passive function in the body with no relationship to the urobilin, urochrome or other pigments containing the pyrrol nucleus. Schulze[25] states that lipochromes are very closely related to the yellow radicle of chlorophyll and members of the group of carotinoid pigments including carotin and xanthophyll. The lipochromes are soluble in fat and fat solvents. Dolley and Guthrie[26] state that these lipochromes can be removed from the body fat almost completely by diet periods free from carotin intake. Van den Bergh[14] states that the lipochrome content of the blood varies with the diet intake of these food pigments. It is well known that the serum of diabetics is rich in lipochrome pigment, and he attributes this to diet factors. At present we have no reason to suppose that the lipochromes have any direct relationship to the other body pigments, but we should not close our minds to this possibility, especially in disease conditions, for example, hemochromatosis and pernicious anemia.

HEMOGLOBIN

Hemoglobin is without question the most important and interesting of all the body pigments. Much of the interest in other body pigments comes from a relationship known or assumed to exist between these various pigments and hemoglobin. A very closely related or identical substance, myohematin (muscle hemoglobin) exists in the striated muscle tissue of the body and undoubtedly plays an important part in the rapid exchange of oxygen and carbon dioxid between the functioning muscle protoplasm and the circulating hemoglobin. Myohematin will not be considered in detail in this paper, but we should always keep this

24. Weiss: Med. Klin. **13**:659, 1917.
25. Schulze: Sitz. Ges. Nat. Freunde. Berlin, 1914, p. 398.
26. Dolley and Guthrie: Science **50**:191, 1919.

substance in mind when we study various gases (for example, carbon monoxid) which are absorbed by hemoglobin in the body. The genesis of myohematin is of fundamental importance, and we have no right to assume that the bone marrow cells are concerned in its production. Is this substance formed from its very elements by the activity of the muscle tissue alone? Or is some partially built up "pigment complex" utilized by the muscle tissue in building this most complex substance? How rapidly is the myohematin used up in the body as compared with the daily wastage and repair of circulating hemoglobin? It will be of great importance to study various conditions in which myohematin may be present in abnormal amounts. It has been pointed out recently [27] that this substance usually amounts to about 10 per cent. of the total body hemoglobin, but much more work is needed to ascertain the conditions under which the myohematin content may be found to depart from normal. Such studies will give information of much value for the complete understanding of the body pigment metabolism. Hoagland [28] has recently completed experiments to show that aseptic anaerobic autolysis of beef muscle will produce measurable amounts of hematoporphyrin. He suggests that this is a normal reduction product of hemoglobin in the body and a substance intermediary to the final end product, bilirubin.

In the adult human it is generally assumed that hemoglobin is fabricated in the protoplasm of red cell groups within the bone marrow. We have suggested that other tissues (for example, the liver) may be concerned in building up "parent pigment substances" which are essential to the proper construction of mature red cells containing hemoglobin. It is worth while reviewing a few facts concerning the development of red cells in the embryo. Sabin [29] has pointed out that blood cells in the second day chick embryo develop from the endothelial cells and angioblasts. Hemoglobin is present at this time but the liver is not functionally active. This seems at first sight to indicate that endothelial cells can produce red cells and the pigment hemoglobin. This may in fact be true but we must not forget the yolk sac with its various storage factors developed by the mature hen and drawn on continuously by the developing embryo. The endothelial cell, however, may be active in a variety of the body pigment reactions and can almost certainly produce bilirubin from hemoglobin.[8]

Therefore, it is possible that these cells have a capacity to build up pigment substances and so take part in hemoglobin production. We recall, too, the interesting relationship in early fetal life (human)

27. Smith, Arnold and Whipple: Am. J. Physiol. **56**:336, 1921.
28. Hoagland: J. Agricul. Res. **7**:41, 1916.
29. Sabin: Anat. Rec. **13**:199, 1917.

between the liver cells and the islands of blood forming cells. This would indicate a possible relationship between the liver cell, the Kupffer cell and the developing red blood cell. It is, of course, possible that this relationship continues through the agency of the circulation during adult life.

DIET FACTORS AND HEMOGLOBIN

We have long been interested in the influence of various diet factors on the regeneration of red cells and hemoglobin during periods of simple anemia in dogs experimentally produced by hemorrhage. This work was begun by C. W. Hooper and me as an outgrowth of our bile pigment investigations and later continued with the cooperation of F. S. Robbins. The investigation is now being continued by Robbins and Whipple. We may refer to certain publications [18] for much of the experimental detail, methods, protocols, etc. At the outset it seemed obvious from simple experiments that hemoglobin regeneration could be influenced easily by a variety of diet factors. We thought it highly desirable to work with animals of sufficient size and suitable type so that blood could be obtained readily for various analyses by venous puncture. Dogs were obviously best suited for these experiments. The removal of small blood samples is very easy and does not complicate the regeneration curve as the amounts removed are so small as compared with the blood volume (from 800 to 1500 c.c.). These dogs are omnivorous and will eat readily all types of food mixtures. Our routine experiments included careful determinations of blood volume, hemoglobin and red cell hematocrit, red cell counts from blood drawn by venous puncture and body weight.

Our experimental data give numerous examples to show the necessity of such complete determinations and the mistaken deductions which may be derived from incomplete experiments. This applies particularly to experiments of long duration where the differences between any given group and the controls are but slight. The general procedure is as follows: A group (usually four) of normal dogs is standardized (blood volume, red cell hematocrit, red cell count, etc.). These dogs are then bled one-fourth of their total blood volume on two successive days, at times a third bleeding is used. After a rest of one day they are again standardized and placed on the experimental food mixture. Complete determinations are done thereafter each week until the end of the experiment.

Two characteristic tables (Tables 1 and 2) may be cited as examples of the wide differences in hemoglobin regeneration which may be associated with sugar feeding (Table 1) and with meat feeding (Table 2). We see that the blood regeneration is but slight—a slight increase over and above the maintenance factor in red cells and an

TABLE 1.—Blood Regeneration After Sugar Feeding

Dog 17-28. White bull, female, adult.

Date, 1917	Pigment Volume = Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	Hb. Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
1/19	1,620	C.c. 1,500	C.c. 600	C.c. 900	% 60.0	% 108	0.76	1.80	7.1	7.4	Kg. 11.00	C.c. 129	Fasting
1/20 1/22 1/23	Bled 375 c.c. Bled 270 c.c. Bled 105 c.c.												
1/24	588	900	603	306	34.0	61	0.80	1.79	3.8	7.8	10.40	87	
1/24	Diet: 50 gm. cane sugar, 25 gm. glucose, 400 c.c. water												
2/ 2	717	1,121	684	437	39.0	64	0.62	1.64	5.2	7.2	9.40	120	*Anis.
2/ 9	636	1,027	637	390	38.0	62	0.65	1.63	4.8	6.2	8.90	115	
2/16	634	961	586	375	39.0	66	0.59	1.69	5.6	10.0	8.50	113	Diarrh.+
2/23	541	933	562	373	40.0	58	0.56	1.45	5.2	9.0	8.00	117	

* Anisocytosis of red cells.
Blood volume with dry oxalate. Hemoglobin with Sahli tubes.
Hemoglobin index equals hemoglobin per cent. divided by red cell hematocrit per cent.

TABLE 2.—Blood Regeneration After Beef Heart and Liver

Dog 18-116. Bull mongrel, female, young adult.

Date, 1918-1919	Pigment Volume = Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	Hb. Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
12/ 2	2,120	C.c. 1,720	C.c. 805	C.c. 907	% 52.7	% 123	0.56	2.32	11.4	1.14	Kg. 14.50	C.c. 115	
12/ 2	Diet: Crackermeal and milk												
12/ 2 12/ 4	Bled 430 c.c. Bled 430 c.c.												
12/ 6	939	1,182	803	369	31.2	79	0.57	2.54	6.9	21.2	14.55	81	
12/ 7	Bled 300 c.c.												
12/ 9	776	1,260	930	323	25.6	62	0.84	2.38	3.7	17.5	13.95	90	
12/ 9	Diet: 250 gm. cooked beef heart;* 610 gm. cooked beef liver*—100 calories per kilo												
12/16	1,682	1,350	844	476	35.8	81	0.88	2.25	4.6	18.2	14.55	91	
12/23	1,890	1,685	860	818	48.5	112	0.57	2.30	9.9	11.5	15.25	110	
12/30	2,270	1,648	747	902	54.7	138	....	2.50	....	....	15.50	106	

* Meat cooked, fat and connective tissue removed and ground.
Hemoglobin index equals hemoglobin per cent. divided by red cell hematocrit per cent.

even smaller increase in hemoglobin within a period of four weeks. The contrast with meat and liver feeding is striking (Table 2) which shows complete return to normal in a period of three weeks. Between these extremes are all types of reaction, and it is easy to understand that a diet containing several food factors may give a complicated reaction. It is easy to understand that one food factor may be inert in this reaction and a second factor may likewise be inert but the two together may have a distinct influence on the curve of red cell and hemoglobin regeneration. For this reason it is necessary to test a given factor under a variety of conditions (supplementary feeding, etc.) before we can feel sure that we understand its reaction under anemia conditions. This is one of several reasons why the accumulation of convincing experimental data is so time consuming. We cannot accept the experiments of Downs and Eddy,[30] who report a positive influence of secretin on the production of red cells in anemia. They record only the red cell count with no figures for red cell hematocrit, hemoglobin or blood volume observations. That secretin may influence the red cell and hemoglobin production may be true but this is neither proved nor disproved by their experiments.

MEAT

Our experiments show that diets of cooked beef muscle or cooked beef heart are very favorable for a rapid regeneration of red cells and hemoglobin (Table 2 and others[31]). Cooked liver ranks with cooked muscle, and these food factors will effect a prompt reconstruction of the anemia picture to normal. These favorable diet factors are also potent when given after long periods of anemia and unfavorable diet intake. This is the severest test for any diet factor as to its influence on red cell and hemoglobin reconstruction. Certain diet factors may give a favorable reaction if given at once after the anemia is produced but may give an unfavorable reaction if given at the end of a long period of anemia and unfavorable diet intake.[31] Meat extracts (commercial) are inert and possess none of the factors which influence red cell and hemoglobin regeneration.

FOOD GRAINS

The common food grains (wheat, barley, rice) in the form of cooked bread or crackers do not furnish many factors which promote red cell regeneration. Full diets of these materials with skim milk may effect a slow rise in the level of hemoglobin and red cells which finally may reach normal in from six to eight weeks. More com-

30. Downs and Eddy: Am. J. Physiol. **58**:298, 1921.
31. Whipple, Robscheit and Hooper: Am. J. Physiol. **53**:236, 1920.

monly the return toward normal will not exceed 90 per cent. of the initial level before the anemia is produced by bleeding. Casein and skim milk may be ranked with these food grains as regards their influence on hemoglobin regeneration and we may say that, as a rule, these foods do not return anemia animals to a high red cell and hemoglobin level.

FASTING

A comparison of anemia fasting experiments with sugar feeding experiments shows that anemic dogs actually produce more red cells and hemoglobin during fasting periods than during periods of sugar feeding. The question of the "sparing action" of carbohydrates comes into this reaction, but we must refer the reader to reviews [18] of this subject in recent papers.[32] There is evidence from these experiments that the body conserves with much care the various pigment construction units, which are then recast into red cells and hemoglobin. It is well to keep in mind the fact that normal dogs during periods of zero nitrogen intake (fasting or sugar feeding) are able to form hemoglobin and red cells over and above the considerable amount needed for daily wastage and repair—also are excreting considerable amounts of bilirubin, stercobilin and urochrome. These must all come directly or indirectly from the host's protein. This careful conservation of red cell and hemoglobin construction factors must be of considerable importance in the body economy.

IRON

Iron furnishes a never failing topic for discussion by internist and physiologist alike. Clinical opinion favors the use of iron in simple anemias, but we question whether this treatment is based on sound evidence. At least, the treatment does the patient no harm and may soothe the doctor's conscience, but we can find no convincing evidence that it gives patients with secondary anemia any real benefit. This discussion does not concern chlorosis, which appears to be a distinct disease entity. All the experimental evidence indicates that iron is inert in secondary anemias and has no influence on blood regeneration. Our experiments [33] indicate that iron in the form of Blaud's pills is inert.[7] Ferric citrate and ovoferrin have little or no influence on blood regeneration—nothing to compare with favorable food factors (meat). Hemoglobin, given by mouth, intraperitoneally or intravenously, does influence the curve of red cell and hemoglobin regeneration in a positive fashion but not to the extent noted with potent diet factors (meat). The iron may be concerned in this reaction but there is even more

32. Davis and Whipple: Arch. Int. Med. **23**:689 (May) 1919.

33. Whipple and Robscheit: Arch. Int. Med. **27**:591 (May) 1921.

evidence in favor of the pyrrol complex. Likewise, arsenic in sodium cacodylate or Fowler's solution is inert in these anemia periods. We believe it will repay the clinical workers to record careful observations on anemic patients, paying particular attention to various diet factors proven to be potent in controlled experiments.

The relation of hemoglobin and chlorophyll has given rise to much speculation in the past and there are many interesting possibilities which call for more work. It has been pointed out that under usual conditions iron is necessary in plant metabolism for chlorophyll production but does not form a part of the chlorophyll nucleus.[34] In the absence of iron plants can form chlorophyll if there is a supply of pyrrol material.[35] These observations are of particular interest when we consider the influence of certain plant leaves rich in chlorophyll on the blood regeneration of anemia dogs (see below). But the evidence that iron is directly concerned in this reaction is not convincing.

It has been reported by Cloetta [36] that the iron present in hemoglobin is not absorbed from the dog's intestinal tract, and he is able to recover the iron quantitatively after blood feeding. Weber [37] has reported experiments to indicate that iron lactate is inert in anemia periods in experimental animals. However, he did not control his diet and reports on hemoglobin values only. The anemia was produced by pyrodin. His experiments are not convincing but give no evidence that this iron salt is potent. Musser [38] has furnished more evidence that iron is inert under experimental conditions. Iron was given as ferrous sulphate in capsules and the dogs rendered anemic by repeated bleedings. He gives complete data on hemoglobin, red cell count, resistance of red cells to hypotonic solutions and blood volume. It is, perhaps, unfortunate that a mixed diet of hospital food scraps was used in all these experiments. As diet factors are important it is very desirable that the investigator knows the amount and type of food intake. A mixed diet gives an opportunity for much variety and also choice by the animal. As a rule, the blood regeneration is very rapid on a mixed diet and gives less opportunity to demonstrate the influence of any given factor on blood regeneration. Some experiments should be included to show the influence of the given drug when administered during a long period of feeding on a diet unfavorable to rapid blood regeneration—for example, a 75 calory per kilo diet of bread and skim milk.

34. Moore: Proc. Roy. Soc. Lond. **87**:556, 1914.
35. Oddo and Pollacci: Gazz. Chim. Ital. **50**:54, 1920.
36. Cloetta: Arch. f. exper. Path. **37**:69, 1895.
37. Weber: Ztschr. f. Biol. **70**:168, 1920.
38. Musser: Arch. Int. Med. **28**:638, 1921.

FATS

Unpublished experiments of Robbins and Whipple indicate that lard is inert in various diets, and influences in no degree the regeneration of red cells and hemoglobin in anemic dogs. Numerous experiments with cod liver oil give no evidence that this oil influences blood regeneration. In striking contrast stand the experiments with butter fat, which indicate that under certain conditions some substance in butter fat is able to influence in a striking way the curve of hemoglobin regeneration and hasten the production of hemoglobin and red cells. When we admit that butter feeding is potent in anemia regeneration of hemoglobin, we can scarcely admit that it actually is built into the hemoglobin molecule. But it may act in some way to facilitate the linkage of the various complexes which go into the large hemoglobin molecule. We have not as yet sufficient data on the influence of butter feeding upon the output of other body pigments during anemia periods.

FISH

Through the friendly cooperation of the California Packing Corporation and the Alaska Packing Corporation we were able to test a variety of food fish. These experiments will be published in the near future. The highly pigmented cooked salmon muscle was used and in a variety of diet tests was shown to be inert in anemia experiments. It is of particular importance to note that this muscle pigment of the salmon is not concerned in the upbuilding of hemoglobin in dogs. We have some evidence that the myohematin of beef muscle is actually concerned in hemoglobin regeneration, which is so rapid after beef feeding. Whale meat was tested and found to act exactly like beef muscle or other striated mammalian muscle. Clams, like fish, are inert in anemia experiments.

VEGETABLES

The data concerning vegetables will be published shortly by Robbins and Whipple. A number of vegetables have no effect on the curve of red cell and hemoglobin regeneration after anemia. Carrots are inert and deserve particular attention because of their high content of carotin, a food pigment which does enter into the body fluids and tissues. Dehydrated celery, parsley and Brussels sprouts are likewise inert, and it is improbable that the dehydration was responsible for the negative reaction as dehydrated spinach is positive and exerts its usual influence on the hemoglobin reaction. Fresh beet tops are negative, as compared with fresh spinach, which is positive and even more potent than the dried spinach meal. Canned spinach is somewhat less potent than is the freshly cooked material. These observations show that by this physiologic test there is a distinct difference

between the chlorophyll of sprouts, celery, parsley, and beet leaves as contrasted with the chlorophyll of spinach.

PERNICIOUS ANEMIA

This is a diseased condition, little enough understood, which is of the greatest interest to any person investigating general body pigment metabolism. Let us examine the facts as known, paying particular attention to this question of pigment metabolism. We find an excess of pigment substances everywhere in the body—increase of pigments in the liver cells, blood stream, bone marrow, feces and, at times, in the urine. There is a high hemoglobin index or we may say the red cells are saturated with hemoglobin as contrasted with the 50 per cent. hemoglobin content of a simple anemia. This suggests that the body has an excess of pigment material available and is producing various pigment substances at an abnormal rate of speed—compare the experiment (the splenectomy bile fistula dog, No. 16-41 [13]) which showed a high color index and enormous overproduction of bile pigment.

We are told that the stercobilin analysis in a case of pernicious anemia is an index of blood destruction. Let us examine some of these figures and, further, let us assume the normal red cell count as 5,000,000 and the pernicious anemia count as 1,000,000 for the sake of simplicity of comparison. If the anemia red cells disintegrate at the same rate of speed as the normal control, and if these products result in bilirubin and then stercobilin we must say the stercobilin figures should be one-fifth of normal. But the stercobilin figures during periods of remission in pernicious anemia often exceed twice or three times normal stercobilin excretion, making no allowance for similar pigments in the urine. This can only mean that the pernicious anemia patient with one-fifth the number of red cells and two or three times the amount of stercobilin output must regenerate its total red cell mass every three days instead of the assumed normal of every thirty days. The normal replacement factor for red cells and hemoglobin is believed to be 3 per cent. per day.[39] We must postulate from 30 to 40 per cent. replacement of red cells per day in a pernicious anemia case if we persist in explaining the stercobilin content as being due to blood destruction. Those who wish to accept this explanation are welcome to do so, but it would be a fleeting and troublous life period endured by the red cell in pernicious anemia!

Ashby [40] has published recent observations to show that the life cycle of the human red cell is variable and may be thirty days or at

39. Ashby: Jour Exper. M. **29**:267, 1919.
40. Ashby: J. Exper. M. **34**:127, 1921.

times 100 days. Further than this she submits observations which indicate that in pernicious anemia the red cells exist in the circulation at least as long as in the normal human case and perhaps for a longer time. She questions the importance of an increased blood destruction in producing the anemia of this disease.

We prefer to explain the observed facts as done in Figure 3, assuming that there is a great stimulus within the body for pigment production. It may well be that there is an overproduction of pigments, including hemoglobin and bile pigments and other abnormal pigments. For example, in certain cases of pernicious anemia Hooper and Whipple have observed an unusual pigment in gallbladder bile obtained at necropsy—a pigment which must be treated with active acetaldehyd before it will give the usual bile pigment tests. It is highly probable that this pigment, after a stay in the intestine, would be reduced to stercobilin and take part in the familiar high reading of stercobilin in such cases.

Our conception of pernicious anemia is that there is a scarcity of stroma building material or a disease of the stroma forming cells of the marrow which limits the output of red cell framework. There is plenty of pigment material (an excess in fact) as evidenced by the high color index or the saturation of the red cell with hemoglobin. Wherever we meet with a high color index we should suspect some deficiency in stroma construction or some overproduction of body pigments including hemoglobin. Conditions of malignancy, for example, with the hematology of pernicious anemia should yield information of value when examined with these points in mind. Nothing in this paper should be construed as minimizing the importance of stercobilin analyses for we are confident that such information is of great value. High stercobilin figures may be a very valuable diagnostic aid in obscure cases of pernicious anemia, as claimed by Hausmann and Howard.[41] That these figures indicate a corresponding destruction of red cells may be doubted and an overproduction of pigment may be a safer assumption.

Under usual secondary anemia conditions we know that this physiologic anemia stimulus causes a rapid production of both stroma and hemoglobin, the production of the stroma even outstripping that of the hemoglobin, as indicated by the low color index. It is possible that stroma production in the body may be fatigued more easily, as suggested by certain anemia conditions of long standing, which may show periods of high color index and a hematology suggesting pernicious anemia. Such cases are deserving of particular attention and a most careful study of the complete pigment metabolism.

41. Hausmann and Howard: J. A. M. A. **73**:1262 (Oct. 25) 1919.

The experiments of McMaster and Haessler [42] may have an interesting bearing on some of these questions. They show that in rabbits the injection of hemoglobin intravenously is a stimulus to the extension of bone marrow tissue in the long bones of the experimental animals. Simple bleeding does not stimulate to the same degree this "spread" of the bone marrow. They believe that there is no evidence for direct utilization of the injected hemoglobin, which is probably broken down before use. So it is possible that the pigment construction factors or "pigment complex" may be radicles which determine the bone marrow spread.

HEMOCHROMATOSIS

This disease is characterized by abnormal deposits of various pigments in many body cells and tissues. By most writers it is thought that this increase in body pigments is to be explained by a great increase in blood destruction. The mere fact that there is no evidence to support his hypothetical increased blood destruction has not deterred writer after writer from this assumption. Sprunt [43] is probably the first writer to object to this interpretation, and he points out convincingly the entire lack of evidence for any increase in red cell destruction—further that the evidence favors some profound disturbance in body metabolism which permits the deposit or production of various pigments in the protoplasm of various body cells. MacCallum [44] has shown the presence of iron in the cystoplasm of ferment forming gland cells of all descriptions. It is interesting to recall the presence of abnormal iron containing pigments in these same cells in cases of hemochromatosis. The liver and pancreas are especially involved in this reaction, and the liver may contain 100 times the normal content of iron. Various observers record normal stercobilin elimination in cases of hemochromatosis. Wilbur and Addis [1] report a long series of observations on a case of hemochromatosis to show normal stercobilin figures and fluctuating amounts of urobilin in the urine. The necropsy disclosed cirrhosis of the liver and the familiar picture of this disease. It would be interesting to speculate about the pigment abnormalities in hemochromatosis, but we must recall that actual observed facts are but few in number. It can be said, however, that there is no evidence of an increase in red cell and hemoglobin destruction. Stercobilin elimination may be normal but we do not know anything as to iron intake and elimination. It will be of great interest to study the various pigment factors in the blood, urine and tissues. It is, at least, possible that the usual paths of pigment elimination and disposal are, in part, blocked at the source

42. McMaster and Haessler: J. Exper. M. **34**:579, 1921.
43. Sprunt: Arch. Int. Med. **8**:75 (July) 1911.
44. MacCallum: Ergebn. d. Physiol. **7**:552, 1898.

so that these pigments which may be present in various cells in traces are unable to escape and heap up within the cell protoplasm. This explanation suggests that various cell protoplasm may at times be concerned with the building up of certain pigment substances rather than with a simple passive storage. We may choose to look on this disease as resembling diabetes in certain respects—one disease with an inability to handle the carbohydrates, the other disease associated with abnormal metabolism of pigment factors. Certain end products are toxic in the first instance (diabetes) and again other products accumulate in the body cells (hemochromatosis) to their detriment and final destruction.

In this connection we wish to refer to experiments of Rous and Oliver,[45] who induced plethora in rabbits by intravenous injection of red cells. After months these animals developed siderosis of the liver, kidney and other tissues. Their experimental findings in animals have many points of similarity to those observed in human cases of hemochromatosis. Their conception that the essential disease factor in hemochromatosis lies in the liver does not wholly satisfy the writer, but their experiments bring some support to the explanation advanced above in favor of a disturbance of the whole intracellular pigment mechanism.

CONCLUSION

In conclusion, we may repeat that the various body pigments have interesting relationships which, perhaps, are not as simple as commonly believed. There may be at times a parallel increase or decrease of related pigments. We wish to make clear our conception of an underlying "pigment complex" which may be an intermediary stage in the development of mature pigments. Perhaps all pigment construction units pass through this stage and, depending upon supply and demand, are used to construct hemoglobin or bile pigment or are discharged as urobilin or urochrome or related pigments, as illustrated in Figure 3.

What may be the fundamental stimulus for pigment manufacture in the body is for future work to determine. The most important single point which we wish to emphasize is that pigment production depends upon constructive body cell activity—a dynamic function which concerns the formation of hemoglobin and bile pigments as well as urobilin and urochrome.

We recall that the output of bile pigment in the dog may be influenced by a variety of food factors but not by the feeding of bile pigment or hemoglobin. Bile pigment output depends on liver

45. Rous and Oliver: J. Exper. M. **28**:629, 1918.

functional activity, and we believe it is a product of liver activity not solely a passive elimination product coming from defunct hemoglobin. Splenectomy and bile fistula combined may give a maximum pigment output and a clinical picture resembling in some respects pernicious anemia. There is convincing evidence that stercobilin is not absorbed from the intestine and further that urobilin as observed in the urine is formed in the liver or body tissues, not absorbed from the intestine. Urochrome is a pigment too little studied. It may represent a shunt for pigment building material not utilized in the body. Lipochrome seems to be an inert pigment taken in with the food and slowly eliminated.

Hemoglobin regeneration following anemia may be influenced by a great variety of diet factors. Among the potent factors exerting a positive influence on hemoglobin stand, first, red meat and cooked liver, hemoglobin and butter fat. Then come spinach and full diets of common food grains and milk. Practically inert are other chlorophyll containing vegetable leaves—celery, parsley, beet tops and sprouts. In the same negative group are fish and clams, onions and beets and animal fats, including lard and cod liver oil. Iron and arsenic in the common drug preparations are likewise inert under these conditions.

Pernicious anemia and hemochromatosis show abnormalities of pigment formation and disposal. We believe these two diseases have this in common—a definite overproduction of pigment in the body but not an increased destruction of hemoglobin and red cells. These are pigment abnormalities which deserve the most careful study from this point of view. Such studies should be sufficiently comprehensive to include simultaneous observations of these pigment elements in the blood, feces and urine, also in the bile and body tissues whenever possible.

It may be that this paper is too speculative, but hypotheses are of some value for further work even if there be little or no truth in them. I hope to furnish more data in the near future bearing on these questions.

OCHRONOSIS

WITH A STUDY OF AN ADDITIONAL CASE *

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Ochronosis is the name given by Virchow in 1866 to a condition characterized by the pigmentation of the cartilages, ligaments, tendons and of the intima of the large blood vessels of the body. In this first reported case the pigment deposits appeared light gray, brown and, in places, black. On thin section, however, the pigment was everywhere found to be yellow or yellow-brown and for this reason the condition was called ochronosis.

Since then, forty additional cases have been studied. From the observations made it may be stated that ochronosis is a condition dependent on a disordered metabolism of phenol or some of its derivatives; characterized by a pigmentation of the cartilages, fibrocartilages, fibrous tissues and epidermis, as well as of areas of degeneration, notably atherosclerotic plaques, albuminous masses and concretions. A further characteristic is the presence of a dark urine due to alkapton, derivates of phenol or to melanin.

The cases of ochronosis may be divided into: (a) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of homogentisic acid; (b) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of melanin; (c) those due to the circulation in the blood of certain aromatic compounds following the external use of phenol.

The metabolic disorder responsible for the ochronosis in the first group is a congenital one and characterized by an alkaptonuria. More than one-half of all the ochronosis cases observed are in this group. The metabolic disorder responsible for the ochronosis in the second group results in an excretion in the urine of melanin. Only a few of the ochronosis cases are in this group. The metabolic disorder responsible for the ochronosis in the third group is an acquired one dependent on the prolonged external use of phenol. Eleven of the ochronosis cases observed are in this group.

Twenty-two of the cases in the literature are females; nineteen are males. The average age of the patients at the time of diagnosis was about 51 years. The youngest patient was 23 years of age. There

* From the Montefiore Hospital for Chronic Diseases.

* Part of the expenses of this publication were defrayed from a fund left by the late Dr. H. S. Oppenheimer.

is a tendency for this condition to occur in families where there has been inbreeding.

The diagnosis offers no difficulty. The cartilages of the ears and nose have a bluish tint. The fibrous tissue, especially about small joints, has a bluish gray appearance. There may be dark pigment deposits in the sclerae and patches of pigmentation of the skin. There is an excretion of dark urine or urine which turns dark on standing, due to the presence of alkapton body or derivatives of phenol, rarely of melanin. The pigment may be excreted to some extent by sudoriferous and ceruminous glands.

The most frequent complications in ochronosis are: (a) deforming arthritis of the spine or larger joints, and (b) cardiovascular lesions.

HISTORICAL RÉSUMÉ

1. *Clinical.*—The early cases of ochronosis were recognized clinically by the pigmentation of the external cartilages. In 1892 V. Hanseman reported a case in which dark urine was passed. Examination of this urine was negative for alkapton body and melanin. In 1902 Albrecht and Zdareck, reporting the seventh case in the literature, called attention to the association of ochronosis with alkaptonuria. In 1904, Osler likewise reported two cases of ochronosis with associated alkaptonuria. No further observations on the nature of the process were recorded until Pick reported a case of ochronosis undoubtedly due to the prolonged external use of phenol. From his chemical study in cases associated with alkaptonuria and in one following chronic phenol poisoning, Pick concluded that in the ochronosis of endogenous origin (congenital, associated with alkaptonuria) a melanin is formed by the action of an enzyme on circulating homogentisic acid and tyrosin, and that in the exogenous form (due to phenol poisoning), a melanin is formed by the action of an enzyme on circulating hydroquinone and pyrokatechin. This explanation of ochronosis, advanced by Pick in 1906, has received no appreciable modification since. In 1908 Gross and Allard reported a case of ochronosis with alkaptonuria in which there was a deforming arthritis of the larger joints. Contrary to Virchow's belief that the pigment was deposited in the inflamed cartilage of the affected joints, they maintained that these arthritic changes were specifically due to the irritation of the deposited pigment. More recently, Söderbergh [1] called attention to a deforming arthritis of the spine in four cases of ochronosis with alkaptonuria. Attention has also been called [2] to the frequent association of cardiovascular lesions with ochronosis and it has been suggested that these changes, like the arthritic ones, are primarily dependent on the metabolic disorder.

1. Söderbergh: Nord. med. Arch. **48**: Nos. 3 and 4. 1915.
2. Beddard: Quart. J. M. **3**:329, 1909.

The accompaning table based on Kolaczek's [3] tables shows the frequency of cardiovascular and arthritic changes in the various groups.

CLASSIFICATION OF OCHRONOSIS CASES WITH ASSOCIATED LESIONS

Group	Reported by	Age, Yrs.	Sex	Pathologic Examination	Arthritis	Cardiovascular Lesions
a. Carbolic acid	Pick, 1906	47?	F	Yes	+?	–
	Pope, 1906	41	F	Yes	meager des.	
	Graeffner, 1907	59	F	No	–	–
	Reid, 1908	68	F	No	–	–
	Poulsen, 1910	55	F	No	–	–
	Poulsen, 1910	44	M	No	?	–
	Poulsen, 1910	63	F	Yes	–	–
	Beddard, 1910	50	F	No	–	–
	Andrews and Branson, 1910 (Keats), 1910	69	M	Yes	–	+
	Beddard and Plumtree, 1911	73	M	Yes	–	–
	Vogelina, 1914	63	F	No	+	–
Total, 11	Average age	52.45	8 F 3 M	5	2 – 2	1
b. Alcaptonuria	Osler, 1904	57	M	No	–	–
	Osler, 1904	49	M	No	–	–
	Ogden, 1895 and 1904	45	M	No	–	–
	Allard and Gross, 1907 u 1908, Landois, 1908	46	F	Yes	+	–
	van Amstel, 1910	42	F	No	–	?
	Poulsen, 1910	56	F	No	+	–
	Poulsen, 1910	19	F	No	–	–
	Poulsen, 1910	35	M	No	–	–
	Poulsen, 1910	68	M	No	+	–
	Poulsen, 1910	61	M	No	–	–
	Kolaczek, 1910	44	F	Yes	+	–
	Kolaczek, 1910	35	F	No	–	–
	Kolaczek, 1910	30	F	No	–	–
	Poulsen, 1912	23	M	No	–	–
	Jantke, 1913	54	F			
	Umber, 1913	51	F	....	+	+
	Umber, 1913	59	M	....	+	+
	Söderbergh, 1915	42	M	....	–	–
Total, 18	Average age	47	9 F 9 M	2	9 –	3 + 1 ?
c. Probably alcaptonuria	Albrecht, 1902	47	M	Yes	–	?
	Clemens and Wagner, 1907-8	31	M	Yes		+
Total, 2	Average age	49	0 F 2 M	2	0	1 + 1 ?
d. Melanuria and probably alcaptonuria Total, 1	Poulsen, 1910	63	F	Yes	+	+
e. Melanuria no alcaptonuria	Hecker and Wolf, 1889	73	M	Yes	+	+
	Oppenheimer, Janney, Kline, 1916	40	M	Yes	+	+
Total, 2	Average age	56.5	0 F 2 M	2	2	2
f. No alcaptonuria and no melanuria Total, 1	Hanseman, 1892	41	M	Yes	–	+
g. Urine not obtained or not tested	Virchow, 1866	67	M	Yes	+	+
	Bostroem, 1891	44	F	Yes	+	+
	Helle, 1900	36	F	Yes	–	+
	Helle, 1900	52	F	Yes	–	+
	Wagner, 1904	67	F	Yes	–	+
	Heymann, 1913	55	M	Yes	..	+
Total, 6	Average age	53.5	4 F 2 M	6	2	6
Total cases, 41	Average age	51	22 F 19 M	19	16 + 2 ?	19 + 2 ?

3. Kolaczek: Beitr. z. Klin. Chir. **71**:254, 1910.

Moderate ochronotic pigmentation of ears, eyes and axillae; tracheal and bronchial cartilages.

Hawthorne Arthur B. S. Oppenheimer, M.D., and B. S. Kline, M.D., Archives of Internal Medicine, June, 1922

In the forty-one cases of ochronosis a chronic arthritis of the larger joints or spine has been noted in sixteen. The associated arthritis has been more frequent in the ochronosis with alkaptonuria.

Cardiovascular changes have been noted in nineteen of the forty-one reported cases. These occurred in about equal frequency in cases with alkaptonuria and in cases following phenol poisoning. Not only was there extensive pigmentation of the intima and endocardium in these cases, but also not infrequently a serious chronic valvular disease.

2. *Pathologic.*—In 1866 Virchow reported on a necropsy in a male, aged 67, with an aneurysm of the ascending arch of the aorta, head

Fig. 1.—Intense ochronotic pigmentation of costal cartilages.

injury and terminal anasarca. The striking lesion, however, was the intense pigmentation of all cartilages and fibrocartilages, with pigmentation to a less extent of ligaments, tendons, perichondrium and periosteum. In this first case there was also some pigmentation of the intima of the larger vessels, especially the aorta, with intense pigmentation of the sclerotic patches in this vessel. The intensely pigmented areas were black or bluish black. The pigmentation of the tracheal cartilages was ochre colored. Histologically, the pigment everywhere was brown or ochre colored, hence the name, ochronosis. Examination of the pigment in this first case by Kühne showed an organic pigment having a definite similarity to hematin derivatives.

Virchow suggested that in ochronosis there is an imbibition from the blood of hematin derivatives occurring in areas poor in vessels and nerves but exposed to irritation. He thought that the process was analogous to the physiologic pigmentation of the rete malpighii, the hair and the choroid and depended on a similar relationship. Furthermore, he believed that there were certain conditions of the cartilages and ligaments which might be considered lower grades of ochronosis. He had occasionally observed that the semilunar plates of the knee joints in old people had a dark yellow or brown appearance and the costal and bronchial cartilages a dark yellowish brown color. In these

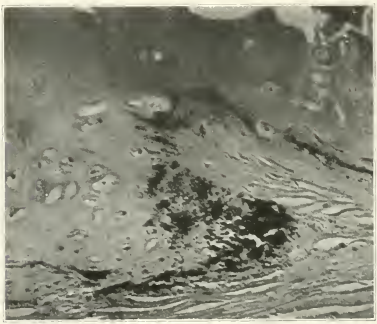

Fig. 2.—Diffuse ochronotic pigmentation of cartilaginous matrix of costal cartilage with granular ochronotic pigment in perichondrium.

instances also, the pigment was deposited in the intercellular substance and was quite homogeneous and diffuse.

Virchow, in this first case, observed changes in the larger joints, particularly the knees, similar to those in arthritis deformans. The deposition of the pigment in these irritated areas gave additional proof to him of his theory, mentioned above. In this first report, no mention of the appearance of the kidneys is made and no mention is made of granular ochronotic pigment.

In concluding his article, Virchow states: "I believe, therefore, that the case here presented, because of the intensity of the pigmentation, was only an excellent example of the more frequent ochronosis."

Hanseman [4] observed diffuse and granular ochronotic pigment in the tissues. In regard to the pigment he states that it is produced in soluble form in the body and in this form absorbed and fixed by certain tissues having but little metabolic activity and in other places changed by cells to granular pigment.

The classical paper on ochronosis is that by Poulsen,[5] who studied ten cases clinically and two after necropsy. He described the pathologic changes as follows:

In all cases one finds a yellowish or brown melanin-like pigment which at times is granular, at times stains the tissues diffusely. This pigment is deposited

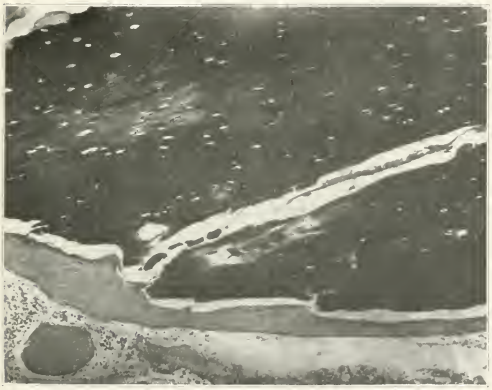

Fig. 3.—Diffuse ochronotic pigmentation of intervertebral disc.

principally in the cartilages: costal, those of the air passages and larger joints. Those of the smaller joints are usually unpigmented. The pigment is also present in all the fibrocartilages, such as the intervertebral discs and in the pelvic and intersternal cartilages. The pigment deposition is less intense in the perichondrium, periosteum, tendons, fascias and joint capsules. The bones, although usually unpigmented have shown pigment in a few cases. Outside of the skeleton, the pigment is deposited as a rule only in the endocardium, intima of the larger blood vessels and kidneys; rarely in other places, such as bits of cartilage in the tonsils, in connective tissue of the lung, and

4. Hanseman: 1892.

5. Poulson: Ziegler's Beitr. z. Path. Anat. **47**: 1910.

thyroid gland, in the fatty tissue about the perichondrium and in the dura mater. The pigment is frequently found in the sclerae, epidermis and in a few cases in the nails. Pigment masses have been observed in the prostate by a few observers, although the authors questioned their specific character. In the cartilage it is deposited in the matrix: the cartilage capsule, and the cells are faintly or not at all colored. Degenerated cells, however, are deeply pigmented. In the other tissues, this pigment is at times in the cells, at times between them. The pigment is excreted in the urine.

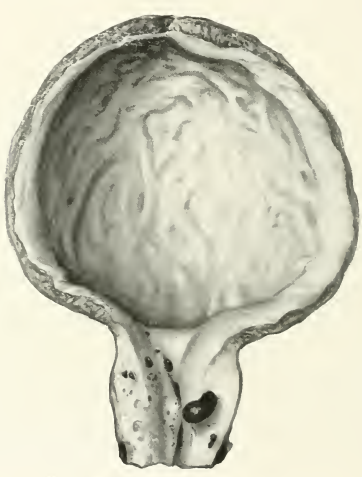

Fig. 4.—Ochronotic concretions in prostate.

REPORT OF CASE

History.—Male, aged 40, presser, admitted to Montefiore Hospital, Nov. 18, 1915.

Chief Complaints.—Lancinating pains along spinal column radiating along the lower intercostal spaces to both sides of the abdomen; slight productive cough; occasional hemoptysis; chronic constipation; general weakness; occasional spells of vomiting.

Family History.—Negative for consanguineous marriage.

Past History.—Occasional attacks of influenza. Frost bite of ears three years ago. Habits: Ten cigarets daily. Eight years before patient's admission to the hospital he was supposed to have had sugar in his urine. Seven years before admission he first noticed peculiar bluish discoloration of the cartilage of each ear.

Present Illness.—Eighteen months before admission, while bathing, he experienced sharp stabbing pains along the spinal column, extending forward along the costal spaces to both hypochondriac regions. He left the water at once and went home. The pains, however, continued to grow more and more severe until the following morning when he was unable to resume his occupation. In addition to this sharp pain he noticed stiffness of all the back muscles. He remained at home for the next six months where he was treated with no apparent relief. He then visited Mt. Clemens, Mich. On his return from Mt. Clemens he began to complain of a persistent cough accompanied by profuse greenish-yellow expectoration, blood tinged only for a period of two days,

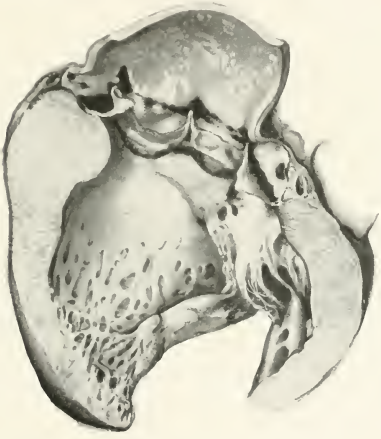

Fig. 5. Ochronotic pigmentation of atherosclerotic plaques of aortic and mitral valves and in neighborhood of attachment of aortic cusps.

three weeks before admission. In addition he suffered with night sweats and general weakness. He lost twenty-five pounds in weight during the first year of his illness. At the time of admission, cough and loss of weight were almost negligible symptoms.

During the first twelve months of the present illness the patient was treated at various clinics. For the past three months the urine has been reddish-black; the underclothes were often stained black. Associated with this there has been marked polyuria and dysuria. The patient became frightened because of this condition and discontinued taking some white medicine which he was then receiving at the St. Paul's Tuberculosis Clinic and which he felt caused the disorder. He claims that the urinary symptoms mentioned subsided when the drug was discontinued and recurred when the drug was again taken. On being

given various drugs to smell he stated that he was positive the drug he took had the same odor as creosote.

Physical Examination.—The patient, an adult male, poorly nourished, appears to be suffering from some chronic illness. Weight, 104 pounds. Gait is very slow and careful. The sclerae of both eyes present a faint bluish tint. In addition there is a wedge shaped bluish-black area of pigmentation of the sclerae to the right of each cornea. Both ears show a peculiar leaden blue discoloration of the cartilage. The same discoloration appears to be present in the nasal cartilage on the right side. Both axillae are diffusely bluish green in color. Some of this discoloration is removable by soap and water and is apparently due to pigment from the sweat and sebaceous glands. There is a pale, brownish diffuse pigmentation of the skin of the neck and temporal regions. The fingers and toes are clubbed; nails pale, not pigmented. Chest: Supraclavicular fossae deep; clavicles exceptionally prominent. Examination of lungs shows few signs at right apex posteriorly suggestive of pulmonary

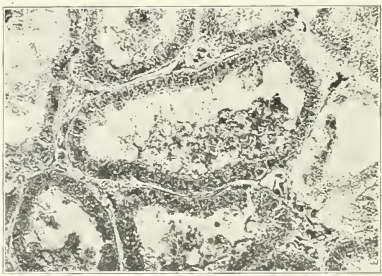

Fig. 6.—Fine ochronotic pigment granules in cells of proximal convoluted tubules of kidney.

tuberculosis. Heart: Not appreciably enlarged. The first and greater part of the second sound at the apex is replaced by a loud harsh murmur transmitted to the axilla. There is some thickening of radial arterial walls; pulse regular; good tension. Liver: Palpable 4 cm. below costal margin in right mammillary line; tender. Extremities: Reflexes increased. Vertebral column: Absolutely rigid, presenting a general bow deformity. Lumbar curve obliterated. There is a great deal of tenderness on any manipulation of either thoracic or lumbar regions of spine.

Laboratory Findings.—Sputum: negative on first five examinations. On sixth examination a few tubercle bacilli were found. Blood: hemoglobin, 80 per cent.; leukocytes, 15,000; 85 per cent. neurotrophils. Wassermann reaction of blood, negative. Urine: First specimen reddish black when voided; second specimen, when voided, light amber color, turning to yellowish black. Next two specimens were voided black. The following three specimens were smoky but on standing became black. The quantity excreted in twenty-four hours was usually 500 c.c.; specific gravity, 1,010. Albumin, marked trace. Sugar, slight reduction with Fehling's. Examination for bile and blood negative. Occasional

hyalin casts. Chemical analysis of the urine by Dr. Janney showed no homogentisic acid. On the other hand, a pigment was isolated exhibiting characteristics similar to the melanins previously obtained from the urine and tumors in cases of melanosarcoma.

Roentgen-Ray Examination of the Bones.[6]—Spine: Almost complete calcification of the intervertebral discs from the first dorsal down. The cervical spine appears practically normal. The lumbar spine shows marked lipping of the lower and upper borders of the bodies of the vertebrae (Spondylitis deformans).

Pelvic Bones: Complete calcification of the interpubic disc. Moderate amount of irregular outgrowth along the outer portions of the crests and the ossa ischii.

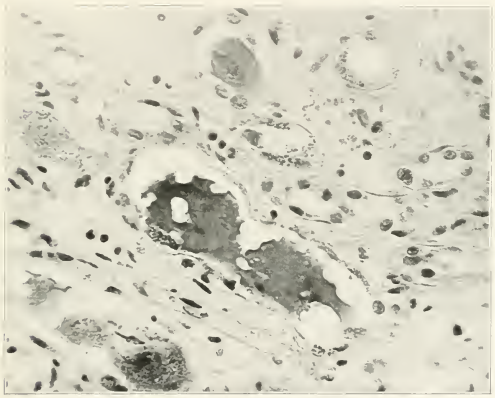

Fig. 7.—Diffuse ochronotic pigmentation of renal casts; granular ochronotic pigment granules in cells of ascending loops of Henle and collecting tubules.

Hips: Marked lipping of the upper portion of the acetabulum. Great amount of calcification around the trochanter major, with some bony excrescenses at its base.

Legs: Some calcification along the insertion of the upper portion of the membrana interossea.

Skull: Marked thinning out of both clinoid processes. Complete obliteration of the frontal sinuses.

Shoulders: The joints are free. The upper portions of the humeri show a condition such as we usually see in osteitis fibrosa; rarefaction, lack of clear demarcation between compacta and spongiosa and beginning cystic degeneration.

Clinical Course.—The patient vomited persistently, ran an irregular subfebrile temperature until the day of death when temperature rose to 103 F. A half hour after death it was noticed that the entire eyeball, exclusive of the

6. We are indebted to Dr. Th. Scholz for the roentgen-ray report in this case.

cornea, had become brownish black in color and the following day at the necropsy it was noticed that the pigment in the axillae had become much darker than during life.

Diagnosis.—The diagnosis of ochronosis in the case was readily made because of the bluish discoloration of the cartilages of the ears and the skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing.

Chemical Report.[7]—Examination of the urine in this case was repeatedly negative for homogentisic acid (alkapton body). On the other hand, the pigment obtained from the urine, from a costal cartilage and from the prostate gave reactions for melanin. The pigment from these sources had similar characteristics.

Pathologic Report.—Anatomic diagnosis: ochronosis. Pigmentation of costal, tracheal, bronchial, auricular and xyphoid cartilages, intervertebral discs, aorta, endocardium, prostate, skin, sclerae, kidneys; deforming arthritis of larger joints and spine; subacute bacterial endocarditis, mitral valve; subacute glomerulitis; infarct, spleen; healed pulmonary tuberculosis; arteriosclerosis of aorta, pulmonary arteries, mitral valve; pulmonary edema.

Necropsy Record (abridged).—Necropsy performed 33½ hours after death. The body is that of a considerably emaciated adult, 153 cm. in length. The skin in general is thin, sallow in appearance. There are tattoo marks on the left forearm. The nails show moderate double curvature. The skin of both axillæ, under the arms, has a purplish color. The cartilages of the ear are deep blue in the inner portion, less intensely colored peripherally. The scleræ have a faint blue tinge, except just below the cornea of each side where there is a much greater deposition of the pigment and, in addition, a wedge shaped, brownish, green-blue area about 2 x 1 cm. (These masses were not present during life, but noticed a few minutes after death.) Eyes: The right pupil is slightly larger than the left which is of about average size; both eyeballs sunken. The ears are small. The auricular cartilages through the skin appear leaden gray. There is a small nodule on the upper margin of the left ear, grape seed in size, shows grayish-pink pigmentation in the deeper portion. The external genitalia show no abnormalities, except a faint bluish discoloration on the upper surface of the glans.

(The organs removed through abdominal incision).

Heart: Somewhat enlarged, weighs 360 gm. There is considerable diminution of fat below the epicardium. The right side of the heart shows no abnormalities, except at the base of one pulmonary valve cusp and at its attachment to the artery in two places there is bluish discoloration of the intima. The left auricle is moderately dilated, the walls not thickened; the endocardium has the usual appearance except at one place above the auriculoventricular ring where there are numerous, small friable vegetations. Mitral valve—the aortic leaflet shows on its upper surface, near the auriculoventricular ring, a number of small friable, grayish vegetations. The other cusp is strikingly altered. There is a large irregular, friable mass along the line of closure and free edge, yellow in color, in part calcified; the vegetation continues down the associated chordae. The left ventricle is moderately dilated, not appreciably thickened. The papillary muscles are stretched, somewhat flattened; the endocardium thin and glistening. Aortic valve: cusps thin and delicate. At the attachment of the cusps to the ventricle and aorta there is extensive bluish black pigmentation of the endothelium over a considerable area. This pigmentation is visible also on the posterior aspect of the aortic leaflet of the mitral valve. The base of the aorta shows numerous slight elevations, due to small,

7. Dr. N. W. Janney has already published a report of the chemistry of this case, Am. J. M. Sc. **156**:59, 1918.

soft, yellow, opaque patches in the intima. The coronary vessels are not tortuous. The walls are somewhat thickened and show scattered soft yellow opaque patches in the intima; just beyond the left coronary orifice there are a few patches of bluish pigmentation of the intima. Left myocardium on section pale and flabby. Here and there are gray flecks replacing muscle. There are also gray streaks associated with the vessels. No abnormal pigmentation of myocardium.

Lungs: The right lung weighs 690 gm. It is voluminous. The upper lobe is strikingly cushiony, especially anteriorly. The lobe also feels soggy. The pleura in general is thin and glistening, except at the apex where there are numerous puckered scars to which are attached dense fibrous tags. Below these pleural scars there is an irregular, indurated pigmented mass about the size of a robin's egg. In portions of this scarred area there are small, dry, cheesy and calciñed masses. The remainder of the lobe has a watery, dull, pinkish red color, mottled with black; although crepitation is made out the air spaces contain a considerable quantity of thin fluid. Dissection of the branches of the pulmonary artery show a number of soft yellow patches in the intima. The bronchi show nothing abnormal. The hilic lymph glands not appreciably enlarged, show intense black pigmentation.

The left lung weighs 650 gm. It is voluminous. The upper lobe is inelastic, cushiony. The lower lobe feels soggy. Dissection of the vessels shows atheromatous patches in the arteries, similar to those on opposite side. The cartilaginous rings of the larger bronchi appear bluish through the mucosa. On cross section, however, they appear ochre colored. The pleura is thin and glistening everywhere. On section the upper lobe crackles. A mottled pink and black surface presents. The air spaces contain a small amount of thin fluid, especially in the lower portion of the lobe. The lower lobe on section shows a pinkish-red moist surface. Thin fluid exudes in considerable quantity from the air spaces.

Liver: Weighs 1,750 gm.; shows no macroscopic abnormalities.

Spleen: Weighs 350 gm.; measures 16 x 9 x 4 cm. About twice average size. It has the average consistency. The capsule is thin. Toward the upper pole there is a triangular area with sides 2½ cm. and base 1¾ cm., yellow in color, opaque, depressed a few millimeters below the general level. On section of the spleen a striking picture presents. The surface is soft and pasty, red in color. Scattered throughout the pulp are numerous small gray areas about pinhead in size. The pulp scrapes off readily on the knife. The trabeculae are increased in number, but not in size. The depressed area noted on the surface is found to be a part of a typical wedge shaped infarct, homogeneous throughout, dry, yellow and opaque, except at the apex where for a considerable distance the tissue has a decidedly bluish color.

Pancreas and Suprarenals: No appreciable abnormalities.

Kidneys: The kidneys together weigh 500 gm. Both are apparently alike. Each measures 12½ x 8 x 6 cm. Each moderately enlarged. The capsule strips readily, showing a smooth surface in which the veins are prominent. In addition, innumerable pinpoint and larger bluish black spots are seen. On section, a striking picture presents. The cortex is quite uniform in width, averages from 8 to 9 mm., has a watery gray-reddish appearance, streaked and dotted with brownish and bluish pigmentation. The striations are not very distinct but are fairly regular. The glomeruli are inconspicuous. Brownish and bluish pigment streaks and dots are quite extensive in the medulla and most striking in the papillae.

Bladder: The bladder of average size, the walls of average thickness, contains turbid urine. The mucosa is pale except for a few scattered areas of injection, especially marked in the trigone. The prostatic urethra presents a striking picture; there are stony, bluish pigment masses varying in size from

pinpoint to grape seed; in some places entirely covered by mucosa, elsewhere only partially covered. There is no injection about these masses.

PROSTATE: The prostate is of average size and consistency. On section it contains a number of bluish black pigment masses varying in size from pinpoint granules, to several as large as peas. The nodules are stony in consistency.

SEMINAL VESICLES: The seminal vesicles are thin walled, not pigmented.

VESSELS: The aorta is elastic, the walls of average thickness, the circumference in upper thoracic portion 5 cm. There are numerous rather broad longitudinal yellow opaque masses in the intima throughout the length of the aorta. Just at the commencement of the thoracic portion there is an atherosclerotic plaque which shows considerable bluish black pigmentation over a surface of about a square centimeter. In addition there is a slight diffuse bluish pigmentation of the intima for a distance of 4 cm. in the neighborhood of the intercostal vessels.

NECK ORGANS: Only the lower part of the trachea was removed. This shows a pale, thin mucosa through which the cartilaginous rings have a decidedly bluish color. This is true also of the bronchi. On cross section, the pigmentation of the cartilaginous rings is found to be central; in some, it is most marked on the convex portion. The outer rim of pigmentation has a bluish cast; the deeper portions are brown.

INTESTINES: There is some apparent hyperplasia of the lymphoid tissue of the small and large intestines. In the colon there are also a number of irregular areas from 1 to 2 cm. square, having a smooth, pearly scarred appearance with thin brown pigmented periphery, suggesting healed ulcers.

SPINE: The bodies of the lumbar vertebrae are considerably flattened, the intervertebral discs are narrower than normal and almost bony in consistency; the striking change of the discs is the diffuse, intense bluish black pigmentation. The anterior ligament of the spine macroscopically shows no pigmentation.

THORAX: The lower portion of the sternum and adjoining costal cartilages and ribs were removed through the abdominal incision. The costal cartilages present a striking picture; they are hard and everywhere show an intense bluish black pigmentation. The removed ribs and portions of sternum, however, show no apparent pigmentation.

Owing to the fact that permission was granted for a partial necropsy only, the larger joints of the body could not be investigated.

Roentgenograms of all the joints were made, however, and showed changes characteristic of arthritis deformans of the spine with well marked changes of the larger joint (hip and knee) especially about the attachments of the capsules. The smaller joints showed very little change. (Dr. Th. Scholz).

Histologic Report.—TRACHEAL CARTILAGES: Sections show diffuse pigmentation of the matrix about the cartilage cells and clumps of fine brown granules in the perichondrium. Most of the pigment is deposited in the matrix and immediately surrounding the cartilage cells.

COSTAL CARTILAGE: Section shows diffuse brown pigmentation of the matrix. In addition, a number of degenerated cartilage cells contain diffuse and granular brown pigment. The perichondrium is pigmented in places: the pigment present in the form of small brown granules.

INTERVERTEBRAL DISC: Intervertebral disc considerably narrower than average, in part composed of fibro-cartilage, in part there are large cartilaginous like plaques. In the matrix of these latter there is diffuse brown pigmentation. In the fibrous portion near the anterior ligament there is considerable granular brown pigmentation.

AORTA: Section shows a few atherosclerotic patches in the intima, associated with which there is a considerable amount of extracellular brown pigment in diffuse and small granular form.

Prostate: The architecture in general is normal. There are rather numerous corpora amylacea in the glands. These vary in appearance. A few show a large amount of diffuse brown pigment in the central portions, the peripheral portions unpigmented, stained pink (eosin). Various stages of pigmentation are seen, including large and small corpora amylacea, diffusely and homogeneously brown stained. About a few of the glands containing the pigmented corpora, there are accumulations of round cells, principally mononuclears. A number of the glands containing these masses show partial or complete absence of the epithelium.

Endocardium: This is considerably thickened. To it is attached a large thrombus mass, composed of strands of fibrin, red cells and fragmented leukocytes. Another section shows an area of the thrombus in which there is beginning calcification. In the deeper layers of the endocardium there are small masses of extracellular brown pigment in the form of fine granules. Section stained by Gram-Weigert stain shows in the outer portions of the thrombus numerous small round diplococci, many in small chains.

Kidney: There is some distortion of the striations. In areas there is an increase in the interstitial connective tissue; in some of these areas there is an accumulation of round cells in considerable number. In a number of these areas and also elsewhere the glomeruli have an altered appearance. The glomerular tuft is adherent to the capsule in one or more places. In places the glomerular sac contains amorphous, pink stained material and a few large mononuclear cells. In a very few glomeruli there are a large number of mononuclear cells within the sac, all filled with fine, brown pigment granules. The neighboring convoluted tubules also show a deposition of a large amount of granular brown pigment in the epithelium. In sections stained with silver nitrate, the ochronotic pigment is found in the form of very fine granules in cells of the proximal convoluted tubules and in the form of larger granules in the intact and desquamated cells of many of the ascending limbs of the loops of Henle and the various collecting tubules. The cells of the distal convoluted tubules contain the granular pigment in moderate amount. In general the pigment in the lumina of the tubules is diffuse. In places, however, desquamated cells containing granular pigment are present. In addition to these changes, a number of the tubules contain nucleated cells mostly polymorphonuclear leukocytes and in places the interstitial tissue shows accumulations of similar cells. In addition, in the interstitial tissue of cortex and medulla there are scattered large mononuclear cells containing brown pigment.

Spleen: Section shows a very large, triangular area of homogeneously pink stained amorphous material in which phantoms of former splenic structures are seen. In addition to the pink stained material there is, in places, some nuclear dust and more strikingly there are clumps of intra and extra cellular brown pigment. The greatest deposits of the pigment are found immediately surrounding this infarct, in the new formed connective tissue, which is present as a fairly wide band; the remainder of the section shows normal looking trabeculae and vessels. The malpighian bodies are very small, and lessened in number. There is, however, an increase in the nucleated cells of the pulp. There are numerous plugs of cocci in the splenic capillaries. Another section of the spleen shows the presence of a number of clumps of yellowish brown pigment scattered throughout the infarct. In the center of this infarct there is the remains of a large blood vessel plugged with homogeneous, pink stained material.

Liver: This shows considerable engorgement of the blood vessels in the central portions of the lobules. There is a striking increase in the number of nucleated cells in the capillaries. In one capillary a very large clump of cocci is seen.

Michrochemical Report.—In sections stained by Nishimura's method, the ochronotic pigment, diffuse and granular, does not show the reaction for iron.

In formalin-fixed material, the diffuse ochronotic pigment is stained orange red by neutral red (1 per cent. aqueous solution, three hours at 56 C.); the granular ochronotic pigment, however, is not stained by this method.

The granular ochronotic pigment behaves microchemically very much like the pigment of brown atrophy. Both are decolorized by (1) potassium permanganate, sodium sulphite, oxalic acid. (Potassium permanganate, 1/4 per cent. solution, one half hour; equal parts of oxalic acid and sodium sulphite, 1 per cent. solution, 10 minutes.); (2) surgical solution of chlorinated soda (from 15 to 30 minutes), and (3) bichromate sulphuric acid solution (potassium bichromate, 10 gm.; sulphuric acid concentrated, 12 c.c.; water, 100 c.c.) one half hour. Both the diffuse and the granular ochronotic pigment are stained brownish black by silver nitrate (fresh 2 per cent. solution silver nitrate, twenty-four hours at 56 C.). The form and distribution of the pigment are best demonstrated by this method.

SUMMARY OF FORTY-FIRST CASE

Clinical.—The diagnosis of ochronosis was made in this case because of the bluish discoloration of the cartilages of the ears and skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing. In addition the patient had a deforming arthritis of the spine and larger joints and a mitral endocarditis: complications frequently present in ochronosis.

Chemical.—Examination of the urine was repeatedly negative for alkapton body. The pigment obtained from the urine, from a costal cartilage and that from the prostate of the case gave the reactions for melanin. The pigment from these three sources had similar characteristics. The chemical findings are in accord with the belief that ochronosis is dependent on a disordered metabolism of phenol derivatives.

Pathologic.—As in the cases previously reported, the cartilages (costal, tracheal, bronchial, auricular and xyphoid), and fibrocartilages (intervertebral discs) are deeply pigmented (bluish black). Large stony masses of bluish pigmentation are found in the prostate and prostatic urethra. The kidneys likewise show extensive pigmentation. The endocardium, intima of the aorta and coronary arteries, skin and sclerae are less intensely pigmented. The pigment is not deposited in any quantity in intact intima and endocardium but in areas of degeneration in these structures, however, macroscopic deposits occur. Diffuse ochronotic pigment is present in albuminous masses (renal casts) and concretions (corpora amylacea of prostate). Fine pigment granules are present in the epithelium of proximal convoluted tubules, and coarser granules are present in the cells of the ascending loops of Henle, distal convoluted tubules and the collecting tubules.

The pigment is predominatingly diffuse in the matrix of the cartilage and fibrocartilage and when associated with albuminous masses and concretions. It is predominatingly granular in perichondrium, periosteum, tendons, fascias, connective tissue and in certain

renal cells. It is present in diffuse and granular forms in injured and degenerated areas.

The histologic picture in the kidney sections suggests excretion of the pigment by the cells of the proximal convoluted tubules. The picture likewise suggests a partial reabsorption of the fine pigment by the cells of the loops of Henle, distal convoluted tubules and collecting tubules, and a transformation of the pigment into a more granular form. The form and distribution of the pigment is demonstrated best in histologic sections stained with silver nitrate.[8]

We are indebted to Mrs. H. G. Friedman for her kind assistance in preparing this paper.

8. Other references bearing on this subject are: Poulsen: Literature to 1910, Beitr. z. path. Anat. u. z. allg. Path. **48**:346, 1910; Literature to 1912, Münch. med. Wchnschr. **59**:364, 1912; Beddard and Plumtree: Quart. J. M. **12**:505, 1911; Umber and Bürger: Deutsche. med. Wchnschr. **48**:2337, 1913; Jantke: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:617, 1913; Heymann-Giessen: 1913; Vogelius: Hospital tidende. 1164, 1914; Sprunt: Ochronosis, Nelson's Living Medicine **3**:211, 1920; Howard: Ochronosis, Oxford Medicine **4**:223, 1921.

AIDS TO BASAL METABOLIC RATE DETERMINATIONS *

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This paper contains charts and tables so arranged as to facilitate considerably the otherwise laborious calculation of basal metabolism values. They are in such form as to be useful in calculating basal metabolic rate from data obtained with any form of apparatus. They are intended primarily for use in connection with determinations made by some method involving the use of a Haldane gas analysis apparatus. Such methods in common use are either that described by Boothby and Sandiford [1] in which the expired air is collected in a large spirometer, or the method of Douglas [2] in which a rubber bag is used for this purpose and the volume of its contents measured with a meter.[3] In either of these methods the gasometric data include figures for volume, temperature, pressure, and carbon dioxid and oxygen content of the expired air. From these are to be computed the respiratory quotient and oxygen consumption at standard conditions of temperature and pressure. The figure for oxygen consumption, when multiplied by the calorific value of oxygen, gives a figure for calory production.

Certain instruments, as for instance the Benedict portable apparatus,[4] read the uncorrected oxygen consumption directly and a respiratory quotient of 0.82 corresponding to a calory value per liter for oxygen of 4.825 is assumed.

In calculating basal metabolic rate, the patient's calory production is compared with the normal. It is generally customary to use as standards the figures of Aub and DuBois, giving the normal calory production per square meter of body surface. The body surface of the patient is calculated from the height weight chart of DuBois. There are also available the standard multiple prediction tables of

* From the Laboratory of the Henry Phipps Institute of the University of Pennsylvania.

1. Boothby, W. M., and Sandiford, I.: Laboratory Manual of Basal Metabolic Rate Determination, Philadelphia, 1920.
2. Carpenter, T. M.: Carnegie Inst. Wash. Pub. No. 216, 1915, p. 67.
3. Newcomer, H. S.: J. Biol. Chem. **47**:489, 1921.
4. Benedict, F. G., and Collins, W. E.: Boston M. & S. J. **183**:449, 1920.

Benedict, as well as certain other data, applying to children.[5] In its simplest form the calculation is laborious and when it is desirable to obtain the additional information to be had by the use of a Haldane apparatus, the computation involves the expenditure of an appreciable amount of time and gives opportunity for the appearance of numerical errors.

The use of the charts and tables at the end of this paper restrict this labor to the performance of a simple algebraic sum. In several instances they condense hitherto available tables of many pages to a single sheet. There follows a description of their derivation and then directions for their use with examples.

Derivation of Formulae and Charts.—Charts 1 and 2 are intended for use with the Haldane gas analysis apparatus and are used to obtain hourly calory production. Chart 2 corrects the gas volume to standard conditions of temperature and pressure and includes a correction for water vapor.

Apparatus such as that of Benedict which reads oxygen consumption directly, that is, which reads the diminution in oxygen volume of a closed system including the patient's respiratory tract, does not involve a correction for water vapor. The observed diminution in oxygen volume is, therefore, to be reduced to standard conditions by a factor which does not include a correction for saturation with water vapor. Chart 3 supplies the logarithm of this correcting factor. The hourly calory production may be obtained by multiplying the oxygen consumption in c.c. per minute by 0.2895 (log. $0.2895 = \bar{1}.4617$). The other charts and tables have to do with basal metabolism standards. In the computation of the charts and tables five figure logarithms were used except that in the case of Chart 1 it was necessary to use seven place tables.

Chart 1 has as abscissae the reading of the Haldane buret after absorption of carbon dioxid, it being assumed that the Haldane buret was filled in the first place to the 10 c.c. mark at atmospheric pressure. The ordinates are the Haldane readings after carbon dioxid and oxygen absorption. It is further assumed that these readings are corrected for any calibration error which the Haldane buret may have, and that the patient breathes outside air. This may be either through a tube out the window, or, if the room can be well aired, it suffices to leave the window open for some time before starting. The chart has two families of lines; the horizontal ones give, by interpolation between them, the value of the respiratory quotient, volume of carbon dioxid production divided by volume of oxygen absorption. The more vertical lines are the logarithms of factors, portion of oxygen absorbed times the calorific value of one liter of oxygen at the equivalent respiratory quotient. The value of the logarithm of this factor corresponding to any pair of Haldane readings is obtained by interpolation between this family of lines.

5. Carpenter, T. M.: Carnegie Inst. Wash. Pub. No. 303, 1921.

TABLE 1.—Barometer Correction for Change in the Value of Gravity with Latitude to Be Subtracted from or Added to the Observed Height of the Barometer Before Going to Charts 2 or 3

Latitude	0° 90°	5° 85°	10° 80°	15° 75°	20° 70°	25° 65°	30° 60°	35° 55°	40° 50°	45° 45°
710 mm. Subtract mm. Add	1.84	1.81	1.73	1.59	1.41	1.18	0.92	0.63	0.32	0.00
760 mm. Subtract mm. Add	1.97	1.94	1.85	1.70	1.51	1.27	0.98	0.67	0.24	0.00

The correction varies with the height of the barometer. To correct for altitude subtract 0.14 mm. of mercury for every one thousand meters above sea level. To correct for the capillary depression of the mercury column see the text. Combine all of these corrections into one and use only if significant.

TABLE 2.—Logarithms of Standard Reciprocal Normal Basal Metabolism Factors for Children 17 Years of Age and Under Referred to Weight in Pounds. (Benedict)

Wt.	Boys	Girls	Wt.	Boys	Girls	Wt.	Boys	Girls	Wt.	Boys	Girls
6	$\overline{1}.264$	$\overline{1}.274$	36	$\overline{2}.498$	$\overline{2}.523$	66	$\overline{2}.333$	$\overline{2}.360$	96	$\overline{2}.270$*	$\overline{2}.288$
8	.106	.093	38	.485	.510	68	.326	.351	98		.287
10	$\overline{2}.996$	$\overline{2}.974$	40	.472	.498	70	.318	.344	100		.286
12	.908	.885	42	.455	.487	72	.311	.337	102		.285
14	.835	.813	44	.444	.475	74	.304		104		.284
16	.774	.758	46	.433	.463	76	.297	.320*	106		.283
18	.724	.712	48	.422	.451	78	.291		108		.282
20	.682	.679	50	.411	.440	80	.285	.305*	110		.281
22	.645	.649	52	.400	.430	82	.280		112		.280
24	.614	.621	54	.390	.419	84	.274	.295	114		.279
26	.589	.595	56	.379	.408	86		.294	116		.278
28	.567	.572	58	.368	.399	88		.292	118		.277
30	.547	.564	60	.358	.389	90		.291	120		.276
32	.529	.549	62	.350	.379	92		.290	124		.274
34	.511	.536	64	.342	.371	94		.289	128	.260*	.272

The figures are the logarithms of reciprocal total calories per hour of children weighing from 6 to 128 pounds. The figures are calculated from data by Benedict and Talbot, and Benedict and Hendry. The numbers with an asterisk are not due to these authors but are supplied as probable values in order to make the table complete

TABLE 3.—THREE FIGURE LOGARITHMS

	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
1	000	041	079	114	146	176	204	230	255	279	4 3 3 3 2	8 7 6 6 5	12 10 9 8 7	16 13 12 11 10	20 17 15 13 12	24 20 18 16 14	28 24 21 18 16	32 27 24 21 19	36 30 26 23 21
2	301	322	342	362	380	398	415	431	447	462	2 2 2	4 4 3	6 5 5	8 7 6	10 9 8	12 11 9	14 12 11	16 14 12	18 16 14
3	477	491	505	518	531	544	556	568	580	591	2 1	3 2	4 4	6 5	7 6	8 7	10 8	11 9	12 10
4	602	613	623	633	643	653	663	672	681	690	1	2	3	4	5	6	7	8	9
5	699	708	716	724	732	740	748	756	763	771	1	2	2	3	4	5	6	6	7
6	778	785	792	799	806	813	820	826	833	839	1	1	2	3	3	4	5	5	6
7	845	851	857	863	869	875	881	886	892	898	1	1	2	2	3	4	4	5	5
8	903	908	914	919	924	929	934	939	944	949	1	1	2	2	3	3	4	4	5
9	954	959	964	968	973	978	982	987	991	996	1	1	1	2	2	3	3	4	4
	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9

The figures of the table are the mantissae of two figure numbers. The columns at the right are the proportional parts to be added to the mantissae to make them the mantissae of three figure numbers. The characteristic of the logarithm is the number less one of integral digits in the number.

TABLE 4.—THREE FIGURE ANTILOGARITHMS

	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
.0	100	102	105	107	110	112	115	117	120	122	0	1	1	1	1	2	2	2	2
.1	126	129	132	135	138	141	145	148	151	155	0	1	1	1	2	2	2	3	3
.2	158	162	166	170	174	178	182	186	191	195	0	1	1	2	2	2	3	3	4
.3	199	204	209	214	219	224	229	234	240	245	1	1	2	2	3	3	4	4	5
.4	251	257	263	269	275	282	288	295	302	309	1	1	2	3	3	4	5	5	6
.5	316	324	331	339	347	355	363	371	380	389	1 1	2 2	2 3	3 4	4 4	5 5	5 6	6 7	7 8
.6	398	407	417	427	437	447	457	468	479	490	1 1	2 2	3 3	4 4	5 5	6 7	7 8	8 9	9 10
.7	501	513	525	537	550	562	575	589	603	617	1 1	2 3	4 4	5 5	6 7	7 8	8 10	10 11	11 12
.8	631	646	661	676	692	708	724	741	759	776	1 1 2	3 3 4	4 4 5	6 6 7	7 8 9	9 10 11	10 11 12	12 13 14	13 14 16
.9	794	813	832	851	871	891	912	933	955	977	2 2 2 2	4 4 4 5	6 6 6 7	8 8 8 9	9 10 11 11	11 12 13 13	13 14 15 16	15 16 17 18	17 18 19 20
	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9

The figures of the table are the numbers corresponding to two figure mantissae. The columns at the right are proportional parts to be added to the numbers to make them numbers corresponding to three figure mantissae. The characteristic of the logarithm is omitted in going to the table. The number is to be pointed off so as to have a number of integral digits equal to the characteristic plus one. If the characteristic is negative the number is to be preceded by a number of decimal zeros equal to the characteristic plus one (with regard to sign).

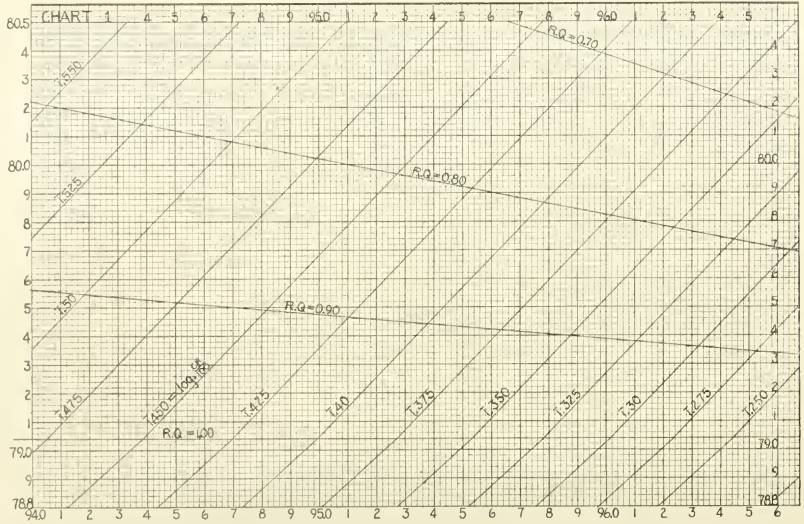
CHART 1
R.Q=0.70
R.Q=0.80
R.Q=0.90
R.Q=1.00
T.50
T.475
T.450
T.425
T.40
T.375
T.350
T.325
T.30
T.275
T.250
80.5
80.0
79.0
78.8
94.0
95.0
96.0

Chart 1A.

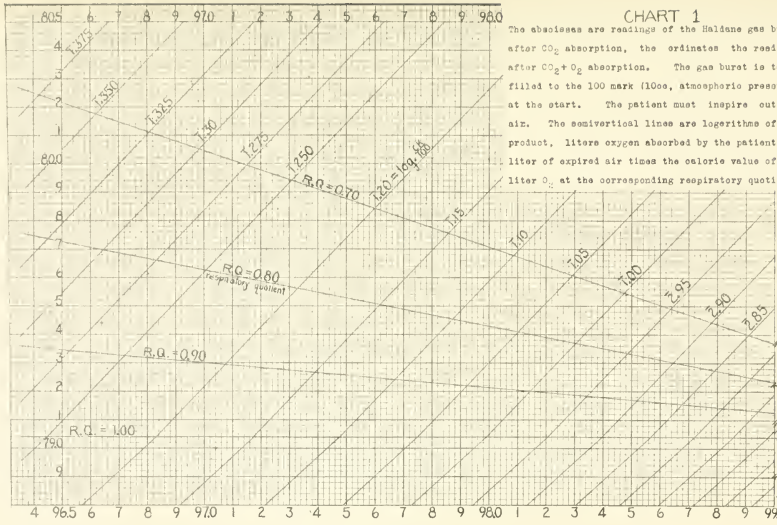

CHART 1

The abscissae are readings of the Haldane gas buret after CO_2 absorption, the ordinates the readings after $CO_2 + O_2$ absorption. The gas burat is to be filled to the 100 mark (100cc, atmospheric pressure) at the start. The patient must inspire outdoor air. The semivertical lines are logerithms of the product, liters oxygen absorbed by the patient per liter of expired air times the caloric value of one liter O_2 at the corresponding respiratory quotient.

Chart 1B.

The derivation of these two families of lines is as follows:

Let x = reading of Haldane after CO_2 absorption
= 100 — CO_2 percentage in expired air
y = reading of Haldane after $CO_2 + O_2$ absorption
(1) = 100 — ($CO_2 + O_2$) percentage in expired air
= nitrogen percentage in expired air

If 20.93 be the value taken for the oxygen percentage in the inspired air, outside air, and 0.03 the carbon dioxid percentage, then 79.04 is the nitrogen and other inert gas percentage in the inspired air. The fraction $\frac{y}{79.04}$ represents the change in volume of the air due to alveolar gas exchange, and the oxygen absorption in per cent. is given by

$$(2) \qquad \frac{20.93\,y}{79.04} - O_2 = K$$

where O_2 is the oxygen percentage of the expired air. From (1) and (2)

$$\frac{20.93\,y}{79.04} + y - 100 + CO_2 = K$$

or

$$(3) \qquad \frac{99.97}{79.04}\,y - x = K$$

These are a family of lines of slope $\frac{79.04}{99.97} = .790637$ giving constant oxygen absorption K. The values of the calorific equivalent, C, of one liter of oxygen for the respiratory quotients 0.707 to 1.00 as tabulated by Lusk[6] are given with an error of less than one part in one thousand by the formula

$$R.\ Q. = 0.813\ C - 3.103$$

But by definition $R.\ Q. = \frac{100 - x - 0.03}{K}$

Therefore

$$\frac{100 - x - 0.03}{K} = 0.813\ C - 3.103$$

$$C = \frac{100 - x - 0.03}{0.813K} + \frac{3.103}{0.813}$$

$$(4) \qquad CK = \frac{100 - x - 0.03}{0.813} + \frac{3.103}{0.813}\,K$$

substituting (3) in (4)

$$CK = \frac{100 - x - 0.03}{0.813} + \frac{3.103}{0.813}\left(\frac{99.97}{79.04}y - x\right)$$

$$CK = 4.8274y - 5.04674x + 122.9643$$

= per cent. oxygen absorbed times its calorific value per liter.

This family of lines is plotted for values of CK whose logarithms are 0.60, 0.65, 0.70, etc., to 1.55. K is the number representing per cent. oxygen absorbed by the patient. The fraction $\frac{K}{100}$ is, therefore, a number which multiplied by the expired volume is the oxygen absorbed by the patient. $\frac{CK}{100}$ is its calorific value and the logarithms of $\frac{CK}{100}$ instead of the above logarithms of CK are assigned as signatures to the family of lines, namely, $\bar{2}.60$, $\bar{2}.65$, $\bar{2}.70$, ... to $\bar{1}.55$.

6. Lusk, G.: The Science of Nutrition, Ed. 3, Philadelphia, 1919, p. 61.

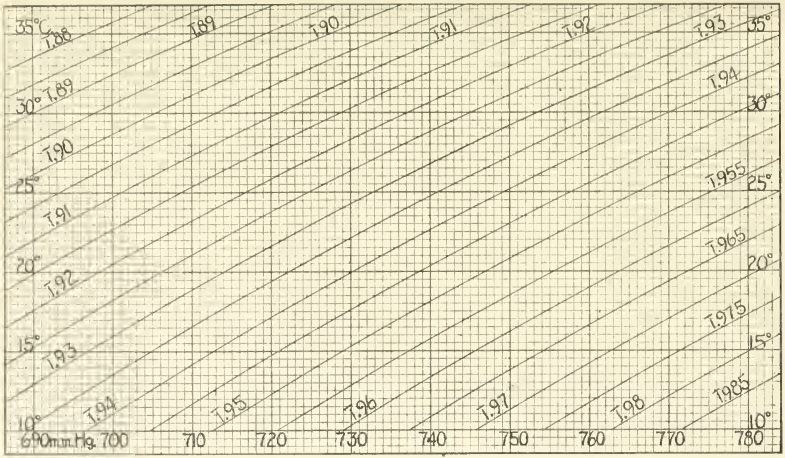

Chart 2.—The ordinates are temperatures centigrade and the abscissas observed barometric pressures in mm. of mercury. The lines are logarithms of the factor reducing observed volume of water vapor saturated air to 0 C., dry. 760 mm. sea level and latitude 45 degrees, including a reduction of the barometer readings, brass scale, to 0. C. Log p—vap. ten. $-\frac{\text{scale correction}}{760} \times \frac{1}{1+0.00367\ t}$

For the other corrections which may be advisable see Table 1:

When the respiratory quotient is greater than unity the heat production is due to the oxygen consumption plus the heat produced in the transformation of the carbohydrate into fat during which the extra carbon dioxid was produced. The heat value of this transformation, according to Lusk, is 0.8 calories per liter carbon dioxid. For readings below the line RQ = 1 carbohydrate is being burned at a rate producing an oxygen percentage absorption corresponding to a CK line of the reading where C is the 5.047 of RQ = 1. In addition, carbohydrate is being converted into fat with a carbon dioxid percentage production equal to the difference between x where the CK line crosses RQ = 1, and the observed x. To this additional CO_2 there corresponds a calory production of 0.8 per liter. In order to calculate the total calory factor, we may draw a line of the family K = constant through the point given by the intersection of the CK line and RQ = 1. If this be considered as a new CK line it is a line along which neither C nor K changes. The new calory factor line is then one passing through the CK, RQ point and having a slope sufficiently steeper than the constant K line to make an observed point on the constant K line and one x unit smaller than the x of the CK, RQ point lie 0.8 of the distance between the new line and a next parallel one having a value one unit larger. Therefore, below the line RQ = 1, the constant calory factor lines bend slightly, as shown in the chart, and for readings below the line RQ = 1, the patient is putting on fat at the moment in question.

Chart 2 is computed from data by Kaye and Laby.[7] It is a family of curves giving by interpolation the logarithms of the factor reducing the observed air volume to 0 C., 760 mm. of mercury at latitude 45 degrees and sea level, dry, together with a correction to 0°C. of the mercury columns and brass scale. The corrections for brass and glass scales are nearly the same. At 10 C. the correction for glass to be subtracted is 0.07 mm., and at 34 C., 0.25 mm. greater than that correction for brass which has been subtracted from the barometric height in computing the curves. The table does not include barometer corrections due to the change in the value of gravity with latitude and height above sea level. If it is desired to correct for latitude, add or subtract from the observed barometer the figures of Table 1 before reading from the chart. The change in gravity due to altitude is such that for every one thousand meters above sea level one should subtract from the observed barometer approximately 0.14 mm. of mercury. It may be proper in addition to correct for the capillary depression of the mercury column. This correction is zero if both mercury levels have the same cross section, as is the case with the usual all glass barometer. For barometers having a mercury reservoir the figures to be added to the barometer reading for bores of 4, 5, 6, 7, and 8 mm. are, respectively, 1.2, 0.7, 0.4, 0.25, and 0.2 mm., provided the height of the meniscus itself is 0.6 mm. For heights of the meniscus greater than this and up to 1.6 mm. these figures are to be increased uniformly per 0.2 mm. of height respectively by 0.4, 0.25, 0.2, 0.15, and 0.1 mm. These corrections for gravity and capillary depression may of course be determined at any place once for all and combined into one single correction for the barometer.

Table 2 is derived from data by Bendict and Talbot[8] and Benedict and Hendry.[9] It gives the logarithms of the reciprocal of the total number of calories produced per hour by children seventeen years of age and under. The numbers are computed from the tables of these authors. The numbers with an asterisk are supplied to make the table complete, the two for girls being easily inserted by interpolation. The additional numbers for boys cannot be supplied with the same assurance. There should be a continued gradual decrease in the

7. Kaye, G. W. C., and Laby, T. H.: Table of Physical and Chemical Constants, Ed. 2, London, 1916.

8. Benedict, F. G., and Talbot, F. B.: Carnegie Inst. Wash Pub. No. 302, 1921, p. 206.

9. Benedict, F. G., and Hendry, M. F.: Boston M. & S. J. **184**:329, 1921.

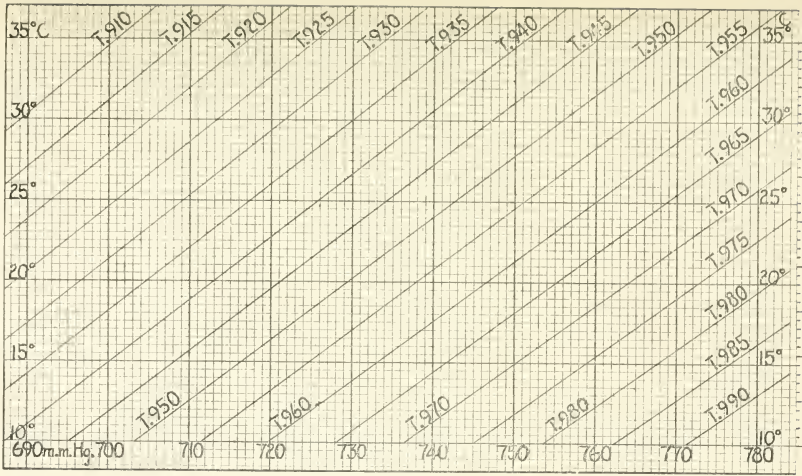

Chart 3.—The ordinates are temperatures centigrade and the abscissas observed barometric pressures in mm. of mercury. The lines are logarithms of the factor reducing observed volume of dry air to 0 C., 760 mm. sea level and latitude 45 degrees, including a reduction of the barometer readings, brass scale, to 0 C Log $\frac{p - \text{scale correction}}{760} \times \frac{1}{1+0.00367\ t}$

For the other corrections which may be advisable see Table 1.

logarithms with increasing weight. The least decrease that could be expected is to the figure $\bar{2}.260$ at 128 pounds. A smaller figure could not well be chosen because of the fact that in adults of the age of twenty-one years, having the extreme range of weights and normal stature (Prudential 1912 statistics), the normal calory production for males (Benedict multiple prediction formula) is not more than 3 per cent. higher than that of females. The antilogarithms of $\bar{2}.260$ and $\bar{2}.272$ differ by about this 3 per cent., and if the first were smaller the percentage difference would be larger.

Chart 4 is calculated from the Harris and Benedict[10] standard multiple prediction tables for normal basal metabolism of adults. It is impossible to put these tables in the form of logarithms. They predict the hourly calories as the sum of two numbers. They are to be used as follows. From the height in inches and the age in years read by interpolation between the family of lines a number corresponding to the lines. From the weight in pounds read on the single line the corresponding abscissa (numbers 20 to 70). The sum of these two numbers is the expected hourly calory production.

EXAMPLE.—Male, age 35, 62 inches tall, 135 pounds.

(35,62)	23
135	38
	61 predicted hourly calories.

The normal metabolism data of Benedict leaves a gap from the seventeenth to the twenty-first year. It is believed that the data of Benedict more nearly predict the normal than do those of DuBois. The data of DuBois are, however, widely used. They are included here as Chart 5 and Chart 6. Chart 5 plots the logarithms of reciprocal square meters of body surface. It is the same family of curves as that of DuBois.[11] Chart 6, due to the data of Aub and DuBois,[12] gives the logarithm of the reciprocal normal calories per square meter per hour.

Chart 3 is similar to Chart 2. It gives the logarithm of the factor reducing the observed air volume to 0 C., 760 mm. of mercury at latitude 45 degrees and sea level together with a correction to 0 C. of the mercury column and brass scale. It does not correct for aqueous vapor tension as does Chart 2 and is to be used with portable respiration apparatus. The above remarks on corrections for latitude and altitude apply equally to this chart.

Table 3 is a three place logarithm table and Table 4 is a table of antilogarithms. The logarithms of the charts consist of a mantissa, the decimal, which is always positive, and a characteristic, the integer in front of the decimal point which is negative. The signs of the characteristic are to be considered in taking the sum of the various logarithms; the characteristic of the sum is an integer which is the sum of the separate characteristics plus any digit carried to this place in adding the adjoining columns in the mantissae. The mantissa only is used in going to the table of antilogarithms and the characteristic plus one represents the number of integral digits to be pointed off in the number of the table. It fixes the position of the decimal point. In reading from Table 3 the logarithm of a number such as the hourly volume in liters assign to the mantissa of the table a characteristic one less than the integral digits in the number.

Calculation of Calory Production and Basal Metabolic Rate.—The charts are so arranged that the only calculation required is the performance of a sum.

10. Harris and Benedict: Carnegie Inst. Wash. Pub. No. 279, 1919, p. 253.
11. DuBois, D., and DuBois, E. F.: Arch. Int. Med. **17**:865 (June) 1916.
12. Aub and DuBois: Arch. Int. Med. **19**:831 (June) 1917.

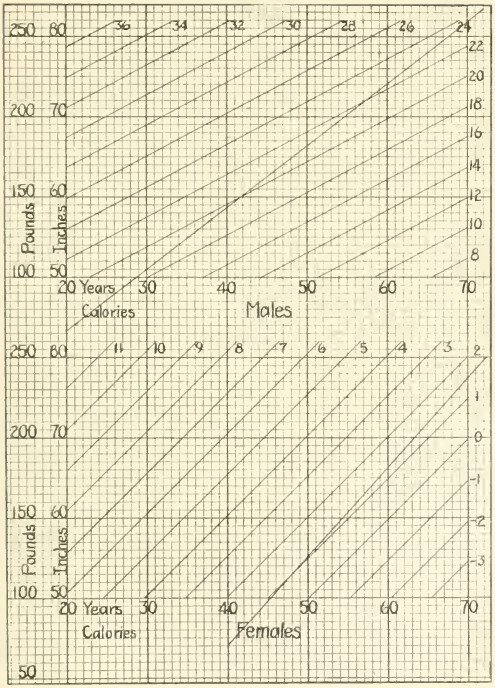

Chart 4.—The chart is based on the standard multiple prediction tables of Harris and Benedict for normal basal metabolism. From the height in inches and the age in years there is read by interpolation between the family of parallel lines a first number. The intersection of the horizontal giving weight in pounds with the single diagonal line gives an abscissa, 20 to 70. The sum of this and the first number is the normal calory production per hour. The tables of Harris and Benedict do not extend to heights below sixty inches.

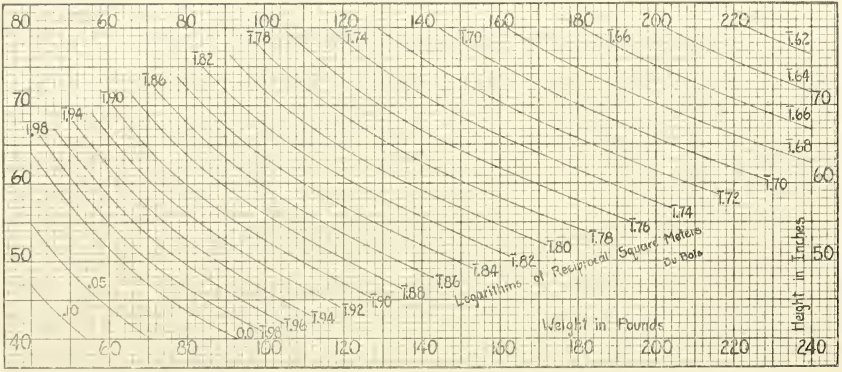

Chart 5. The ordinates are height in inches and the abscissas weight in pounds. The curves are derived from the DuBois Height Weight formula for square meters body surface. They have been chosen so as to assign as signatures to them logarithms of the reciprocals of square meters of body surface.

To determine hourly calory production:

(a) using the Haldane apparatus.

Add the figures obtained by interpolation from Charts 1 and 2 and the logarithm, from Table 3, of the hourly volume in liters, as read on a meter or spirometer. The antilogarithm, from Table 4, of this sum is the calory production. The respiratory quotient is read directly by interpolation between the lines of Chart 1.

(b) using a direct reading oxygen consumption apparatus (Benedict, etc.).

Add to 1.4617 the logarithm, from Table 3, of the observed oxygen consumption per minute in c.c. and the figure obtained by interpolation from Chart 3. Before going to Chart 3 for the volume correction add to the observed temperature of the bell 1 F. as suggested by Benedict ($\frac{1}{2}$ C). The antilogarithm of the sum is the calory production. The respiratory quotient is assumed to be 0.82.

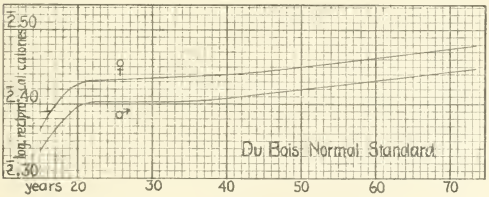

Chart 6. The curves are the logarithms of the reciprocal of the normal hourly calory production of males and females as given by Aub and DuBois. DuBois data for males under 15 years is omitted, the data of Table 2 being preferred. In the 15 to 20 year interval DuBois data are higher than the data of Benedict. Above 20 years comparison cannot be made simply.

The hourly calory production as determined under (a) or (b) may be compared directly with the normal obtained from Chart 4. The basal metabolic rate is the quotient of the actual by the predicted. In the case of children, the basal metabolic rate determination may be made by simply adding the figure of Table 2 to the sum as obtained above under (a) or (b). The antilogarithm of this sum is then the basal metabolic rate. If it is desired to refer to the DuBois standard, add as a part of the sum the figures from Charts 5 and 6. The antilogarithm of the sum is the basal metabolic rate.

The results are given with no greater error than that inherent in the data. Each chart or table is calculated with a slightly greater degree of accuracy than the data warrant. The charts and tables are such that the basal metabolic rate is given correctly to within one unit in the second decimal place, that is

to within one per cent., and the total calory production correctly to within one-half unit in the second figure. This amount of precision necessitates the reading of Chart 1 to within two units in the third decimal place. This latter may be accomplished by applying a scale between the two CK lines in which interval the point lies and turning the scale diagonally until the ends of a ten unit interval on it fall on the two CK lines. The proportionate distance from the one line to the next of the point to be interpolated is then read off directly from the scale. The error is not over two per cent. when Chart 1 is not so taxed to its capacity. Chart 1 can easily be read more closely than the data can be calculated with a four place logarithm table and more closely than the Haldane gas buret can be read. Chart 4 can be read correctly to one-half calory, Chart 5 can be read to one-half unit in the second decimal place, and the other charts and tables are readily read to three decimals. The logarithm tables are calculated so as to be correct to one unit in the third decimal place.

EXAMPLE 1.—Haldane readings 97.32 and 79.48. Temperature 20 C.; barometer 751 mm. Hourly volume 452 liters. Male, age 38, height 65½ inches, weight 150 pounds.

Chart 1.	$\bar{1}.19$	R.Q. .83	
Chart 2.	$\bar{1}.9525$		
Log. vol.	2.655		
	1.7975	antilog. 62.7	calories per hour (actual)
		Chart 4. 24	
Chart 5.	$\bar{1}.755$	41.5	
Chart 6.	2.406		
		65.5	calories per hour (expected)
	$\bar{1}.9585$	antilogarithm 0.909 B. M. R. (Du Bois)	

EXAMPLE 2.—Haldane readings 95.6 and 79.74. Temperature 18 C.; barometer 740 mm. Hourly volume 234 liters. Girl, aged 11, weight 80 pounds.

Chart 1.	$\bar{1}.405$	R.Q. .83	
Chart 2.	$\bar{1}.950$		
Log. vol.	2.369		
Table 2.	2.305		
	0.029	antilogarithm 1.07 7 per cent. above the normal.	

EXAMPLE 3.—Average reading for contraction of Benedict spirometer bell, per minute 240 c.c. Average temperature of bell plus 0.5 F. (26 C.); barometer 746 mm. Female, aged 32, height 62 inches, weight 125 pounds.

Cal. factor	$\bar{1}.4617$		
Log. 240	2.380		
Chart 3.	$\bar{1}.9505$		
	1.7922	antilog. 62.0	calories per hour (actual)
		Chart 4. 6	
Chart 5.	$\bar{1}.805$	50	
Chart 6.	2.435		
		56	calories per hour (expected)
	0.0322	antilogarithm 1.08 B.M.R. (DuBois)	

SUMMARY

Tables and charts have been prepared by means of which the basal metabolic rate may be calculated by simply adding five numbers.

The charts condense the usual tables into a very small space. They include one reducing saturated gas volumes to 0 C. dry, 760 mm. mercury, sea level, 45 degrees latitude with a temperature pressure correction for the brass or glass scale of the barometer.

THE NATURE OF THE SO-CALLED "CAPILLARY PULSE"

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The "capillary pulse" has been of interest to clinicians ever since Quincke [1] first called attention to it in 1868. Nothing, however, has been added to his original description of the condition, nor to his discussion of the probable mechanism by which it is brought about. Two observers before Quincke noted the phenomenon in isolated cases, but failed to appreciate the frequency of its occurrence or its significance. Lebert [2] cites the case of a patient with an aortic aneurysm who exhibited systolic flushing and diastolic paling of the cheeks. Ascherson [3] observed a child 7 years of age with varicella following scarlatina, in whom the papules and the bases of the vesicles reddened in diastole and paled in systole. This was very evident for four days, but after that it was only demonstrable when the skin about the lesion was stretched. Both authors attributed the phenomenon to a pulsation of the capillaries. It was Quincke, however, who observed the flushing and paling of the tissues under the finger nail not only in aortic insufficiency, but in a variety of other conditions. In patients with incompetent aortic valves it is most manifest, but it can be observed in many normal individuals. Quincke calls to mind that ordinarily, because of the elasticity of the arteries, the blood flows through the capillaries in a continuous stream; but that with venous obstruction, or with a marked lowering of the blood pressure associated with a slow pulse rate, the capillary flow may become pulsatile. A marked relaxation of the arterial wall may have the same effect. Thus Claude Bernard explained the pulsation of the capillaries and veins of the submaxillary gland which he observed on stimulation of the chorda tympani. In a later paper Quincke [4] emphasizes that a great difference between the systolic and diastolic pressures is essential for the visualization of the capillary pulse. He observed the phenomenon in anemic individuals, and in those with low blood pressure, an overactive heart, and a pulse

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1. Quincke, H.: Beobachtungen ueber Capillar und Venenpuls, Berl. klin. Wchnschr. **5**:357, 1868.

2. Lebert: Handb. der praktischen Medicin, Ed. 3, **1**:746, 1863.

3. Ascherson: Variola Versicolor. Medizin. Ztg. d. Ver. f. Heilk. in Preussen, 1834.

4. Quincke, H.: Ueber Capillarpuls und Centripetalen Venenpuls, Berl. klin. Wchnschr. **27**:263, 1890.

of the collapsing type, as well as in those with a leaking aortic valve. In his first paper Quincke described the pulsation under the finger nail, both with and without the application of gentle pressure. Subsequently, however, he noted it on the mucous membrane of the lip, when compressed with a glass slide, and on the skin of the forehead after it had been rubbed with a blunt object. When a patient exhibiting this phenomenon presents a skin lesion, such as erisypelas or urticaria, the pulsation becomes very evident.

Quincke's observations and conclusions have been generally confirmed and accepted, and we find in most textbooks of medicine, as well as of physiology, a presentation of the views first set forth by him fifty-three years ago. Lombard [5] in 1912 described a method by which the human capillaries can be studied directly under the microscope, but in the United States little use has been made of his observations, save by Danzer and Hooker,[6] who devised a method of measuring the capillary pressure, based on this principle. If a drop of glycerin or castor oil be applied to the skin at the base of the finger nail, and this area be then studied through the microscope under direct illumination, with a magnification of from 40 to 80 diameters, the capillary loops are beautifully visualized. Not only can the architecture of the capillary bed be studied, but the blood flow can be observed almost as well as in the classical demonstration of the capillary circulation in the web of the frog's foot. For details of technic, Danzer and Hooker's article, as well as of Weiss' [7] studies should be consulted.

While engaged in a study of the capillary morphology and blood pressure in a series of many different types of cases, I had the opportunity to observe the capillaries in eleven patients who exhibited a well marked clinical capillary pulsation under the finger nail. The capillaries in these cases were studied most assiduously under all kinds of conditions, and in no instance was a pulsatory stream of the blood in the capillaries seen.

Method.—A description of the method employed will be in place A drop of clear castor oil is placed on the dorsum of a finger just below the nail bed, and the finger is then placed on the finger rest of Danzer and Hooker's microcapillary tonometer, which stands on the stage of the microscope at heart level. Light is thrown on the area

5. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, Am. J. Physiol. **29**:335, 1912.

6. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Micro-capillary Tonometer, Am. J. Physiol. **52**: 136, 1920.

7. Weiss, E., and Dieter, W.: Die Strömung in den Kapillaren und ihre Beziehung zur Gefässfunktion, Zentralbl. f. Herz. u. Gefässkrankh. **12**:295, 1920.

to be observed by an electric bulb whose rays are focused by a condenser. A magnification of eighty diameters is employed. The capillaries are thus clearly brought into view and can be studied at leisure. Patients with a clinical capillary pulse are, however, difficult to study, because the finger moves with each pulse beat and the capillaries are thus thrown out of focus. This results in a very deceptive microscopic picture, for the finger movements rhythmically alter the focus of the microscopic field under observation. Thus with each pulse beat the capillaries become indistinct and may even disappear from view, to reappear immediately thereafter with their original clearness. This movement in and out of the focal field can readily be mistaken for a pulsation of the capillaries themselves. However, a close study, which, to be sure, is somewhat trying on the eyes, will convince the observer that the blood stream through the capillaries is at all times continuous and never pulsatile.

When the capillary blood stream is studied in this manner, it will be found that in most instances the flow is so rapid and steady that it can hardly be visualized. Each capillary is of a constant and uniform caliber. However, in individual capillaries the flow may be slow and almost halted at times but soon resumes its rapid streaming. Some individuals have a slower flow than others, and some a more rapid flow. With hypertension the velocity of the capillary blood appears to be increased; in arteriosclerosis it is decreased. But in spite of these individual variations, a capillary pulse was never observed. There was no intermittency of the circulation in the capillaries, nor was there any systolic lateral displacement of the capillaries.

Because of the fact that clinically the "capillary pulse" is usually observed best under slight pressure of the tissues, such pressure was exerted on the area studied by means of the Danzer-Hooker instrument. The pressure was elevated until the flow through the capillaries ceased, and was then gradually released to zero. At no pressure, not even with the first reappearance of the flow, was there the slightest departure from the normal continuous stream of blood. Both Weiss [7] and Jürgensen [8] have described pulsation of the capillaries observed through the microscope, but I am compelled to disagree with their findings. It is probable that the pulsation of the finger, discussed above, led them astray. I have seen this simulated capillary pulsation when the capillary flow was at a standstill because of the high pressure in the air chamber of the tonometer. Such an observation allows of no two interpretations and shows clearly with what care the studies must be made to avoid error.

The accompanying table gives a brief summary of the cases studied, together with the capillary pressure found in each instance. For reasons which will be detailed in a subsequent article, I have not averaged the pressures read in the different capillaries as advocated by Danzer and Hooker, but prefer to record them as individual readings. It seems quite certain that the variations of pressure observed in the same individual are of significance, and are not due to inaccuracy of measurement.

PATIENTS EXHIBITING CLINICAL CAPILLARY PULSE BUT NO MICROSCOPIC PULSATORY CAPILLARY FLOW

Case	Age	Sex	Diagnosis	Blood Pressure	Capillary Pressure, Mm. Hg	Room Temp., F.	Appearance of Capillaries
1	21	Male	Aortic insufficiency, rheumatic	140/ 50	10 10	..	Arrangement regular, some looped; subpapillary plexus visible
2	23	Male	Aortic insufficiency, rheumatic	115/ 60	20 20 18 25 22 23 26 15	78	Capillaries long, few loops
3	28	Male	Aortic insufficiency, rheumatic	140/ 50	20 18.5 10 13.5 17 10 11 8	65	Capillaries numerous, many rows, few tortuous; subpapillary plexus visible
4	18	Female	Aortic insufficiency, rheumatic	190/ 0	17 17.5 17	67.5	Capillaries numerous, not tortuous; subpapillary plexus visible
5	20	Male	Aortic insufficiency, mitral stenosis, rheumatic	150/ 20	8 5 7 12 12 7 10 16.5 15	70	Capillaries very long and numerous
6	12	Male	Aortic insufficiency, rheumatic	110/ 40	10 16 9 10.5	70	Capillaries very convoluted and irregular
7	8	Male	Aortic insufficiency, mitral stenosis, rheumatic	100/ 40	5 4 5 3	70	Capillaries normal
8	76	Male	Hypertension right hemiplegia	180/ 60	25 24 21 25 27 21 20	68	Capillaries long, convoluted; extensive subpapillary plexus
9	55	Male	Hypertension	205/110	17 31.5 12 19.5 23 22.5 18 18 17 26.5 34 38 29 28	65	Capillaries long, many convoluted; some giant capillaries
10	57	Female	Hypertension	145/ 75	25 20 27 33 18 14 30 31	75	Capillaries very convoluted; several rows; flow rapid
11	63	Female	Hypertension, diabetes	210/ 85	26 13 27 15 22 21 25 23 10 11.5 17 14.5	88	Longer and more tortuous than normal; subpapillary plexus prominent

Since, according to these observations the current views on the nature of the "capillary pulse" are erroneous, we must seek a new explanation of the phenomenon. At first thought it would seem that if the capillaries are not concerned in the production of this pulsation, it must be the minute arterioles in the subpapillary plexus of the skin which bring it about. This may be so in many instances, but Quincke's observations on the centripetal venous pulse, published in the same articles as those on the capillary pulse, suggest another possible interpretation. In some patients who exhibited clinical capillary pulsation he noted a post systolic centripetal pulsation of the veins on the dorsum of the hand. He believed it to be due to the propagation of the arterial pulse wave through the capillaries to the veins. In his second paper, however, he states that the capillary pulse is uncommonly found associated with the venous pulse. It is not quite clear how this comes about. Jürgensen [8] offers a possible explanation. He reviews the work of Hoyer,[9] Grosser [10] and Schumacher,[11] who demonstrated direct anastomoses between the arterioles and venules in the subpapillary plexuses, to explain some of the phenomena which he has observed in his studies of the capillaries. It is possible that the venous pulse, when it occurs, is caused by the transmission of the pulse wave through these subpapillary anastomoses, and that the clinical capillary pulse may be due to a pulsation of the subpapillary venules as well as arterioles. Additional evidence that the capillaries are not necessarily associated with the color of the skin is found in Weiss' [12] observation that on the skin of the cheek the capillaries are relatively scanty while the subpapillary venous plexuses are especially well developed, thus playing a dominant part in the production of the color of the skin of the cheek.

CONCLUSIONS

The so-called "capillary pulse" is not a manifestation of a pulsation of the capillaries, but is due to an exaggerated pulsation of the arterioles and possibly of the venules of the subpapillary plexus of the skin. In view of this fact it would be well to discard the term "capillary pulsation" and to speak of the systolic flushing of the skin.

8. Jürgensen, E.: Microkapillarbeobachtungen, Deutsch. Arch. f. klin. Med. **132**:204, 1920.

9. Hoyer, H.: Ueber unmittelbare Einmündung kleinster Arterien in Gefässe venösen Charakters, Arch f. mikroskop. Anat. **13**:603, 1877.

10. Grosser, O.: Ueber arteriovenöse Anastomosen an den Extremitätenden beim Menschen und den krallentragenden Säugethieren, Arch f. mikroskop. Anat. **60**:191, 1902.

11. v. Schumacher, S.: Ueber das glomus coccygeum des Menschen, etc., Arch. f. mikroskop. Anat. **71**:58, 1908.

12. Weiss, E., and Holland, M.: Zur Morphologie und Topographie der Hautkapillaren, Ztschr. f. exper. Path. u. Therap. **22**:108, 1921.

THE ETIOLOGY AND DEVELOPMENT OF GLOMERULONEPHRITIS *

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There are four well established types of renal disease that must be considered in a discussion of nephritis. A brief explanation of each of these will be given in order to establish the limitations of the group under discussion.

1. *Pyelonephritis.*—This is an acute or chronic exudative inflammation distributed in patches throughout the kidneys, and extending from the cortex throughout the pyramids into the pelvis. It is caused by bacteria, usually staphylococci or colon bacilli. In most instances the bacteria are carried to the kidney by the blood; but in cases of obstruction of the lower urinary tract they may enter from the urine. In the earlier stages of a hematogenous infection, before there has been extension to the pelvis, the lesions are spoken of as abscesses. Extension of the infection to the capsule may produce perinephritis or perirenal abscess. Infection of a dilated pelvis causes pyonephrosis. The disease is frequently unilateral and acute cases are sometimes mistaken for appendicitis or other acute abdominal conditions. Cases vary in intensity from mild to severe. The treatment of severe unilateral cases is usually surgical. Bilateral pyelonephritis may result in renal insufficiency but there is seldom any confusion clinically with Bright's disease.

Acute interstitial nephritis is related to this group in that it is an exudative inflammation of the interstitial tissues. The kidneys show areas of cortex infiltrated with lymphocytes of intermediate size and plasma cells. Apparently there is never enough of the kidney involved to produce renal insufficiency. There is evidence in one of our cases (Case 51) that the exudate remains in the kidney indefinitely and gives rise to areas of cortical atrophy; but no chronic nephritis of this type is known. Acute interstitial nephritis occurs frequently during scarlet fever, and rarely in other infections, such as diphtheria and congenital syphilis. It is seldom of much importance clinically, being overshadowed by the associated disease.

The spontaneous chronic nephritis of laboratory animals is more closely related to pyelonephritis than to any other form of human renal

* From the Department of Pathology, University of Minnesota.
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disease. It is characterized by lymphocytic exudates in the renal parenchyma, which ultimately cause cortical atrophy to such an extent that the kidneys are shrunken and their surfaces covered with small depressions. The pelvis is not extensively involved, as a rule. Death from renal insufficiency is rare, and the majority of cases result in healing. This is the form of nephritis usually obtained in animals by experimental procedures. There is a gross resemblance between the kidneys of chronic Bright's disease and those of this animal infection; but clinically, histologically and in manner of development there is no similarity.[1] There is no known animal disease corresponding to chronic Bright's disease.

2. *Nephrosis.*—This term is applied to renal lesions of a purely degenerative character in contrast to *nephritis* in which the phenomena of reaction (exudation, proliferation) have appeared. This group is not sharply separable from glomerulonephritis since cases of degeneration occur in which it is very difficult to determine whether there are any reactive changes in the glomeruli. Again, there are degenerative changes of greater or less degree in practically all cases of glomerulonephritis, and in a large percentage of arteriosclerotic kidneys. It is, however, very desirable to limit the term nephrosis to degenerative lesions in which there is no pronounced involvement of the glomeruli or blood vessels.

Nephrosis is by far the commonest form of renal disease seen at necropsy and it is the most frequent cause of albuminuria. It is found at necropsy in practically all severe infectious diseases and infections, in obscure toxemias such as the toxemia of pregnancy, in chemical poisoning (mercury, arsenic, phosphorus, and many other substances), in severe jaundice, and in severe cardiac decompensation. It is presumably present in life in the above named conditions when albumin or casts are found in the urine. When found at necropsy it is proof of some form of toxemia.

The amyloid kidney, although usually classified as a nephrosis, is better understood as a special form of glomerulonephritis.

Clinically, nephrosis is usually definitely secondary to some associated disease, and the differentiation from Bright's disease under these circumstances presents no difficulties; but in cases of obscure etiology the distinction is not made so readily. There are no cases in our series of chronic nephrosis such as is described by Volhard and Fahr [2] as "genuine" nephrosis. It seems that a case of primary chronic renal disease should rarely, if ever, be regarded as a nephrosis.

1. Bell and Hartzell: Spontaneous Nephritis in the Rabbit, J. Infect. Dis. **24**: 628, 1919.

2. Volhard and Fahr: Die Brightsche Nierenkrankheit, Berlin, 1914.

The clinical findings attributable to the kidney in nephrosis are usually mild; but renal insufficiency may develop in severe cases. There is never hypertension or cardiac hypertrophy. Severe nephroses are usually rapidly fatal.

In mild nephroses at necropsy the kidneys show cloudy swelling. In severe cases there is cloudy swelling, fatty degeneration and sometimes necrosis of tubules and glomeruli.

3. *Arteriosclerosis of the Kidneys.*—Two forms of this disease may be distinguished on clinical and anatomic grounds.

(*a*) THE SENILE TYPE (Arteriosclerotic atrophy): In advanced age and especially in association with generalized senile arteriosclerosis, one often finds small kidneys with adherent capsules and rough granular or pitted surfaces. This appearance is due to an irregular atrophy of the more superficial parts of the cortex which is caused by narrowing of some of the arteries. Usually the larger branches are the ones chiefly affected and the disease is never restricted to the arterioles. The senile kidney is seldom of any clinical importance since the amount of cortex destroyed is relatively small; but in occasional instances the atrophy is so extensive that renal insufficiency develops. It has not been determined how often arteriosclerotic atrophy gives rise to the clinical picture of chronic Bright's disease.

(*b*) THE HYPERTENSION TYPE: In many cases of chronic hypertension normal kidneys are found at necropsy and in some a glomerulonephritis is found; but a large percentage of cases are associated with disease of the renal arteries. When no disturbance of renal function is demonstrable we speak of essential hypertension, but when there is evidence of serious renal injury we consider the condition chronic Bright's disease. The kidneys from cases of essential hypertension usually show hyaline degeneration of some of the afferent glomerular arteries and often there is also disease of medium sized and small arteries, and there are gradual transitions between the slight involvement of the arteries in these cases and the extensive involvement in chronic Bright's disease of the vascular type. The majority of patients with essential hypertension die of cardiac or cerebral complications without developing serious renal involvement, but some cases extensive destruction of renal tissue occurs and they are then regarded as being cases of chronic Bright's disease of the arteriosclerotic type. There are about twenty-six examples of this form of Bright's disease in our series of 3,300 necropsies. We expect to discuss this subject fully in a subsequent report.

4. *Glomerulonephritis.*—This group includes renal disease in which the structural changes are due almost entirely to primary inflammatory and degenerative changes in the glomeruli. It includes all acute and subacute and a majority of chronic cases of Bright's disease.

The older terms "chronic parenchymatous" and "chronic interstitial" correspond to stages or degrees of severity of glomerulonephritis. They do not designate any important feature of the disease and a large number of cases are intermediate in type, i. e., neither typical parenchymatous nor typical interstitial. This terminology has another element of confusion in that some observers consider the arteriosclerotic kidney as chronic interstitial nephritis. The literature of nephritis would be clearer if these older terms were discarded.

Chronic glomerulonephritis is not sharply separable from the arteriosclerotic kidney since a few cases of the former show some disease of the renal arteries; but these borderline cases are not very numerous and we see no justification for the view that the two diseases are indistinguishable (Moschcowitz [3]). Certainly the great majority of cases are anatomically distinct, although they may be indistinguishable clinically. It may be, as Ophüls [4] believes, that the same toxin attacks the arteries in one case and the glomeruli in another and that the differences are really only anatomic; but it seems better to adhere to anatomic distinctions until we know more about the etiology of arteriosclerosis.

MATERIAL

Microscopic sections from the kidneys of about 3,300 consecutive necropsies have been examined. Small pieces of kidney from nearly all of these had been preserved so that it was possible to make serial sections when desirable. The clinical history and gross necropsy findings were always considered, but the final diagnosis was usually made on the microscopic appearances. All the subacute and chronic cases had been recognized clinically or at necropsy, but many of the acute cases had been overlooked. Sixty-nine cases of glomerulonephritis were identified. In a number of the acute cases nephritis was not the main cause of death, and these kidneys furnish abundant illustrations of the early stages of the disease.

We have arranged our cases somewhat arbitrarily into acute, subacute and chronic groups. There are striking clinical and pathologic differences between typical examples of each group, but there are many intermediate forms and one may easily become convinced from the study of a large series that there is a fundamental relationship between the different forms of glomerulonephritis. Senator [5] called attention to this point many years ago. As will be brought out later, one of the

3. Moschcowitz, E.: Clinical and Anatomic Relations in Chronic Nephritis, Arch. Int. Med. **26**:259 (Aug.) 1920.

4. Ophüls, Wm.: Arteriosclerosis and Cardiovascular Disease, Stanford Univ. Pub., Med. Sc., **1**:1, 1921.

5. Senator, H.: Nothnagel's Encyclopedia of Practical Medicine, 1905, Am. Ed., p. 180.

arguments for the infectious origin of chronic glomerulonephritis is that it is linked to the acute form by numerous intermediary cases.

ACUTE GLOMERULONEPHRITIS

There are thirty-two acute cases. Brief protocols of each will be given. Cases 1 to 9 are mild cases in early stages in which death was due to extrarenal causes. In Cases 1 and 2 only a minority of the glomeruli are involved.

Case 1 (A-16-182).—Female, aged 35 years. Case of advanced chronic aortic and mitral endocarditis with fresh thrombi on the thickened leaflets. Kidneys weighed 260 gm.; no gross changes. Some of the glomeruli showed changes in a few of their lobules. These changes consisted in swelling of the endothelium, partial closure of capillaries, and accumulation of polymorphonuclears in the capillaries. The majority of the glomeruli are entirely normal. This represents an early glomerulitis of very limited extent.

Case 2 (A-19-276).—Male, aged 16 years. Acute endocarditis. During the last week of life, blood culture on two occasions gave hemolytic streptococci. Hematuria. Leukocytes, from 20,000 to 42,000. Necropsy: Heart weighed 620 gm.; many large thrombi on mitral and aortic leaflets. Infarcts in kidneys and spleen. Kidneys not enlarged. Many petechial hemorrhages. Some glomeruli showed swelling of endothelium with partial closure of capillaries. Majority were normal.

Case 3 (A-19-58).—Male, aged 39 years. Chronic mitral endocarditis with fresh thrombi on the stiffened leaflets. Leukocytes, 11,200. Heart weighed 585 gm. Kidneys not enlarged; all glomeruli much enlarged. There are a number of polymorphonuclears in the capillaries. The endothelial swelling is not sufficient to close any of the capillaries. There is moderate injury of the tubules but no atrophy.

Case 4 (A-20-94).—Male, aged 61 years. Had a suppurative infection of the right carpus for two months before death. Erysipelas of face and neck the last five days of life. No examination of urine. Necropsy: Suppuration of carpus with partial destruction of the os magnum. Erosion of the cartilaginous surfaces. Spleen weighed 550 gm. Hemolytic streptococcus in pure culture from the spleen. Large numbers of gram-positive cocci demonstrable in sections of the spleen. Kidneys weighed 370 gm. Cloudy cortices. Glomeruli are not enlarged, but their capillaries contain many polymorphonuclear leukocytes.

Case 5 (A-20-118).—Female, aged 15 years. Normal labor February 11. Fever began four days later. Continuous fever and leukocytosis. Streptococcus from blood culture, February 28. Death, March 13, 1920. Necropsy: 1,500 c.c. pus in right pleural cavity. Large thrombus on tricuspid valve. Abscess of right lung. Spleen weighed 260 gm. Kidneys weighed 295 gm. Cloudy cortices. Glomeruli not enlarged. No swelling of endothelium. A number of polymorphonuclears in some of the glomerular capillaries.

Case 6 (A-20-220).—Male, aged 55 years. Death from chronic myocardial degeneration and chronic alcoholism; no clinical history; no edema. A small amount of fluid found in the pleural cavities. Heart weighed 520 gm.; spleen, 335 gm.; kidneys, 367 gm. Glomeruli are all enlarged. There is moderate swelling of the endothelial cells, with partial closure of some capillaries. Many polymorphonuclears in the capillaries.

Case 7 (A-21-144).—Male, aged 20 years. Measles in November, 1919, complicated by bilateral suppurative otitis media. Discharge from the ears for several weeks. Present illness began about four weeks before death with septic sore throat, complicated by acute bilateral suppurative otitis media. Both

tympani were incised. Discharge from ears continued until March 20. Symptoms of meningitis appeared March 20. Lumbar puncture, March 21, gave a purulent fluid. The urine showed a faint trace of albumin at times. Death March 22. Necropsy: purulent meningitis; streptococci in smears. Bilateral suppurative otitis media with mastoiditis. Kidneys were not enlarged but showed cloudy cortices. Glomeruli not enlarged. There is no notable swelling of the endothelium but the capillaries contain large numbers of polymorphonuclears.

Case 8 (A-17-114).—Female, aged 44 years. Death from lobar pneumonia. No edema. No urinalysis. May 19, 10,900 leukocytes. Blood pressure 115/88. Death May 23. Necropsy: lobar pneumonia. Heart weighed 310 gm.; kidneys, 310 gm. Pale cloudy cortices. All glomeruli slightly enlarged. Large numbers of polymorhponuclears in the capillaries. No swelling of the endothelium.

Case 9 (A-13-24).—Male, aged 55 years. Had nosebleed at frequent intervals for two weeks before death. No edema. Urine not examined. Necropsy: pneumococcus bacteremia; acute bronchopneumonia (small areas); localized suppuration in the pharynx which extended deep into the pharyngeal tissues. Kidneys weighed 400 gm. and contained a large number of small peripheral infarcts which were due to thromboses of the small arteries. Most of the glomeruli are enlarged and the capillaries are partly occluded by the swollen endothelial cells. An occasional polymorphonuclear leukocyte is seen in the glomerular capillaries.

Cases 10 to 21 are examples of fairly severe glomerulonephritis in which the renal condition was obscured by the associated disease.

Case 10 (A-13-190).—Female, aged 35 years. History of many sore throats. Inflammatory rheumatism at 15. Has deformities of joints and swelling of feet. November 7, blood pressure 126/110. Urine: faint trace of albumin, November 6 and November 28. Leukocytes, December 6, 5,500; December 26, 26,600; 95 per cent. polymorphonuclears. Streptococcus from blood culture. Clinical diagnosis: cardiac hypertrophy, endocarditis, mitral insufficiency, terminal bacteremia. Death, December 27. Necropsy: edema of ankles. Heart weighed 525 gm.; mitral stenosis; fresh thrombi on mitral valve and mural thrombosis of left ventricle. Kidneys not enlarged, but cloudy. Glomeruli are all greatly enlarged. A large percentage of the capillaries are partly or completely occluded by the swollen endothelium. Many capillaries contain numerous polymorphonuclear leukocytes.

Case 11 (A-14-46).—Male, aged 25 years. Has had arthritis at intervals for many years. Present illness began about Dec. 1, 1913, with dyspnea and swelling of the legs and face. Admitted to Hospital, Feb. 13, 1914. Marked dyspnea. Temperature, 102 F. on admission; later not over 100 F. Urine: traces of albumin during February, severe albuminuria in March. Feb. 14, 13,600 leukocytes. Clinical diagnosis: cardiac hypertrophy and endocarditis. Death, April 4, 1914. Necropsy: general anasarca, ascites, hydrothorax. Heart weighed 575 gm.; chronic mitral endocarditis; many large thrombi on aortic leaflets. Spleen, greatly enlarged. Kidneys enlarged and cloudy. Glomeruli are all enlarged and show partial closure of the capillary lumina, due to swelling of the endothelium. There are very few polymorphonuclears in the glomeruli. No tubular atrophy.

Case 12 (A-14-255). Male, aged 39 years. Patient was taken ill with a cough and fever after working three days in a wet trench. Diagnosis of pneumonia, made by a physician four days later (Nov. 23, 1914). Admitted to hospital, December 1. Leukocytes, 20,000. Urine: moderate albuminuria, numerous hyalin and granular casts. No edema. Clinical diagnosis: lobar pneumonia. Death, December 12. Necropsy: Lobar pneumonia; large thrombi on aortic leaflets. Kidneys weighed 405 gm. The glomeruli are greatly enlarged

and the capillary lumina are partially occluded by swollen endothelial cells. There are many polymorphonuclear and some large mononuclear cells in the capillaries. No atrophy of the tubules.

Case 13 (A-13-165).—Male, aged 33 years. Had acute articular rheumatism a few years ago. Four months ago he first noticed shortness of breath and swelling of feet. Symptoms became more intense. Purpuric rash appeared on lower extremities on October 1. Admitted to hospital, October 4. Leukocytes, 15,800. Urine: albumin, numerous hyalin and granular casts. Death, October 21. Necropsy: moderate anasarca, ascites. Heart weighed 640 gm.; chronic mitral endocarditis with many fresh thrombi on mitral and aortic leaflets. Spleen weighed 595 gm.; kidneys, 460 gm. Glomeruli moderately enlarged. Partial closure of capillaries. A number of polymorphonuclears in the capillaries. No tubular atrophy.

Case 14 (A-15-97).—Female, aged 29 years. Illness of nine weeks' duration. Continuous high fever. Pus in urine. No edema. Leukocytes, 13,500. Necropsy: acute vegetative mitral and aortic endocarditis. Infarction of spleen. Kidneys cloudy but not enlarged. Glomeruli are all moderately enlarged. The capillaries are partially closed and contain large numbers of polymorphonuclears.

Case 15 (A-15-230).—Male, aged 34 years. Acute symptoms began about April 1, 1915. Cough, night sweats, pulmonary hemorrhage. Temperature 97 to 102. Tubercle bacilli in sputum. No edema. Death, July 16, 1915. Necropsy: ascites (700 c.c.). Pulmonary tuberculosis with cavities. Intestinal ulcers. Heart weighed 320 gm.; kidneys, 490 gm. Glomeruli all moderately enlarged. Increased number of nuclei. Partial closure of many capillaries by swollen endothelium; complete closure of some. A number of polymorphonuclears in some glomeruli. No tubular atrophy (Fig. 1).

Case 16 (A-15-323).—Male, aged 49 years. First hospital admission in June, 1914. Discharged. Readmitted, Aug. 3, 1915. Recurrent attacks of arthritis. Loss of weight and strength. Dyspnea. Edema. Enlarged heart. Dilated aortic arch. Right pleural cavity aspirated several times. Blood Wassermann, positive. Urine, August 5: albumin and casts. Blood pressure, August 11, 160/110. Death, Oct. 18, 1915. Necropsy: ascites (200 c.c.) hydrothorax. Enlarged heart; advanced mitral stenosis with ulceration; aneurysm of arch of aorta. Kidneys weighed 320 gm. A number of glomeruli appear as abscesses because of the enormous number of polymorphonuclears present (Fig. 2); in other glomeruli there are only a few polymorphonuclears. A fairly large proportion of the glomeruli show epithelial crescents (the extracapillary type of glomerulitis). There is no appreciable swelling of the endothelium. This case represents a blending of the pyelonephritis group with the extracapillary form of glomerulonephritis. There are large numbers of polymorphonuclears in the tubules. No tubular atrophy.

Case 17 (A-16-48).—Male, aged 58 years. Diabetic gangrene of foot. No edema. Blood pressure, February 8, 140/110. Urine, February 9: trace of albumin and a small amount of pus. February 5, 13,500 leukocytes; 91 per cent. polymorphonuclears. Death, February 10. Necropsy: ascites (200 c.c.); right hydrothorax (400 c.c.). Heart weighed 370 gm. *Streptococcus pyrogenes* secured from heart's blood. Kidneys weighed 573 gm. Cloudy cortices. Large numbers of polymorphonuclears in the glomeruli, tubules and interstitial tissue (Fig. 3). Glomeruli are all enlarged. Marked increase of nuclei and partial closure of capillaries by swollen endothelium. No tubular atrophy.

Case 18 (A-16-165).—Male, aged 35 years. Became intoxicated and was injured in an automobile accident April 20. Superficial injuries. No broken bones. Admitted to hospital, April 22. Temperature around 101 F. Excessive hematuria, vomiting, hiccoughing. Leukocytes, 15,000; 82 per cent. polymorphonuclears. No edema. Death, April 26. Necropsy: heart weighed 345 gm.; kidneys, 415 gm.; cloudy cortices. No focus of infection found. Blood

culture sterile. Glomeruli are all moderately enlarged and show great increase of nuclei. Capillaries are partially closed by swollen endothelium. Many polymorphonuclears in the capillaries. No atrophy of tubules.

Case 19 (A-17-202).—Male, aged 25 years. Acute arthritis in 1908 and again in 1909. Smallpox in 1910. History of cardiac disease for the past six years. Frequent appearance of petechial hemorrhages in the skin since February, 1917. These would disappear, then reappear after a variable interval. Admitted to hospital Aug. 20, 1917. On admission there was marked cardiac hypertrophy, enlargement of spleen and edema. Urine: abundant albumin, casts found at one examination. Leukocytes, August 21, 4,700; 70 per cent. polymorphonuclears. Septic temperature. Phenolsulphonephthalein, August 23, 65 per cent.; September 14, 45 per cent. One blood culture sterile. Blood pressure, October 3, 140/80. Death, Oct. 4, 1917. Necropsy: anasarca, ascites, hydrothorax. Adherent pericardium. Heart weighed 900 gm.; old ulcerative

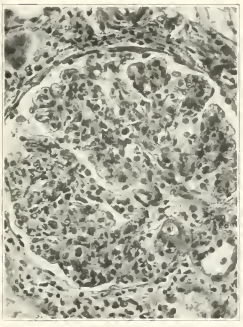

Fig. 1.—Case 15. Proliferative glomerulitis, intracapillary type. Low magnification.

mitral lesion with many large fresh thrombi. Spleen weighed 1400 gm.; kidneys, 515 gm. All glomeruli are greatly enlarged with a notable increase of nuclei. The capillaries are largely closed by the swollen endothelium. There are only a few polymorphonuclears in the glomeruli. Some of the tubules show an early stage of atrophy. There are no embolic lesions in the glomeruli although one would expect this lesion with the type of involvement of the heart and spleen.

Case 20 (A-18-9).—Female, aged 3 months. Marked jaundice developed October 2. Admitted to hospital, Oct. 4, 1917. Marked jaundice and exophthalmos. Enlargement of liver and spleen. Emaciation. No edema. Wassermann positive. Hemoglobin, 35 per cent. Erythrocytes, 2,500,000. Bile and pus in the urine. Treated for congenital syphilis. Attack of lobar pneumonia, Jan. 3, 1918. Partial recovery from the pneumonia, but fever and listlessness persisted. Leukocytes, Jan. 16, 1918, 14,800. Death, January 17. Necropsy: 100 c.c. of thick pus in peritoneal cavity, and fibrinopurulent exudate over

both lungs. Kidneys weighed 45 gm.; pale, cloudy cortices mottled with hemorrhages. Pneumococci in smears from pus from serous cavities and in pure culture from the blood. A large percentage of the glomeruli show infarction due to thrombosis of the afferent arteriole (Fig. 4). The majority of the glomeruli show no special abnormality. There is no swelling of the endothelium, and there are very few polymorphonuclears in the capillaries. There is severe tubular degeneration.

Case 21 (A-18-122).—Male, aged 30 years. Dated his present trouble from March 1, 1918. Abundant albumin in urine. No other clinical data. Death, June 11, 1918. Necropsy: general anasarca, hydrothorax, hydropericardium. Heart weighed 565 gm. Numerous large vegetations on mitral and aortic valves. Spleen weighed 680 gm.; contained several infarcts. Kidneys weighed 530 gm. Cortices thickened, clouded and yellowish. Chronic passive congestion of viscera. The glomeruli are nearly all moderately enlarged and

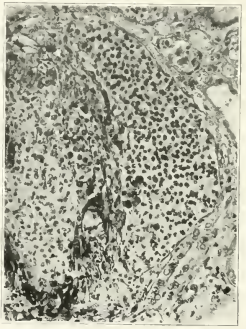

Fig. 2.—Case 16. Glomerular abscess.

show an increased number of nuclei. There is swelling of the endothelium and narrowing of the capillaries, but only a small per cent. of the capillaries are completely closed. There are many mononuclear leukocytes in the capillary lumina. Some of these may be endothelial cells that have separated off from the walls. There is moderate injury of the tubules but no atrophy.

Cases 22 to 32 may be considered fairly typical clinical examples of acute glomerulonephritis.

22. (A-13-140).—Female, aged 12 years. After a severe cold, about June 7, 1913, patient developed fever with swelling of the face and feet. She was confined to her bed for two weeks at this time. On the third day of the illness a diagnosis of pneumonia was made. About June 28, a severe generalized edema appeared and persisted until death. Admitted to hospital, Aug. 9, 1913. Empyema was recognized, and was drained by rib resection August 15. Urine was scanty and contained many granular, waxy and hyalin casts, and large quantities of albumin. Phenolsulphonephthalein, 39 per cent. August 25;

36 per cent., September 1. Death, September 24. Duration of nephritis about three months. Necropsy: Purulent peritonitis. Pure growth of pneumococci from peritoneal exudate. Empyema. Kidneys cloudy and swollen. Severe glomerulitis; capillaries largely closed by the swollen endothelial cells (Fig. 5). Polymorphonuclears rare in most glomeruli; numerous in a few. A few glomeruli show beginning hyaline degeneration with early tubular atrophy.

Case 23 (A-13-150).—Male, aged 35 years. Illness began three and one-half months before death with frequent chills, fever and vomiting. Became better and went back to work. About one month later he developed a cough with weakness, loss of appetite and pain in the right chest. Admitted to hospital Sept. 18, 1913. Temperature of septic type. Slight edema of both legs. Abundant albumin and many casts in the urine. Leukocytes, 18,000. Death, Oct. 4, 1913. Necropsy: double empyema. Kidneys swollen and cloudy. Glomeruli are not enlarged but the capillaries contain large numbers of polymorphonuclear leukocytes. These cells are also found occasionally in the tubules and in the interstitial tissue. There is very little swelling of the glomerular endothelium. This may be considered an exudative glomerulitis.

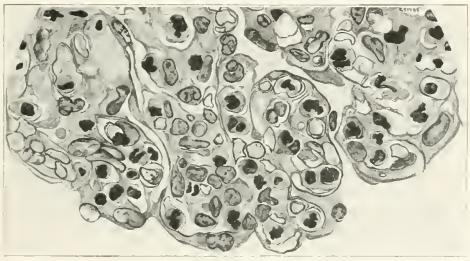

Fig. 3.—Case 17. Acute exudative glomerulitis. Note the polymorphonuclears. There is some enlargement of the endothelial cells.

Case 24 (A-13-153).—Female, aged 13 years. Developed a sore throat, Sept. 22, 1913. This continued with some improvement until September 28 when there was frequent emesis, anorexia and malaise. September 30 there were definite symptoms of peritonitis, and two days later a laparotomy revealed seropurulent peritonitis. Many streptococci were shown in smears of the exudate. Leukocytes, October 2, 24,000. During the next five days there was a very small amount of urine. Each specimen contained abundant albumin, blood and many casts. There was no edema. Death, Oct. 7, 1913. Necropsy: Purulent peritonitis; great enlargement of spleen and kidneys. Glomeruli are all enlarged and the capillaries are for the most part closed by the swollen endothelial cells (Figs. 6 and 7). There are many polymorphonuclears in some of the glomerular capillaries, and there are large numbers of them in the lumina of the tubules. There is severe tubular injury and many tubules are filled with blood. Many mononuclear leukocytes are seen in the interstitial tissue. There is no tubular atrophy. The total duration of the illness was only fifteen days.

Case 25 (A-15-144).—Female, aged 6 years. April 28, 1915, child was dull and tired and had lost her appetite. Severe diarrhea and vomiting for the

next six days. No edema. Convulsions, May 7. Urine: marked albuminuria; hyalin, granular, waxy, pus and blood casts. Leukocytes, 10,600; erythrocytes, 2,400,000. Death, May 7. Necropsy: No anasarca. Edema of lungs. Kidneys weighed 175 gm.; very cloudy cortices. Severe tubular degeneration and necrosis of many tubules. Large numbers of casts. Glomeruli are not enlarged but many of them show extensive hyaline, granular, hydropic and fatty degeneration and occasionally some necrosis of the endothelium. These changes are due to thromboses of the afferent glomerular arteries. Rarely a mitotic figure is seen in the endothelium. This case may be considered a severe nephrosis, since the changes are almost entirely degenerative in character.

Case 26 (A-15-165).—Male, aged 55 years. Illness of about six weeks' duration. Began with severe pain in the chest, dyspnea, edema of legs and anorexia. Urine: abundant albumin, hyalin and granular casts, leukocytes and erythrocytes. Temperature about 100 F. Necropsy: Marked anasarca, ascites and hydrothorax. Edema of lungs. Heart weighed 410 gm. No focus of

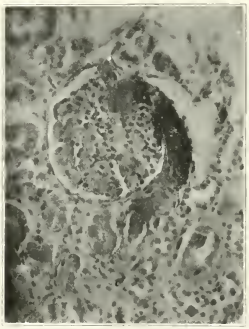

Fig. 4.—Case 20. Degenerative glomerulitis. Thrombosis of afferent artery.

infection found. Kidneys not enlarged, but cortices are grayish yellow. Glomeruli are all enlarged. Enormous increase of nuclei. Almost complete obliteration of all glomerular capillaries. Many polymorphonuclears mark the position of the capillaries. No tubular atrophy.

Case 27 (A-17-176).—Female, aged 66 years. Severe bronchitis first week of August, 1917. This was followed by dyspnea, precordial pain, vertigo and general weakness. Gradual increase in severity of symptoms. On admission to hospital, Aug. 25, 1917, there was edema of the feet. Urine, August 28 and September 6, contained a large amount of albumin and many casts of all types. August 28, leukocytes, 17,000; 94 per cent. polymorphonuclears. Blood pressure, August 30, 220/180; September 6, 200/80. August 29: urea nitrogen 72; creatinin 1.7. August, 31, urea nitrogen 46.5; creatinin 2.5. Phenolsulphonephthalein, August 31, 27 per cent.; September 6, 12 per cent. Death, September 8, 1917. Necropsy: a large amount of seropurulent fluid in each pleural cavity. Small areas of bronchopneumonia. Heart, normal. Kidneys weighed 300 gm.; cloudy surfaces. Glomeruli are all moderately enlarged.

There is a notable increase in the number of nuclei. Nearly all the capillaries are completely closed by swollen endothelium. Many disintegrating polymorphonuclears are seen in the positions of the closed capillary lumina. The tubules connected with a few of the glomeruli show a definite early stage of atrophy. The glomeruli are not all injured to the same degree; a few have a number of permeable capillaries. Duration of illness about one month.

Case 28 (A-18-62).—Male, aged 27 years. Right kidney removed February 21. This kidney showed tuberculosis but no glomerulonephritis. Extensive suppuration of the surgical wound developed. Septic temperature. Urine: March 10 and March 14, large amount of albumin, pus and casts. Erysipelas appeared April 1. Death, April 2. Necropsy: edema of left leg. Enormous dissecting abscess of abdominal wall extending from the surgical wound. A small amount of excess fluid in the serous cavities. Left kidney weighed 260 gm. Cortex opaque with yellowish and reddish mottling. A majority of the malpighian bodies show epithelial crescents which compress the glomeruli (Fig. 8). There is very little swelling of the endothelium. There are large numbers of polymorphonuclears in the glomeruli, capsular spaces, and surrounding the malpighian bodies. There is severe tubular degeneration. This is the extracapillary type of glomerulonephritis.

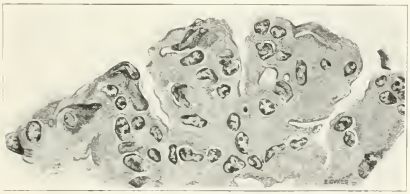

Fig. 5.—Case 22. Acute proliferative glomerulitis—small portion of a glomerulus. Note complete obliteration of the capillaries.

Case 29 (A-18-251).—Female, aged 18 years. Admitted to hospital Nov. 27, 1918. Septic temperature. Severe prostration. Peritonsillar abscess. Abscess was opened November 27 and again November 28. There was erysipelas of the face on admission and the entire face was involved before death. Blood pressure, 96/54. November 27, 2 ounces of urine was removed by catheter. November 28, 1 ounce removed by catheter. Urine contained a large amount of albumin with enormous numbers of casts. Death, December 1. Necropsy: Slight edema of ankles. No fluid in the serous cavities. Heart not enlarged. Extensive bronchopneumonia. Hemolytic streptococcus from the blood. Kidneys weighed 540 gm. Cortices were swollen and very cloudy. All the glomeruli are moderately enlarged. There is a little swelling of the endothelium. There are large numbers of polymorphonuclears in the glomeruli capillaries, in the capsular spaces, and in the tubules. There is severe tubular injury.

Case 30 (A-19-152).—Male, aged 12 years. Attack of smallpox about the middle of June, 1919. Has had edema of the face and extremities ever since. Vomiting and convulsions July 18. Admitted to hospital July 19. Dyspnea. Frontal headache. Rales throughout the chest. Dulness over right lower lobe. Leukocytes, 19,800; 94 per cent. polymorphonuclears. Blood pressure, 132/94.

Urine: abundant albumin, many granular and epithelial casts. Death, July 21, 1919. Necropsy: Ascites (500 c.c.); hydrothorax (each cavity about 1,000 c.c.), edema of face. Heart weighed 200 gm. Small areas of bronchopneumonia. Spleen weighed 220 gm.; kidneys, 245 gm. Swollen, cloudy cortices. All glomeruli enlarged. Nearly all the capillaries closed by swelling of the endothelium. Very few polymorphonuclears. Severe tubular injury. No tubular atrophy.

Case 31 (A-21-62).—Female, aged 7 weeks. A few days after birth the mother noticed puffiness of the eyelids which gradually increased. On the eighth day there was a profuse purulent discharge from the eyes with swelling of the lids. This discharge continued. When the child was 5 weeks old it was brought to the university dispensary for treatment. No gonococci were found. Some improvement under treatment. February 4, the mother first noticed swelling of the face, hands and neck. Admitted to hospital, Feb. 7, 1921. General anasarca. Systolic murmur at base of heart. No convulsions. No

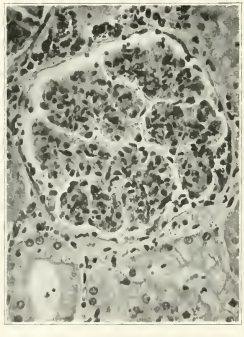

Fig. 6.—Case 24. Proliferative glomerulitis, intracapillary type. Low magnification. Note solid lobules, also polymorphonuclears in lumina of tubules.

spasticity of muscles. Phenolsulphonephthalein, a trace. Creatinin, 4.25 mg.; urea nitrogen, 29.16 mg. Very little urine excreted. A few drops removed by catheter showed hyalin, granular, epithelial and erythrocyte casts. Hemoglobin, 63 per cent. Leukocytes, 24,800; 30 per cent. polymorphonuclears; 65 per cent. lymphocytes. Temperature from 97 to 98.6 F. Death Feb. 14, 1921. Acute fibrinopurulent pleuritis of right side. Infected infarct of right lung (streptococci in smears). Streptococcus in pure culture from heart's blood. Kidneys weighed 50 gm. Cloudy yellowish cortices. Smooth external surfaces. Extensive involvement of nearly all the glomeruli. The capillaries are closed, and there is beginning hyaline degeneration in many glomeruli. There are very few polymorphonuclears. There is beginning tubular atrophy.

Case 32 (A-20-215).—Male, aged 60 years. Admitted to hospital May 25, 1920, in coma. Temperature as high as 105 F. Blood pressure, 160/80. Urine: specific gravity 1020; moderate amount of albumin; many erythrocytes; many granular casts. Leukocytes, 21,000; 70 per cent. polymorphonuclears. Blood

chemistry: creatinin, 5.8 mg.; urea nitrogen, 86.4 mg.; sugar 0.19 per cent. Death, May 26, 1920. Necropsy: ascites 1300 c.c. Heart weighed 350 gm. Edema of lungs. Extensive ulcerative colitis. Kidneys weighed 305 gm., cloudy cortices. Severe degenerative changes in both tubules and glomeruli. Very slight evidence of reaction in glomeruli. This may be considered a severe nephrosis.

The Clinical Phenomena in Acute Glomerulonephritis.—In twenty-one of the thirty-two cases, the renal symptoms were so masked by the associated disease that a diagnosis of nephritis would have been very difficult; and in Cases 1 to 9 the involvement of the kidneys was

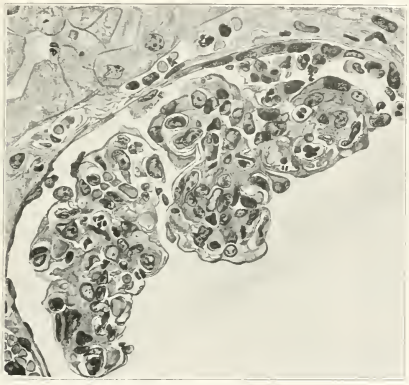

Fig. 7.—Case 24. Acute glomerulitis, proliferative and exudative. Note swelling and increase of endothelial cells with closure of capillaries. There are a number of polymorphonuclears.

probably too slight to produce any prominent findings. Cases of this kind are, of course, not ordinarily considered as Bright's disease by the clinician; but they are very valuable in the study of the early stages of the disease, since the changes in the kidneys are of the same type as those of typical clinical acute Bright's disease.

Considering only the eleven typical cases (Cases 22 to 32), it will be noted that eight showed edema of some part of the body. In Cases 24, 25 and 32, edema was absent. All showed heavy albuminuria and numerous casts, usually granular. Renal function was tested in four patients. Cases 27 and 31 showed a slight, and Case 32 a marked

retention of metabolites in the blood. The phthalein elimination was found decreased in Cases 22, 27 and 31. The phthalein measurement in Case 31 is not consistent with the blood chemistry and was probably incorrectly determined because of the very small amount of urine excreted. The duration is difficult to determine in many instances but seems to vary from a few days to three months. In only three patients (Cases 25, 26 and 30) did death seem to be due mainly to renal involvement; in the other eight cases there were very severe complicating infections. The data as to age and sex have little value because of the small number of cases.

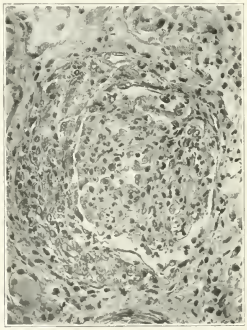

Fig. 8.—Case 28. Fresh epithelial crescent.

Gross Changes in the Kidneys.—With the exception of the very mild cases the cortices are invariably cloudy, and in the more severe cases the cloudiness and opacity are very pronounced and sometimes a yellowish tinge can be detected. The kidneys are not always enlarged. In general, the enlargement is proportional to the severity, but occasionally severe injury is found in kidneys of normal weight (Cases 26, 27 and 32). Among seventeen adults whose weights are recorded there are eight cases in which the kidneys weighed more than 400 gm., and four weighed more than 500 gm. The single kidney in Case 28 weighed 290 gm. It is apparently not possible to distinguish a nephrosis from acute glomerulonephritis by the gross appearance.

The Normal Glomerulus.—Before studying the glomerular changes in acute nephritis attention should be directed to the structure of the

normal glomerulus. The microscopic appearance of a glomerulus varies with the amount of blood it contains. When distended, the lumina of the capillaries are large, their endothelial walls are thin and the individual capillaries are fairly distinct. When empty, the endothelial walls of the capillaries are thicker, their lumina are very small or even invisible, and it may not be possible to see the individual capillaries. The glomerulus is, of course, much larger when distended than when empty. In necropsy material the great majority of the glomeruli ordinarily contain only a little blood; and it is often difficult in disease to distinguish an empty capillary from one in which the lumen has been closed by endothelial swelling. Thin sections of well fixed material are necessary for the study of glomerular structure.

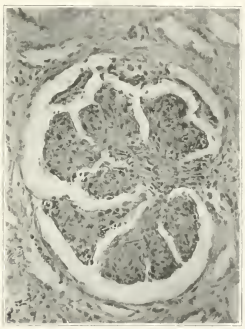

Fig. 9.—Case 55. Chronic case. Section through entrance of artery. Note lobules. A few polymorphonuclears are visible at the site of closed capillaries.

The glomerulus is composed almost entirely of capillary loops which anastomose freely. The arrangement of the capillaries is shown well in Johnston's [6] reconstruction. Corresponding with the capillary loops, the glomerulus is subdivided into a number of small lobules which have their narrow apex in common near the point of entrance of the artery and their wider bases free at the periphery. This lobulation is best seen in diseased glomeruli where there has been some shrinkage but is sometimes visible in the normal. The lobulation is well shown in Figure 9 in a section through the entrance of the artery. In ordinary histologic

6. Johnston, W. B.: A Reconstruction of a Glomerulus of the Human Kidney, Anat. Anzeiger **16**:260, 1899.

preparations no connective tissue is visible between the capillaries, but Johnston was able to demonstrate fine reticulum fibrils. These fibrils apparently do not take any part in inflammations of the tuft.

In Figure 10 a small part of a normal congested glomerulus is shown under high magnification. Most of the capillaries are distended with erythrocytes, and the endothelial cells appear as thin plates where the plane of the section is about perpendicular to the course of the vessel.

The capsule of Bowman lines the outer wall of the capsular space and is reflected over the glomerulus. The inner layer is prominent in infancy but apparently does not form a continuous layer in the adult kidney. Some of the cells of this layer are found in the clefts between the glomerular lobules (Fig. 10). It is often prominent in shrunken

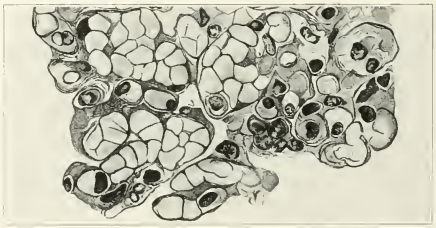

Fig. 10.—Normal congested glomerulus. Note the thinness of the endothelium when the capillaries are distended.

glomeruli. The outer layer takes a prominent part in the extracapillary type of lesion which will be described below.

The Glomerulus in Acute Inflammations.—The three fundamental phenomena of inflammation, viz., degeneration, exudation and proliferation—occur in the glomerulus as they do in other tissues and their relative prominence determines the microscopic appearance. The peculiar structure of the glomerulus, however, influences markedly the course and outcome of the inflammatory process. In most instances the only fixed tissue concerned is capillary endothelium and the occlusion of capillaries produces permanent damage that seems out of proportion to the intensity of the injury. In accordance with the prominence of the fundamental processes three types of glomerulitis may be described.

(*a*) *Degenerative Glomerulitis.*—In this form there is disintegration and necrosis of the glomerular endothelium with escape of blood into the capsular space. It is usually associated with severe tubular injury

also. The reactive changes are very slight. Case 32 is a good example of a severe case with involvement of all the glomeruli. In Cases 25 and 20 the degenerative changes are largely due to thrombosis of afferent arteries and many glomeruli escaped serious injury (Fig. 4).

Mild degenerative changes may be responsible for a hematuria. Figure 11 is from a case of severe hematuria apparently due to a bacteremia. A large percentage of the glomeruli show a similar appearance. The blood escapes from ruptured capillaries but the glomerulus as a whole shows no signs of permanent injury. It is possible that some of the cases in children described by Hill[7] as hemorrhagic nephritis have only trivial glomerular injuries such as this. Hill states

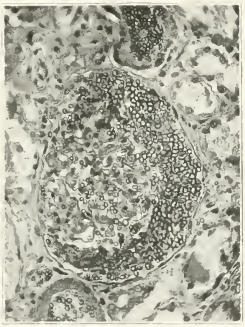

Fig. 11.—Degenerative glomerulitis. No permanent renal injury. From a case of bacteremia with severe hematuria.

that these cases have an especially favorable prognosis. Renal hematuria does not necessarily indicate a serious glomerular injury. A few erythrocytes in the urine may be due to passive congestion or to mild injuries such as occur in any nephrosis.

(b). Exudative Glomerulitis.—This type is characterized by the appearance of an unusual number of polymorphonuclear leukocytes in the glomerular capillaries. The leukocytes pass through the capillary walls into the capsular space and are carried away in the urine. There is usually an associated swelling of the endothelium but in seven of

7. Hill, L. W.: Studies in the Nephritis of Children, Am. J. Dis. Child. **17**:270 (April) 1919.

our cases this is inconspicuous and the lesions are mainly exudative. Some polymorphonuclears were found in the glomeruli in nearly all our cases of glomerulitis, but in ten of them they were very rare. Figure 3 (Case 17) is a good example of an exudative glomerulitis. There is apparently no narrowing of the capillary lumina in this case and it does not appear that any serious permanent damage has been done. Possibly the plugging of the capillaries with leukocytes may interfere with function to some extent. It is an attractive hypothesis that mild cases of acute Bright's disease are of the exudative type, but there are no supporting observations. We do know, however, that our severe clinical cases were either mainly proliferative or mainly degenerative.

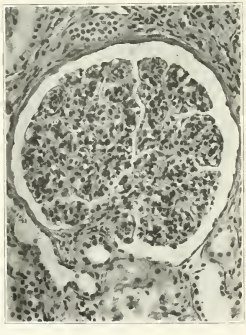

Fig. 12.—Case 47. From a chronic case. Low magnification. Note polymorphonuclears in the solid lobules. See Figures 13 and 14.

When acute cases become chronic the leukocytes remain permanently in the occluded capillaries and remnants of them are recognizable for a long time (Figs. 12, 13, 14). This feature helps to establish the relationship between the acute and the chronic case.

In one instance (Case 16) the exudate was so abundant that a number of glomeruli were converted into small abscesses (Fig. 2). The other glomeruli showed the changes characteristic of typical glomerulonephritis. There was a large amount of exudate in the interstitial tissues also. This case shows the close relationship between the pyelonephritis group and glomerulonephritis, and furnishes an argument in favor of the infectious nature of the latter disease.

(c) *Proliferative Glomerulitis.*—Occurs in two forms: the extracapillary and the intracapillary. The extracapillary type consists in proliferation of the cells of the outer layer of Bowman's capsule. These newly formed cells usually become arranged in the form of a crescent (Fig. 8), which compresses the glomerulus and ultimately causes it to undergo atrophy and hyaline degeneration. The epithelial crescent itself finally undergoes hyaline degeneration but remnants of nuclei are visible for a long time. The presence of old epithelial crescents in a chronic case (Fig. 15) suggests an acute beginning. Extracapillary lesions are not frequently seen. They were found in only two of our acute cases (Cases 16 and 28). According to Volhard and Fahr they occur especially in infections with violent onset, and this view is sup-

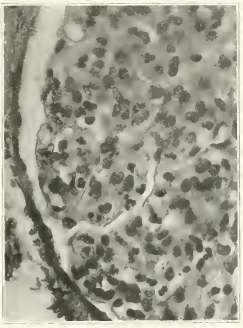

Fig. 13.—Case 47. High magnification of Figure 12. Polymorphonuclears are visible in the solid lobules at the site of capillaries which have been closed by swelling of their endothelium.

ported by our cases, Case 28 being the most severe infection of the entire series.

The intracapillary type is the most common and the most important form of glomerulitis. It consists in swelling of the endothelial cells and increase in their number. The glomerulus as a whole is enlarged and there is usually a notable increase in the number of nuclei. Rarely a mitotic figure is seen. More important than the increase in the number of the endothelial cells is their increase in size. The capillary lumina are obliterated so that entire lobules may appear solid (Fig. 5). Low power views of the acute stages in the glomeruli are shown in Figures 1 and 6, and high power views of a few lobules are seen in Figures

5 and 7. Polymorphonuclear leukocytes are frequently present, occasionally in large numbers (Fig. 7); but some times they are absent entirely from large portions of the glomerulus (Fig. 5). These leukocytes are frequently seen also in the lumina of the tubules (Fig. 6), and in the interstitial tissue (Fig. 16). They are often caught in the closed capillaries where they are easily recognized in subacute stages before hyaline degeneration of the glomerulus begins (Figs. 12, 13 and 14); and they may be seen by careful examination in many chronic stages (Figs. 9 and 17). This microscopic feature furnishes an important connecting link between acute and chronic glomerulonephritis. As a result of intracapillary glomerulitis, the entire capillary network of the tuft may be closed completely, in which event the glomerulus undergoes hyaline degeneration and its tubule atrophies to the point of complete disappearance. Frequently, however, some of the capillaries are not occluded (Fig. 17), and the glomerulus continues to function to a limited extent, in which event only a partial atrophy of the associated

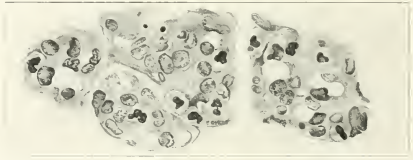

Fig. 14.—Case 47. See Figures 12 and 13. High magnification, showing remnants of polymorphonuclears in the solid lobules. Capillaries are largely obliterated by growth of endothelial cells.

tubule occurs. This type of damaged glomerulus is very common in chronic glomerulonephritis.

The tubules in acute glomerulonephritis usually show some degenerative changes. An increased amount of fat is often demonstrable; and hyaline granular degeneration is occasionally seen. In the degenerative type there may be some necrosis. As soon as the glomerulus ceases to function the tubule begins to atrophy, but this is never marked in an acute case. In Cases 27 and 31 atrophy of tubules had begun.

The interstitial tissues frequently show an exudate of mononuclear or polymorphonuclear leukocytes (Fig. 16). This exudate, however, does not seem to destroy any tubules and probably does not affect the course of the disease to any noteworthy extent.

ETIOLOGY OF ACUTE GLOMERULONEPHRITIS

The prevailing opinion in the literature is that acute glomerulonephritis is closely associated with infectious processes. Our experience

is entirely in accord with this view. Table 1 gives the associated infections found at necropsy or determined clinically in our thirty-two cases. The numbers refer to the individual cases. It will be noted that some of the patients had more than one infection.

The frequency of acute endocarditis in our series is very impressive —twelve times in thirty-two cases, or 37.5 per cent. In seven of these hearts the valve leaflets showed chronic changes also, so that these are to be regarded as acute exacerbations of a chronic endocarditis. That the frequent association of these two conditions is not accidental

TABLE 1.—Associated Infections in Cases of Acute Glomerulonephritis

Associated Infections	*Cases*
Vegetative endocarditis	1,2,3,5,10,11,12,13,14,16,19,21
Puerperal sepsis	5
Empyema, or purulent pleuritis	5,20,22,23,27
Peritonitis	20,22,24
Streptococcic bacteremia	2,5,10,17,29,31
Pneumococcic bacteremia	9,20
Septic sore throat	7,24,29
Erysipelas	4,28,29
Lobar pneumonia	8,12
Suppurative otitis media	7
Suppurative pharyngitis	0
Streptococcic arthritis and osteomyelitis	4
Infected surgical wound	28
Meningitis	7
Acute arthritis (not present at time of death)	10,11,13,16
Severe bronchitis	27
Variola	30
Tuberculosis with cavities	15
Ulcerative colitis	32
Diabetic gangrene	17
Purulent conjunctivitis	31
No localized infection	6,18,25,26

is shown by the fact that in our 3,300 consecutive necropsies, not including those with acute nephritis, there were only sixty-three with acute endocarditis, or only 1.9 per cent.

This relationship has been observed by others. Leyden [8] noted the association of rheumatism, endocarditis and nephritis. Councilman [9] found ten instances of acute endocarditis in twenty-eight cases of acute nephritis. Klotz [10] also found endocarditis and nephritis in frequent association. Ophüls [11] cites three cases of acute nephritis associated with acute exacerbations of a chronic endocarditis.

8. Leyden. Cited from Mannaberg.[6]

9. Councilman, W. T.: An Anatomical and Bacteriological Study of Acute Diffuse Nephritis, Am. J. M. Sc. **114**:23, 1897.

10. Klotz, O.: Chronic Interstitial Nephritis and Arteriosclerosis, Am. J. M. Sc. **150**:832, 1915.

11. Ophüls, Wm.: A New Series of Cases with a Review of Recent Literature, Stanford Univ. Med Bull. No. 3, 1915.

Four cases in our series gave a history of rheumatic fever prior to the terminal illness, and several writers seem to consider this disease closely related to acute nephritis.

The relation of tonsillitis to acute glomerulonephritis has been discussed by a number of investigators. Kannenberg [12] in 1879 reported three cases of tonsillar infections (two were peritonsillar abscesses) followed by acute nephritis. In one cases the urinary changes appeared on the seventh day. Mannaberg [13] mentions tonsillitis among the infections sometimes followed by Bright's disease. Bluhm [14] reported

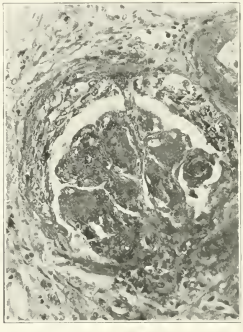

Fig. 15.—Case 56. Old epithelial crescent. Compression of glomerulus with beginning hyaline degeneration.

that five out of seventy-four cases of tonsillitis developed Bright's disease. Löhlein [15] and Aschoff [16] mention angina among the causes of glomerulonephritis. Volhard and Fahr [1] attribute to angina seventeen out of seventy-one acute, and seven of thirty-two subacute cases. In one instance cited by these authors nephritis appeared fourteen days

12. Kannenberg: Ueber Nephritis bei acuten Infectionskrankheiten, Ztschr. f. klin. Med. **1**:506, 1879.

13. Mannaberg, J.: Zur Aetiologie des Morbus Brightii acutus, etc., Ztschr. f. klin. Med. **18**:223, 1890.

14. Bluhm, A.: Zur. Aetiologie des Morbus Brightii, Deutsch. Arch. klin. Med. **47**:193, 1891.

15. Löhlein, M.: Ueber Nephritis nach dem heutigen Stande der path.-anat. Forschung, Ergeb. der inn. Med. u. Kinderh. **5**:411, 1910.

16. Aschoff, L.: Pathologische Anatomie, **2**:483, 1921.

after an attack of sore throat. Ophuls[17] attaches great importance to tonsillar infection as a source of glomerulonephritis, and Herxheimer[18] seems to hold a similar view. Hill[19] found tonsillitis the most frequent cause of nephritis in children, and James'[20] observations are in agreement with those of Hill. Hill states that the renal symptoms usually appear about one week after the tonsillar infection.

Evidently there is a close relationship between tonsillitis, endocarditis, arthritis and acute glomerulonephritis. It seems probable from all the accumulated evidence that the pathogenic bacteria gain access

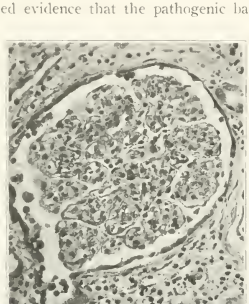

Fig. 16.—Case 43. From a chronic case. The capillary network of the lobules is largely closed. Many polymorphonuclears in the interstitial tissues.

to the blood stream from an infected throat and that the subsequent clinical picture depends on whether they attack the heart valves, joints or glomeruli.

There were three cases of septic sore throat in our series, and there were ten cases with acute endocarditis in which the throat was a possible source of the infection.

17. Ophuls, Wm.: The Etiology and Development of Nephritis, J. A. M. A. **69**:1223 (Oct. 13) 1917.

18. Herxheimer, G.: Ueber den jetzigen Stand unserer anatom. Kenntnisse der Nephritis u. Nephropathien, Munch. med. Wchnschr. **65**:283, 1918.

19. Hill, L. W.: Acute Nephritis in Childhood, J. A. M. A. **73**:1747 (Dec. 6) 1919.

20. James, R. F.: Prognosis of Nephritis in Childhood, J. A. M. A. **76**:505 (Feb. 19) 1921.

Scarlet fever was one of the first diseases in which a relationship to nephritis was observed. According to Friedlander [21] post-scarlatinal glomerulonephritis was first described by Klebs. Urinary disturbance occurs in from 20 to 25 per. cent. of cases of scarlet fever (McCrae,[22] 25 per cent. of 1,034 cases; Sorensen,[23] 20 per cent. of 365 cases). But the abnormal urine is usually due to acute interstitial nephritis or nephrosis. Only 2 per cent. of McCrae's patients had physical signs and symptoms of a true nephritis. Friedlander, Sorensen and others believe that true glomerulonephritis usually develops in the convalescent stage, during the third or fourth week after the onset of the disease.

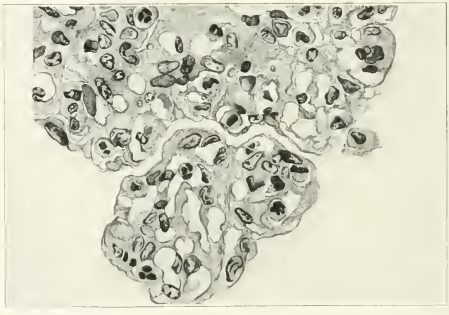

Fig. 17.—Case 43. A common form of damaged glomerulus in chronic glomerulonephritis. Some capillaries are closed but many are permeable. The tubule associated with this glomerulus showed moderate atrophy.

In fatal cases of scarlet fever glomerulonephritis is frequently seen (Friedlander, in 18 per cent. of 220 necropsies; Reichel,[24] in 20 per cent. of fifty-eight necropsies). Aschoff considers scarlet fever a frequent cause of glomerulonephritis. Volhard and Fahr found nineteen of seventy-one acute cases, and two of thirty-two subacute cases due to scarlet fever. The older observers considered the glomerular

21. Friedlander, C.: Ueber Nephritis scarlatinosa, Fortschr. d. Med. **1**:81, 1883.

22. McCrae, J.: Incidence of Nephritis Following Scarlet Fever, Tr. Assn. Am. Phys. **28**:194, 1913.

23. Sorensen, S. T.: Ueber Scharlachnephritis, Ztschr. f. klin. Med. **18**:298, 1890.

24. Reichel, H.: Ueber Nephritis bei Scharlach, Ztschr. f. Heilk. **6**:72, 1905.

injury due to poisonous substances excreted by the kidneys, but recent investigators attribute it to streptococcic infection.

There are no cases in our series in which a history of scarlet fever was obtained.

One of our cases followed an attack of variola, but apparently this is not a common cause since Bluhm found only one case of Bright's disease among 481 cases of variola.

Lobar pneumonia appears twice in our series as a possible source of infection; but Councilman found glomerulonephritis only once in 107 cases of pneumococcus pneumonia.

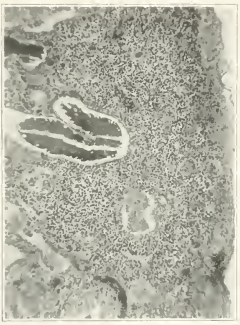

Fig. 18.—Case 51. Chronic case six years after an attack of scarlet fever. These areas are probably the result of an acute interstitial nephritis during the attack of scarlet fever.

Three of our series were associated with erysipelas and Bluhm found Bright's disease seven times in 162 cases of erysipelas. This disease is mentioned by several observers as a cause of acute Bright's disease.

A large number of other infections, some of which appear in our series, are mentioned by various investigators as having a causal relationship to acute glomerulonephritis. Among these are infected wounds, puerperal sepsis, peritonitis, empyema, impetigo, osteomyelitis, tuberculosis with cavities, otitis media, etc. Gaskell [25] describes a case

25. Gaskell, J. F.: On the Changes in the Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidney Disease, J. Path. & Bacteriol. **16**:287, 1911.

of less than one week's duration following peritonitis. McElroy[26] cites a characteristic case developing two or three weeks after a severe infection of one hand. Cases such as these are apparently frequent in the practice of many clinicians, and there are probably few of wide experience who have not seen a case of acute Bright's disease that followed some infectious process.

The various infections which apparently cause acute glomerulonephritis are generally due to streptococci, less frequently to pneumococci. In scarlet fever it is believed that a streptococcic infection of the throat develops in the period of convalescence, which gives rise to the renal involvement. Löhlein, Volhard and Fahr, Aschoff and Ophüls

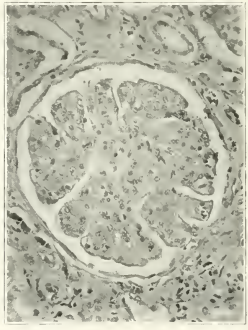

Fig. 19.—Case 53. Chronic case, showing almost complete occlusion of all the capillaries. No hyaline degeneration. Marked atrophy of associated tubule.

all agree that streptococci are chiefly responsible for acute glomerulonephritis. Ophüls apparently believes that other bacteria, e. g., *B. influenzae* and *B. coli*, may occasionally produce this disease.

In our series there were six cases with streptococcic bacteremia. In three of these the organisms were hemolytic; but there is no record as to the type in the other three cases. Nonhemolytic streptococci have not been found in our cases of acute glomerulonephritis, but they have been cultured from the blood in several cases of embolic glomerulonephritis. Further study is necessary to determine whether the nonhemolytic strains are ever responsible for acute Bright's disease.

26. McElroy, J. B.: Nephropathies, M. Clin. N. America **1**:1457, 1918.

Two instances of pneumococcic bacteremia appear in our series—one associated with suppurative pharyngitis and bronchopneumonia, the other with suppurative pleuritis and peritonitis.

It has not been determined whether the bodies of the bacteria or some diffusible toxin produces the glomerular injury. In favor of the toxin theory is the absence of bacteria in the glomeruli, and the diffuse uniform character of the lesion—practically all the glomeruli are usually involved. A few of the earlier workers described bacteria in the glomeruli, but Ophüls has pointed out that more recent contributors by careful histologic examination have failed to find bacteria in the glomerular endothelium. Sections from ten of our acute cases were

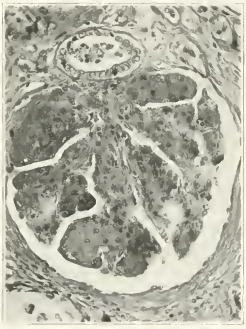

Fig. 20.—Case 56. Chronic case, showing complete closure of capillaries and beginning hyaline degeneration. Lobules are very distinct. Note disintegrated polymorphonuclears in the lumina of the tubules.

stained by the Gram-Weigert method, but no bacteria were found in the endothelium. However, in sections from an acute case following erysipelas, which were furnished us by Dr. J. P. Schneider, large numbers of gram-positive cocci were easily seen in the swollen endothelial cells of the glomerular capillaries. Ophüls has suggested that the bacteria undergo rapid lysis in the endothelium and are therefore seldom seen. This view is supported by Pappenheimer, Hyman and Zeman,[27] who injected bacteria directly into the renal artery of the

27. Pappenheimer, Hyman and Zeman: Acute Glomerular Lesions Following Injections of Bacteria Into the Renal Artery, Proc. New York Path. Soc. **16**:73, 1916.

rabbit. They found that the bacteria were taken up by polymorphonuclears and endothelial cells in the glomeruli within a few minutes and that within four hours they had nearly all undergone complete intracellular digestion.

War nephritis is anatomically acute glomerulonephritis, according to all who have studied necropsy material. It differs clinically in its epidemic character. Several observers have noted a frequent association with infectious processes (Brown,[28] Tytler and Ryle,[29] Ameuille [30]); but all seem to agree that a localized primary infection is not demonstrable in a majority of cases. Streptococci have been demonstrated in the

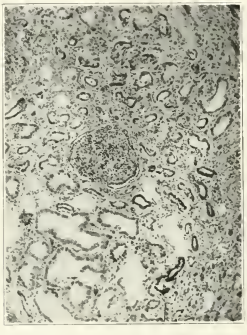

Fig. 21.—Case 60. Typical chronic case, low magnification. The larger tubules on the left are connected with a glomerulus that has a number of permeable capillaries.

urine but they may have been secondary invaders. No satisfactory etiologic studies have been reported.

SUBACUTE AND CHRONIC GLOMERULONEPHRITIS

The arrangement of our cases into subacute and chronic groups is arbitrary, since these subdivisions are not sharply defined. Cases 33 to 41 may be considered subacute. When the known duration of the disease is over one year it is considered chronic. When as many as

28. Brown, L.: Epidemic Nephritis, Brit. M. J. **2**:723, 1916.

29. Tytler and Ryle: Clinical and Pathologic Notes on Trench Nephritis, Quart. J. M. **11**:112, 1917.

30. Ameuille, P.: Du role de l'infection dans les néphrites de guerre, Ann. de méd. **3**:298, 1916.

ten per cent. of the glomeruli have become complete hyalinized and their tubules show advanced atrophy, the case is considered chronic, since the study of cases of known duration has shown that a long time is required for this change to occur. But the rate of tubular atrophy is not the same in all cases and it is probable that this feature is not an accurate index of the duration of the disease.

Case 33 (A-12-131).—Male, aged 33 years. Admitted July 17, 1912. About one month before admission he developed dyspnea which was increased by exertion and gradually became worse. One week before admission his feet began to swell and dyspnea became very alarming. On admission he com-

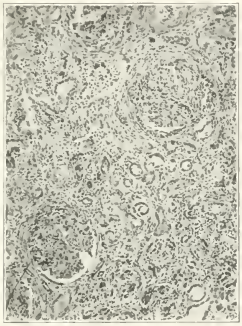

Fig. 22.—Case 69. Chronic case, showing old epithelial crescents, atrophied tubules and interstitial exudate.

plained of precordial pain, cough, dyspnea, and swelling of the feet. The urine contained albumin at all times. The specific gravity was 1.030 July 18; 1.012 September 8. Death, Oct. 7, 1912. Necropsy: Edema of ankles, moderate ascites and hydropericardium; edema of lungs. Heart weighed 460 gm.; moderate thickening and retraction of the mitral and aortic leaflets. Kidneys weighed 415 gm.; cloudy cortices; smooth external surfaces. The glomeruli are all involved but in varying degrees. There are a number of epithelial crescents which compress the glomeruli. Most of the glomeruli show swelling of the endothelium with partial or complete closure of the capillaries but none of them show any hyaline changes. Nearly all the tubules are moderately atrophic. A few polymorphonuclear leukocytes are seen.

Case 34 (A-13-8).—Female, aged 26 years. Attack of pericarditis in October, 1912. The pericarditis cleared up but hematuria appeared and persisted. Readmitted to hospital Dec. 23, 1912. Edema was never very prominent. Blood and casts were continuously present in the urine. Toward the end of her illness there was severe hematuria and hemorrhages from the vagina and mouth. Death Jan. 10, 1913. Necropsy: No edema; ascites (200 c.c.). Heart not

enlarged. Kidneys not enlarged. External surfaces smooth. Cortices cloudy. Glomeruli are all involved. The great majority show epithelial crescents with compression of the tufts. Some show endothelial swelling with closure of the capillaries. There are numerous polymorphonuclears in some glomeruli. Many tubules and capsular spaces are filled with blood. Numerous mononuclear leukocytes (mainly plasma cells) are seen in the interstitial tissues. Nearly all the tubules show notable atrophy. No hyaline glomeruli.

Case 35 (A-16-223).—Infant, aged 6 months. Normal at birth. At end of fourth month developed pallor, slight jaundice and weakness. At end of fifth month (May 29, 1916) was very anemic—hemoglobin 20 per cent.; erythrocytes 2,000,000. Blood stained vomitus and stools. Transfused. Suppuration of the transfusion wound. General anasarca. Urine at various times showed albumin, blood and pus cells. Death, June 26, 1916. Suppurating wound of thigh (site of transfusion). Seropurulent pleuritis. Bronchopneumonia. Kidneys weighed

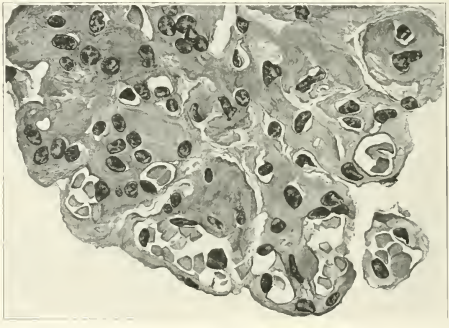

Fig. 23.—Case 53. Chronic case showing only a few permeable capillaries. The associated tubule was very small but had not disappeared.

54 gm.; swollen; pale and cloudy; smooth surfaces. Nearly all the glomeruli show marked swelling of their endothelium with closure of the capillaries. Very few capillaries are patent. There are no hyaline glomeruli. Some tubules are filled with polymorphonuclears, but these cells are very rare in the glomeruli. Tubular atrophy is marked.

Case 36 (A-18-118).—Male, aged 21 years. Syphilitic infection in October, 1917. Treated for three months with mercury injections. One injection of neodiarsenol early in December, 1917. Three days after this injection the patient developed edema with a large amount of albumin, blood and casts in the urine. Phenolsulphonephthalein at this time, 15 per cent.; urea nitrogen, 14 mg.; creatinin, 1.7 mg. December 30, lobar pneumonia developed in right lower lobe. Crisis six days after the attack. April 15, 1918, thrombosis of right popliteal vein developed. Blood pressure at this time was 130/80. Later blood pressure was 140/80. Ascites was present a long time before death. Death, June 2, 1918. Necropsy: Edema of feet and scrotum. Ascites (2,000 c.c.); hydrothorax (1,000 c.c.). Heart weighed 375 gm. Fibrinopurulent pleuritis. Kidneys weighed

425 gm. Cloudy cortices. Smooth external surfaces. Nearly all the glomeruli are severely injured. There is a great increase of nuclei with closure of most of the capillaries, and beginning hyaline degeneration in a few glomeruli. Numerous adhesions between the layers of Bowman's capsule. A few polymorphonuclears in some glomeruli. Rather marked atrophy of tubules.

Case 37 (A-15-67).—Female, aged 35 years. Appendix, ovaries and tubes removed about seven years ago. Has had swelling of feet for several years. Abdominal paracentesis several times recently. Urine; abundant albumin and casts. Necropsy: marked general anasarca, ascites (3,000 c.c.), hydrothorax (1,500 c.c.) and hydropericardium. Heart weighed 400 gm. Thromboses of pelvic veins with infarction of lungs. Kidneys normal size; surfaces slightly uneven; cortices yellowish. The great majority of the glomeruli are enlarged and show a great increase in number of nuclei. Their capillaries are largely closed by swollen endothelium, and hyaline changes have appeared in many. Many polymorphonuclears are seen in the interstitial tissues and capsular spaces, and there are a few in the closed glomerular capillaries. There is moderate atrophy of most of the tubules. This case appears to be of longer duration than Nos. 33 to 36.

Case 38 (A-15-253).—Male, aged 51 years. Smallpox at age of 32 years. Well until about April 19, 1915, when he developed a cold with cough following wetting of his feet. There was a yellowish expectoration. About April 26 his face began to swell, and shortly afterwards his legs and abdomen became swollen. There was shortness of breath, headache and some decrease in the amount of urine. Admitted to hospital, May 10, 1915. Blood pressure 172/100. Leukocytes, 13,200. Urine: specific gravity, from 1.020 to 1.030; moderate amount of albumin; casts. Death, Aug. 5, 1915. Necropsy: Pronounced general edema, ascites, hydrothorax and hydropericardium. Heart weighed 375 gm.; kidneys, 500 gm. Smooth external surfaces. A number of glomeruli are completely sclerosed, but these are probably not concerned with his terminal illness. The great majority are somewhat enlarged and their capillaries are largely occluded by endothelial swelling. There is a notable increase in the number of nuclei. No hyalin changes have appeared. There is marked tubular atrophy. Polymorphonuclears are abundant in the interstitial tissues but rare in the glomeruli.

Case 39 (A-18-237).—Female, aged 22 years. Admitted to hospital, Nov. 1, 1918. A diagnosis of nephritis had been made by a physician three or four months previously, and a therapeutic abortion had been performed about two months before. On admission the patient was in coma and was having convulsions every hour. Albuminuric retinitis was noted. She recovered from the coma but had irrational periods and was stuporous most of the time until her death. There was no urine voided on some days and only from three to six ounces on other days. A friction rub over the heart was heard on November 7. Abdominal paracentesis was performed several times. Blood pressure 220/120. Urine: specific gravity, 1.018; numerous waxy and pus casts, many erythrocytes, large amount of albumin; creatinin, 11.4 mg.; urea nitrogen, 33 mg. Death November 13. Necropsy: Marked anasarca, ascites and hydrothorax. Fibrinous pericarditis. Some pus cells and cocci in plueral and pericardial exudates. Heart weighed 300 gm.; kidneys, 260 gm. External surfaces smooth. Marked atrophy of nearly all the tubules. Very few hyalin glomeruli. Numerous epithelial crescents. Most of the glomeruli show closure of their capillaries with little or no hyaline degeneration. Many disintegrated polymorphonuclears in some of the tubules and in the interstitial tissue.

Case 40 (A-19-5).—Male, aged 55 years. Was in the hospital about one year ago at which time albumin and casts were found in the urine. There was no edema then. Readmitted, November, 1918. Edema appeared about three weeks before admission. Blood pressure, 200/120. Albuminuric retinitis. Ascites. Phenolsulphonephthalein on admission 20 per cent.; shortly before

death, 0 per cent. Death, January, 1919. Necropsy: Marked general anasarca. Ascites (1,000 c.c.)—fibrinopurulent exudate on a few intestinal coils. Hydrothorax (1,500 c.c.). Edema of lungs. Heart weighed 420 gm.; kidneys, 520 gm. External surfaces smooth. There are very few glomeruli that are completely sclerosed. Nearly all of them show closure of most of the capillaries with beginning hyaline degeneration of the lobules. There are many remnants of polymorphonuclears enclosed in the lobules. A number of epithelial crescents are to be seen. There is moderate atrophy of all the tubules.

Case 41 (A-21-108).—Male, aged 51 years. First admitted to the hospital in October, 1919, with an attack of acute articular rheumatism. The heart was enlarged at this time but the urine was normal. The second admission was Feb. 26, 1921. At this time he had edema of the arms, legs and back, dyspnea and epistaxis. Blood pressure, 228/110. Width of heart 19 cm. Urine: specific gravity, 1.020; large amount of albumin; a few hyalin and granular casts, a few erythrocytes. Hemoglobin, 80 per cent. Erythrocytes, 4,800,000; 16,950 leukocytes—82 per cent. polymorphonuclears. Blood pressure, March 3, 190/100. Ammoniacal odor to the breath. Fever developed during the last few days coincident with the appearance of the physical signs of bronchopneumonia. Death, March 2, 1921. Necropsy: Marked edema of all dependent portions; no ascites; 500 c.c. of thin purulent fluid in the left pleural cavity. Heart weighed 475 gm.; no valvular lesions. Bronchopneumonia. Kidneys weighed 630 gm. External surfaces smooth. No hyalin glomeruli. Large numbers of fairly fresh extra capillary lesions. A great many polymorphonuclears in the swollen glomeruli. Fairly well marked atrophy of nearly all the tubules.

Cases 42 to 45 are apparently intermediate between subacute and well defined chronic cases. The kidneys are not shrunken and there are not many hyalin glomeruli. The tubular atrophy and the hyalinization of the glomeruli are more pronounced than in the previous group. The inflammatory exudate (polymorphonuclears) appears fresher in Cases 42 and 43 than in Cases 44 and 45.

Case 42 (A-16-368).—Male, aged 39 years. Father and one brother died of renal disease. Severe attack of scarlet fever in childhood. Diphtheria at 20. Acute arthritis at 25. Present illness began May 30, 1916, with gastric disturbances and nausea. June 19 he first noticed puffiness of the face, and shortly afterward a general edema developed. Precordial pain for two or three weeks before death. Admitted to hospital in extremis, Oct. 26, 1916. Had generalized edema, ascites, gastric disturbances and precordial pain. Urea nitrogen, 104 mg.; creatinin, 10.2 mg.; blood sugar, 0.074 per cent.; hemoglobin, 35 per cent. Phenolsulphonephthalein, 0 per cent. Urine: specific gravity, 1.024; abundant albumin, many casts. Leukocytes, 12,000. Death, Oct. 27, 1916. Necropsy: Marked edema of lower half of body; ascites (5,000 c.c.), left hydrothorax (3,000 c.c.), hydropericardium (500 c.c.). Heart weighed 375 gm.; kidneys, 280 gm.; finely granular surfaces. Nearly all the glomeruli show beginning hyaline degeneration. Very few glomerular capillaries are visible. Large numbers of partially disintegrated polymorphonuclears are seen in the closed capillaries and in some of the dilated tubules. There are large numbers of old epithelial crescents. There is advanced atrophy of nearly all the tubules.

Case 43 (A-19-220).—Male, aged 43 years; was well until one year ago when he began to have severe headaches and weakness. He was told by his physician that he had kidney trouble. Admitted to hospital Oct. 2, 1919, complaining of weakness, dyspnea, palpitation of heart, anorexia, precordial pain

and constipation. His heart was enlarged. Blood pressure, 140/60; hemoglobin, 30 per cent.; erythrocytes, 1,300,000; leukocytes, 13,300. Urine: specific gravity, from 1.012 to 1.014; trace of albumin; many granular casts. Phenolsulphonephthalein, October 4, 2 per cent.; October 7, 0 per cent. Blood chemistry: October 7, creatinin, 13 mg.; urea nitrogen, 125 mg.; blood sugar, 0.13 per cent.; October 22, creatinin, 17 mg.; urea nitrogen, 155 mg.; blood sugar, 0.19 per cent. Eye-grounds negative. Death, Oct. 23, 1919. Necropsy: No edema; no ascites; hydrothorax (300 c.c.). Heart enlarged. Kidneys weighed 300 gm.; finely granular surfaces. Some of the glomeruli are completely sclerosed but the great majority show the hyaline change just beginning. There are enormous numbers of disintegrated polymorphonuclears in the interstitial tissues and in the damaged glomeruli (Fig. 16). There is advanced atrophy of most of the tubules and moderate atrophy of the others.

Case 44 (A-10-145).—Male, aged 32 years. Duration unknown. Urine: abundant albumin, hyalin and granular casts. No other clinical data. Necropsy: Ascites, hydrothorax, hydropericardium, edema of the lungs. Heart weighed 530 gm.; kidneys, 314 gm. Nearly all the glomeruli are of about the same appearance. They are enlarged, their capillaries are practically all closed by swollen endothelium, but none of them has yet become hyaline. Occasional remnants of polymorphonuclears are seen in glomeruli and tubules. There is very marked tubular atrophy.

Case 45 (A-11-77).—Male, aged 70 years; admitted to hospital June 7, 1911. Complained of edema and shortness of breath. Urine: albumin, hyalin and granular casts. Specific gravity, from 1.018 to 1.024. Death, July 18, 1911. Necropsy: General anasarca, ascites, hydrothorax and hydropericardium. Heart weighed 475 gm.; old mural thrombus in left auricle. Kidneys weighed 335 gm.; smooth external surfaces. There are a few hyalin glomeruli; but the great majority are not so far advanced. There is complete closure of all but a very few capillaries in each glomerulus. Occasional nuclear fragments are seen in the glomeruli which may be remnants of polymorphonuclears. There are many partially disintegrated polymorphonuclears in the tubules. There are a large number of old epithelial crescents. Tubular atrophy is very marked.

There is very little clinical history available in Cases 46 and 47, but the microscopic structure suggests cases of long duration with a fairly recent inflammation in the persistent glomeruli.

Case 46 (A-12-40).—Male, aged 33 years. Duration of illness unknown. Was comatose and breath had a uremic odor. Edema of face. Systolic blood pressure, from 200 to 210. Diarrhea. No marked changes in eye-grounds. Moderate amount of albumin and numerous casts. Necropsy: Slight edema of face and neck. A little fluid in the serous cavities. Heart weighed 735 gm.; kidneys, 250 gm.; granular surfaces. A large percentage of the glomeruli are hyaline. Other glomeruli are enlarged and show closure of most of the capillaries. Numerous well preserved polymorphonuclears are visible in the open and closed capillaries, suggesting a recent acute attack.

Case 47 (0-12-83).—Female, aged 17 years. For several years the patient had symptoms which were referred to the urinary tract. No details of the clinical picture were recorded. A diagnosis of renal tuberculosis was made and one kidney was removed Nov. 18, 1912. Subsequent history unknown. The kidney shows a finely granular surface. A large number of glomeruli are hyaline; the others are enlarged and show a great increase of nuclei with closure of most of their capillaries. Large numbers of disintegrating polymorphonuclears are to be seen in the closed capillaries (Figs. 12, 13 and 14). The tubules belonging to the hyaline glomeruli have completely disappeared; the others show varying degrees of atrophy.

Cases 48 to 51 give histories which may be interpreted as examples of chronic nephritis following acute nephritis, and in Cases 49 and 51 there is good evidence of a terminal acute exacerbation.

Case 48 (A-15-363).—Male, aged 30 years, has had frequent urination for past five or six years. Three years ago he suddenly developed general edema. Was in the hospital three weeks at this time. Left hospital much improved. Has had attacks of edema and shortness of breath since then. Edema is worse after alcoholic excesses. Has been confined to his home since about Sept. 10, 1915. Admitted to hospital Oct. 10, 1915, with a severe attack similar to the one he had three years ago. Phenolsulphonephthalein, October 16, a trace. Urine: specific gravity, from 1.010 to 1.014; abundant albumin; many casts. Leukocytes, 7,400. Death, Nov. 14, 1915. Necropsy: Marked edema of lower half of body, ascites, hydrothorax and hydropericardium. Heart weighed 575 gm.; kidneys, 155 gm.; granular surfaces. A large majority of the glomeruli are hyaline and their associated tubules show extreme atrophy; the others are damaged in varying degrees, due to closure of part of their capillaries. Many of the tubules associated with these injured glomeruli show very little atrophy.

Case 49 (A-17-62).—Female, aged 27 years. Mother died of Bright's disease at 49. One brother has kidney trouble now. Patient had otitis media in 1906, and smallpox in 1908. In October, 1909, she developed severe headaches, high fever, edema of ankles and ascites. Blood pressure during this attack, 160 systolic. She was in bed from October, 1909, to April, 1910. There was gradual improvement but she had recurring attacks of headache, edema of ankles and vomiting. Had a mastoid infection in 1915. Scarlet fever in the fall of 1916. Polyuria the past three years. Eyesight always poor. In October, 1916, she had a sore throat with high fever and the edema became worse. Vision has gradually grown poorer. Has been in bed since Feb. 24, 1917. Admitted to hospital March 1, 1917. Urine: specific gravity, from 1.005 to 1.008; large quantities of albumin, many leukocytes, a few granular casts. Hemoglobin, 40 per cent.; erythrocytes, 2,300,000; leukocytes, 11,000 (March 3); 22,400 (March 13)—92 per cent. polymorphonuclears. Blood pressure, March 1, 185/100. Temperature about normal. Blood chemistry: creatinin, March 1, 26 mg.; March 16, 22.2 mg. Urea nitrogen, March 1, 101.2 mg.; March 16, 68 mg. Phenolsulphonephthalein, 0 per cent. March 2 and March 10. Death, March 17, 1917. Necropsy: Marked edema of face, ascites, hydrothorax and hydropericardium. Heart weighed 455 gm.; kidneys, 150 gm.; rough granular surfaces. A large majority of the glomeruli are completely sclerosed and their tubules have almost disappeared; the others are enlarged and show closure of most of their capillaries, and partial atrophy of their associated tubules. In this latter group of glomeruli there are many polymorphonuclear leukocytes in both the open and closed capillaries. These histologic features suggest an acute exacerbation of a chronic nephritis. There are a few old extracapillary lesions.

Case 50 (A-18-117).—Male, aged 32 years. No history of scarlet fever or rheumatism. Ten years ago he was in a hospital with a condition diagnosed Bright's disease by his physician. He remembers that he had a considerable amount of edema at that time. His present illness began about the end of March, 1918, with weakness, loss of appetite, vomiting after eating and unproductive cough. Admitted to hospital May 21, 1918. Patient thinks he has lost about 20 pounds during the last two months. Physical Examination: Enlarged heart, systolic murmur at apex, dyspnea, slight edema of lungs. Blood pressure, 190/140. Daily urine excretion from 175 to 225 c.c. Moderate albuminuria, casts; many erythrocytes. Phenolsulphonephthalein, 0 per cent. on two occasions. Urea nitrogen, from 15.5 to 17 mg.; creatinin, from 2 to 3.6 mg. Blood sugar, from 0.092 to 0.11 per cent. Death, June 3, 1918. Necropsy: No edema; ascites (100

c.c.); hydrothorax (1,300 c.c.). Fibrinous pericarditis. Heart weighed 630 gm.; spleen, 240 gm.; kidneys, 405 gm.; granular surfaces. About one half of the glomeruli are completely sclerosed, and their tubules have almost disappeared. The others are enlarged and show closure of most of their capillaries but no definite hyaline changes. Their tubules are notably decreased in size. A number of these glomeruli show hyaline degeneration of the afferent arteriole. Remnants of polymorphonuclears are visible in most of the enlarged glomeruli and throughout the interstitial tissues. There are many epithelial crescents. It is probable that the sclerosed glomeruli are due to the attack ten years ago.

Case 51 (A-19-264).—Male, aged 29 years, had scarlet fever at 23. Was unable to work for six months following this disease (no information as to edema or albuminuria). Had an attack of rheumatism at 27 which lasted six months. At 28 he had arthritis in the ankles and wrists, relieved by tonsillectomy in the spring of 1919. In October, 1919, he contracted a severe cold from exposure in a cold rain. The next day he was in bed with severe headache, palpitation, dyspnea, precordial pain, edema around the eyes, epistaxis and blurring of vision. He has grown worse gradually since that time. Admitted to hospital, Nov. 6, 1919. Examination showed enlargement of heart with a systolic murmur, puffiness of face and conjunctival hemorrhages. Blood pressure, 170/80. During his stay in the hospital he had frequent attacks of vomiting, nosebleed, hiccough, headache and dizziness. Became unconscious December 8. Hemoglobin, from 32 to 25 per cent. Erythrocytes from 2,650,000 to 1,800,000. No fever. Urine: large amount of albumin, hyalin and granular casts, a few erythrocytes. Phenolsulphonephthalein, November 14, a trace; November 21, 5 per cent. Blood chemistry: November 9, creatinin, 7.4 mg.; urea nitrogen, 87 mg.; blood sugar, 0.153 per cent.; November 20, creatinin, 10.8 mg.; urea nitrogen, 36 mg.; blood sugar, 0.189 per cent. Alkaline reserve, November 20, 40.6. Death, Dec. 8, 1919.

Necropsy: Slight edema of face; hydropericardium (100 c.c.). Heart weighed 435 gm.; vegetations on wall of left auricle. Spleen weighed 365 gm.; kidneys, 340 gm.; finely granular surfaces. A number of glomeruli show complete sclerosis with disappearance of their tubules. A large number show old extracapillary lesions without hyalinization of the tuft but with well advanced atrophy of their tubules. More than one third show an appearance corresponding with the subacute stage, i. e., great enlargement due to swelling and proliferation of the endothelium, with many polymorphonuclears in the closed capillary loops. The tubules belonging to this latter group show moderate to well advanced atrophy. There are masses of polymorphonuclears in some of the tubules. There are large areas of cortical tissue densely infiltrated with mononuclear leukocytes—an appearance characteristic of the acute interstitial nephritis of scarlet fever (Fig. 18). The appearances suggest an old nephritis dating from the attack of scarlet fever, and an acute attack of rather recent date.

Case 52 is a good illustration of terminal acute glomerulitis in a case of very long duration.

Case 52 (A-17-207).—Female, aged 46 years, has had a discharge from the left ear as long as she can remember. Frequent attacks of sore throat and pleurisy. Operation for myoma of uterus when 27 years old. Present trouble began in 1900 with nocturia and gastric disturbances. Some improvement on a milk diet. Was refused life insurance in 1906 because of albuminuria. Was under treatment for this condition from time to time but did not improve. In bed, on a milk diet, for eight days in August, 1915. Admitted to hospital, May, 1917. Poor vision. Cramps in muscles. Urine: trace of albumin; casts very rare. Hemoglobin, 49 per cent.; leukocytes, 11,000. Phenolsulphonephthalein, a trace. Blood pressure, 117/80. Urea nitrogen, from 39 to 66 mg.;

creatinin, from 9.7 to 16.8 mg.; blood sugar, from 0.16 to 0.2 per cent. Discharged June 23. Readmitted, Sept. 29, 1917. Headache, nausea, vomiting, dyspnea, swelling of face and legs, loss of appetite, cramplike pains in fingers and frequent urination. Eleven hundred c.c. of fluid was drawn from right pleural cavity. October 3, urine: moderate amount of albumin, occasional hyalin casts. Hemoglobin, 25 per cent.; erythrocytes, 3,000,000; leukocytes, 7,600. Blood pressure, 160/110. Phenolsulphonephthalein, a trace. Urea nitrogen, 89 mg.; creatinin 16.2 mg. Temperature normal. Death, Oct. 6, 1917. Necropsy: general anasarca; ascites (1,500 c.c.); hydrothorax (800 c.c.). Heart weighed 400 gm.; spleen, 120 gm. Pus in left middle ear. Slight general arteriosclerosis. Kidneys, weighed 120 gm.; rough, granular surfaces. A large percentage of the glomeruli are completely sclerosed; the others show an acute or subacute glomerulitis. These latter are enlarged with greatly swollen endothelium, which closes most of the capillaries. The numerous polymorphonuclears in the capillaries and tubules as well as fresh epithelial crescents indicate that there has been a recent acute attack.

Cases 53 to 59 are clinically examples of the type with slow insidious onset and long duration. Microscopically they show very old lesions without any acute processes.

Case 53 (A-11-76).—Female, aged 44 years. Admitted to hospital Aug. 9, 1910. Complained of edema which had been present at varying intervals since her first pregnancy nearly fifteen years before. Had scarlet fever when a child. Has had headaches and vomiting spells for many years. Shortness of breath and swelling of feet for the past three years. Albumin and casts continuously present in the urine. Hemoglobin, from 50 to 60 per cent. Systolic blood pressure, 140 to 170. Extreme edema. Eighty-one gallons of fluid was drawn from the pleural and peritoneal cavities during her stay in the hospital. Multiple abscesses of the skin of the arms and legs appeared a few months before death. Streptococci were found in these abscesses. Low fever during most of her stay in the hospital. Death, July 17, 1911. Necropsy: Anasarca, ascites, hydrothorax and hydropericardium. Heart weighed 492 gm. Fresh mural thrombus in left ventricle. Kidneys weighed 260 gm. Granular surfaces. About one-third of the glomeruli are completely hyalinized and their tubules have largely disappeared. Most of the other glomeruli are associated with markedly atrophic tubules and show closure of nearly all the capillaries with beginning hyaline degeneration (Fig. 19). A few glomeruli show a number of permeable capillaries, and these glomeruli belong to tubules of normal size. Renal function was performed by a number of damaged glomeruli.

Case 54 (A-13-178).—Female, aged 32 years. Many attacks of tonsillitis when young; none recently. Present illness began about one year ago with shortness of breath on slight exertion. In June, 1913, she first noticed swelling of legs which would disappear after a night's rest. Was in bed sixteen weeks before admission to hospital. On admission, Nov. 21, 1913, there was general subcutaneous edema, enlargement of heart, and hypertrophied tonsils. Urine: abundant albumin, many hyalin granular casts. Leukocytes, November 22, 13,700; 80 per cent. polymorphonuclears. Blood pressure, November 24, 160/110; December 8, 110/100. Death, Dec. 9, 1913. Necropsy: General anasarca, hydrothorax, hydropericardium, ascites and edema of lungs. Heart weighed 543 gm. Double pyosalpinx. Streptococcus from heart's blood. Kidneys weighed 190 gm. Granular surfaces. Large majority of glomeruli sclerosed. Other glomeruli show partial closure of their capillaries with a corresponding atrophy of the associated tubules.

Case 55 (A-13-184).—Female, aged 34 years. Duration of illness about 10 months. Hemoglobin 30 per cent. No clinical history available. One

kidney removed at necropsy; granular surface. Many sclerosed glomeruli. No normal glomeruli are found. The great majority show severe injury and are connected with markedly atrophic tubules. These injured glomeruli are enlarged and nearly all their capillaries are closed (Fig. 9). There are a number of polymorphonuclear remnants in the closed capillaries. A number of old epithelial crescents are seen.

Case 56 (A-17-108).—Male, aged 39 years. Has had scarlet fever, date unknown. Present illness began three years ago with swelling of ankles. Later his legs and face began to swell. Still later he developed dyspnea and palpitation of the heart. Admitted to hospital, April 18, 1917. Had edema of ankles, headache, poor vision. Urine: specific gravity, 1.014; albumin, trace to a large amount. Leukocytes, 11,800. Phenolsulphonephthalein, 0 per cent, May 2. Death, May 18, 1917. Necropsy: No edema; no ascites; hydrothorax (600 c.c.); hydropericardium (200 c.c.). Heart weighed 640 gm.; kidneys, 350 gm.; surfaces roughened and pitted. Large numbers of hyalin glomeruli are seen; the other glomeruli are all enlarged, most of their capillaries are closed and there are varying degrees of hyaline degeneration in the lobules (Figs. 15 and 20). Numerous degenerated polymorphonuclears are seen in the closed capillaries and in atrophic tubules. There are a few rather recent epithelial crescents. An occasional afferent glomerular artery shows hyaline degeneration.

Case 57 (A-17-118).—Male, aged 69 years. One brother died of Bright's disease. Patient first noticed swelling of his feet, especially at night, thirteen years ago. For the last few years he has noticed puffiness under the eyes. He has been in a hospital on two previous occasions for the same condition that troubles him now. Admitted to hospital, April 18, 1917. Has severe dyspnea. Left leg is greatly swollen. Blood pressure, April 27, 185/140. Urine: trace of albumin, many casts; specific gravity from 1.012 to 1.022. Leukocytes, 9,600. Phenolsulphonephthalein, April 27, 12 per cent. Blood chemistry, April 27: creatinin, 1.5 mg.; urea nitrogen, 28 mg. Alkaline reserve, 46. Death, June 8, 1917. Necropsy: Marked edema of lower extremities; left hydrothorax (100 c.c.); edema of lungs. Heart weighed 495 gm.; extensive sclerosis of aorta and large vessels. Kidneys weighed 160 gm.; rough granular surfaces. A large number of glomeruli are completely sclerosed; many others are enlarged with closure of most of their capillaries. There are a number of old extracapillary lesions. Many of the afferent glomerular arteries show hyaline degeneration, and the obliteration of some of the glomeruli is evidently due to this cause.

Case 58 (A-18-94).—Male, aged 50 years. Never had scarlet fever, rheumatism or tonsillitis. Well until his present illness began six or seven years ago, when he first noticed swelling above the tops of his shoes, especially in the evening. This condition grew worse and at times there was also swelling of the hands. For the past five years he had noticed weakness and dyspnea, most pronounced during the past few weeks. Admitted to hospital, April 7, 1918. Physical Examination: Loss of weight; enlargement of heart to the left; systolic murmur at aortic area and at apex. Urine: specific gravity from 1.006 to 1.015; trace to a heavy precipitate of albumin; numerous granular casts. Low fever. Hemoglobin, 75 per cent. Erythrocytes, 4,420,000; leukocytes, 7,800. Blood pressure, April 11, 188/124. Death, May 3. Necropsy: Edema of face; no fluid in serous cavities. Heart weighed 640 gm.; kidneys, 205 gm.; finely granular surfaces. A large majority of the glomeruli are completely sclerosed; the others are enlarged and show closure of most of their capillaries.

Case 59 (A-19-2).—Male, aged 25 years. No history of scarlet fever, tonsillitis or rheumatism. In good health until April 1, 1918, when he began to have attacks of headache and vomiting. The attacks would last a day, after which he would be able to work again. Has had a few attacks of precordial pain, one of which lasted eight hours. Shortness of breath was first noticed about the

middle of November, 1918. He has been in hospitals on four different occasions since April 1, 1918. Admitted to University Hospital Dec. 14, 1918. No edema. Mitral regurgitation. Blood pressure, December 15, 210/118. Urine: large amount of albumin; many granular casts; specific gravity, 1.010. Leukocytes, December 19, 10,500. Low fever. Blood chemistry: December 27, urea nitrogen, 57.3 mg.; creatinin, 12 mg.; January 4, urea nitrogen, 72 mg.; creatinin, 12.4 mg. Phenolsulphonephthalein, December 20, a trace. Albuminuric retinitis. Death, Jan. 5, 1919. Necropsy: No edema; ascites (150 c.c.); hydrothorax (400 c.c.); early bronchopneumonia. Heart weighed 500 gm.; kidneys, 195 gm.; rough granular surfaces. Over three fourths of the glomeruli are completely sclerosed and their tubules have almost disappeared. The remainng glomeruli are badly damaged, only a small part of their capillaries being permeable. Their tubules are moderately atrophic. An occasional old extracapillary lesion is seen. There are no polymorphonuclears in the glomeruli.

Cases 60 to 68 are cases with short clinical histories but with gross and microscopic evidence of very long duration.

Case 60 (A-13-145).—Male, aged 35 years, has had diphtheria and scarlet fever. Present illness began three months before admission with dyspnea and swelling of feet. Admitted to hospital Sept. 10, 1913. Chief complaints were gastric distress and edema. Heart was enlarged. Urine: specific gravity, 1.010; abundant albumin; hyalin, granular, waxy and leuckocyte casts. Systolic blood pressure, September 27, 132. Died in coma, Sept. 29, 1913. Necropsy: Ascites and hydrothorax. Heart weighed 475 gm.; kidneys, 169 gm.; surfaces very granular. Apparently about two thirds of the glomeruli are hyalinized and their tubules have disappeared. The remaining glomeruli are enlarged, and a large percentage of their capillaries are occluded (Fig. 21). In some of these, there are remnants of polymorphonuclears in the closed capillaries. The tubules connecting with these defective glomeruli are moderately atrophic. There are large areas of lymphocytes in the cortex, probably representing an interstitial exudate which occurred during the attack of scarlet fever. This suggests that the glomerular involvement may date from the attack of scarlet fever.

Case 61 (A-14-192).—Male, aged 30 years. Admission, Sept. 28, 1914. No clinical history. Urine: specific gravity from 1.008 to 1.018; abundant albumin, many casts. Blood pressure, October 7, 192 systolic. Death, Oct. 13, 1914. Necropsy: Slight edema of extremities; ascites. Heart weighed 490 gm.; kidneys, 360 gm.; granular surfaces. A small proportion of the glomeruli are completely sclerosed; the majority show extensive obliteration of their capillaries with marked atrophy of their tubules. A few glomeruli are normal. Rarely an old extracapillary lesion is seen. A great many disintegrating polymorphonuclears are found in the atrophic tubules.

Case 62 (A-15-373).—Male, aged 23 years, admitted to hospital Sept. 26, 1915, has had frequent attacks of sore throat and rheumatism (?). About one month before admission he noticed slight swelling of his feet, and gradually increasing weakness and shortness of breath. Kept at work until about Sept. 12, 1915. On admission he complained of weakness, dizziness, headache, cough and nocturia. Urine (nine examinations): specific gravity, from 1.010 to 1.012; albumin, trace to a heavy precipitate; many casts. Blood pressure, October 13, 180/115. Phenolsulphonephthalein, October 1, 11 per cent. Leukocytes, November 15, 5,800. Death, Nov. 23, 1915. Necropsy: No edema; no fluid in serous cavities. Heart weighed 557 gm. Kidneys small with granular surfaces. A large percentage of the glomeruli are completely hyalinized, and the others show partial closure of their capillaries.

Case 63 (A-15-394).—Male, aged 54 years, admitted to hospital, Oct. 19, 1915. Seven years ago he had an attack of acute arthritis (ankles were swollen,

red and painful). Nine days before admission he began to have dyspnea and five days later his legs began to swell. Abdomen has been distended since about October 5. On admission he had marked edema of lower extremities and external genitals, and enlargement of the heart with mitral regurgitation. Urine (sixteen examinations): albumin, trace to a heavy precipitate; casts. Blood pressure, October 19, 150/90; November 4, 168/90; December 6, 100/58. Death, Dec. 7, 1915. Necropsy: No edema; hydropericardium. Heart weighed 650 gm. Mitral leaflets greatly thickened and retracted; aortic leaflets adherent. Lobar pneumonia. Advanced sclerosis of aorta. Kidneys weighed 319 gm.; roughened granular surfaces. A large percentage of the glomeruli are completely sclerosed; the others show partial closure of their capillaries. There is advanced sclerosis of some of the larger arteries and a few of the afferent arterioles. The fact that most of the afferent arterioles are not diseased indicates that the vascular disease is not the main cause of the glomerular changes.

Case 64 (A-16-132).—Male, aged 27 years. About three months before admission he began to have attacks of nosebleed. These recurred frequently and have gradually become more severe. About seven weeks before admission his left wrist pained him severely. Entered hopsital, March 26, 1916, complaining of frequent epistaxis, pain in stomach with occasional vomiting, sore throat and general weakness. Small hemorrhages were noted on the left wrist and on the palate. There was edema of the uvula and pharynx, and a mitral systolic murmur. Temperature, from 100 to 101 F. Hemoglobin, 36 per cent.; erythrocytes, 2,800,000; leukocytes, 9,200; 87 per cent. polymorphonuclears. Urine: large amount of albumin; some blood. Death, March 30, 1916. Necropsy: No edema; ascites (50 c.c.); hydrothorax (100 c.c.). Aorta, normal. Heart weighed 425 gm.; kidneys, 150 gm.; roughened granular surfaces. More than three fourths of the glomeruli are completely sclerosed, and the others show many closed capillaries. Occasional partially atrophied tubules shows masses of disintegrating polymorphonuclears. A few afferent arterioles show hyaline degeneration.

Case 65 (A-16-384).—Male, aged 24 years. One brother died of Bright's disease at 23. Patient stated that he had been perfectly well until August, 1916, when he had an attack of nosebleed. At first the attacks came about once a week, and would last one to two hours, but later, they became more frequent. He gradually became weaker. Did not notice swelling of feet or puffiness of eyes until about November 5. Admitted to hospital, Nov. 12, 1916. Urine: specific gravity, 1.010; large amount of albumin; many casts of all kinds. Hemoglobin, 20 per cent.; erythrocytes, 1,500,000; leukocytes, 7,500. Blood pressure, 170/90. Phenolsulphonephthalein, November 12, 0 per cent. Blood chemistry, November 13: creatinin, 27.2 mg.; urea nitrogen, 131 mg.; sugar, 0.26 per cent.; alkaline reserve, 18.3. Death, November 18, 1916. Necropsy: No edema; no ascites; hydrothorax (200 c.c.). Heart weighed 415 gm. Aorta normal. Kidneys weighed 205 gm.; roughened granular surfaces. Practically all the glomeruli are severely involved. There is advanced atrophy of all the tubules. Many atrophic tubules contain masses of disintegrating polymorphonuclears. There are some old extracapillary lesions.

Case 66 (A-19-160).—Male, aged 32 years. Recently discharged from the army because of heart and kidney trouble. No details of history available. Admitted to hospital July 26, 1919. Normal temperature. Frequent vomiting. Became irrational July 27. Blood pressure, 120/80. Systolic murmur at apex. Dilated heart. Urine: large amount of albumin; no casts; no erythrocytes. Death, July 30, 1919. Necropsy: No edema; no fluid in serous cavities. Heart weighed 350 gm.; dilated. Kidneys weighed 140 gm.; finely granular surfaces; thinned cortices. A large majority of the glomeruli are completely sclerosed, and most of the others are severely damaged and their tubules are markedly atrophic. An occasional glomerulus is practically normal. There are a large number of old extracapillary lesions.

Case 67 (A-18-180).—Male, aged 26 years, admitted to hospital, Sept. 17, 1918. Death, Sept. 18, 1918. No history was obtained. Urine: specific gravity, 1.015; small amount of albumin; many granular casts. Necropsy: Edema of ankles; marked ascites, hydrothorax and hydropericardium. Heart weighed 360 gm.; spleen, 235 gm.; kidneys, 290 gm.; external surfaces smooth. About one-third of the glomeruli are completely sclerosed and their tubules are very small. The other glomeruli are moderately enlarged, most of their capillaries are closed and their tubules are moderately reduced in size. There are numerous disintegrated polymorphonuclears in the closed capillaries and some of the tubules. Many glomeruli show a thick band of hyaline around the afferent artery after its entrance into the glomerulus; but there is very little change in the artery before it reaches the glomerulus.

Case 68 (A-20-204).—Male, aged 34 years. Typhoid fever at age of 17 years; was in bed 10 weeks. In March, 1920, he first noticed impairment of vision. At this time he had frequent headaches with a catarrhal condition in the upper respiratory tract. His physician told him that he had nephritis. May 4, 1920, examination revealed enlargement of heart, albuminuric retinitis, and a blood pressure of 200/120. Death, May 20, 1920. Necropsy: Slight edema of face; ascites (100 c.c.); hydrothorax (2,200 c.c.); edema of lungs. Heart weighed 425 gm.; kidneys, 195 gm.; granular surfaces. Many sclerosed glomeruli with disappearance of their tubules. Majority of glomeruli are enlarged and their capillaries are largely occluded by swollen endothelium but there is very little hyaline degeneration. There is a notable proliferation of the capsular epithelium. The tubules show advanced atrophy.

Case 69 (A-17-230).—Male, aged 45 years. Well until the autumn of 1916 when he developed swelling of the feet and abdomen with marked weakness. Improved under hospital treatment but was too weak to return to work. In the summer of 1917 he had another similar attack. There was marked general edema and a systolic murmur at the apex of the heart. Admitted to hospital Sept. 29, 1917. Blood pressure, October 1, 140/70; October 20, 130/80. Urine, September 29 to November 6; abundant albumin, many casts of all types. Leukocytes, October 15, 8,700. Phenolsulphonephthalein, October 1, 35 per cent.; October 15, 31 per cent. Blood chemistry, October 2: urea nitrogen, 24.2 mg.; creatinin, 2.3 mg. November 1, left side of face became swollen and six teeth were extracted. Lobar pneumonia was recognized November 9. Leukocytes 26,000 on November 9. Death, Nov. 11, 1917. Necropsy: No edema; no fluid in serous cavities. Extensive old pleuritic adhesions. Lobar pneumonia. Heart weighed 400 gm.; spleen, 120 gm.; kidneys, 360 gm.; adherent capsules; slightly roughened external surfaces; grayish yellow cortices. Very few glomeruli are hyaline. The great majority of the corpuscles show old epithelial crescents surrounding small partially collapsed glomeruli with few or no permeable capillaries. The tubules connected with these glomeruli are markedly atrophic but still easily visible (Fig. 22). There are a number of glomeruli, however, that have many permeable capillaries and are connected with fairly normal tubules. These presumably explain the fairly good renal function.

Age.—The age of the subacute and chronic cases at the time of death is shown by decades in Table 2. It will be noted that two-thirds of the cases occurred in the third and fourth decades. Fitz[31] at the Massachusetts General Hospital, found an average age of 32 years in cases of chronic glomerulonephritis, and 52 years in the arterio-

31. Fitz, R.: The Phenolsulphonephthalein Test and the Nonprotein Nitrogen of the Blood in Chronic Nephritis, Boston M. & S. J. **183**:247, 1920.

sclerotic form of Bright's disease. Two-thirds of our cases of arteriosclerotic renal disease were over 50 years old.

TABLE 2.—AGE AT DEATH

Age	Number of Cases
0-10 years	1
11-20 years	1
21-30 years	12
31-40 years	12
51-50 years	5
51-60 years	4
61-70 years	2

Sex.—There were twenty-seven males and nine females, but the proportion of males to females in our necropsies is approximately 2:1 (2,325 males and 1,063 females in 3,388 necropsies) so that there is probably only a slight preponderance of the disease in males.

Duration.—The duration of the subacute cases was usually less than four months; but one patient (Case 36) lived six months, and another (Case 40) had an abnormal urine one year before death.

The actual duration of a chronic case cannot be determined entirely by the patient's statement as to when his illness began. Seven well defined chronic cases with contracted kidneys gave histories of an illness of only two or three months' duration. Probably the disease could have been recognized long before in these patients, but it evidently did not produce serious discomfort until well advanced.

Twelve patients had symptoms of nephritis for one year or more before death, and in seven of these the disease was present over three years. Case 49 lasted eight years and Case 52 over eleven years.

Symptoms.—The disease usually develops slowly, but sometimes the onset is rapid, even in cases in which extensive destruction of renal tissue must have been present long before the appearance of symptoms. The most frequent initial complaints are dyspnea and edema; but in occasional cases epistaxis or gastrointestinal disturbances, such an anorexia, vomiting and gastric distress may bring the patient to his physician. Other symptoms which may be prominent at some time during the course of the disease are headache, weakness, precordial pain, frequent urination and disturbances of vision.

Edema.—This is a very common sign of nephritis. Subcutaneous edema was present in thirty-one of thirty-six cases in which data were available; and even in the five dry cases there was a little fluid found in the serous cavities at necropsy. The intensity of the edema varies greatly in different patients and in the same patient from time to time. It is influenced by rest, the amount of salt in the diet and other unknown factors. It may disappear before death. The accumulation of fluid in the serous cavities is sometimes a prominent and serious

feature of the disease. Eighty-one gallons of fluid were drained from the pleural and peritoneal cavities of one patient (Case 53) during a period of eleven months. Hydrothorax and edema of the lungs are partly responsible for dyspnea, which is a very frequent symptom.

Hypertension and Cardiac Hypertrophy.—These are almost constantly present in chronic glomerulonephritis. Blood pressure was recorded in twenty of the chronic cases, and in only two instances was the systolic reading below 140. These low pressures were both taken shortly before death and may not be exceptional since it frequently happens that the pressure falls a short time before exitus. The systolic pressure was from 160 to 180 in six patients, and 180 or above in ten.

The average weight of the heart in twenty-six chronic cases was 498 gm. Only three hearts weighed less than 400 gm. One of these (Case 42) was a case of comparatively short duration, judged both by the clinical history and the structural changes in the kidneys. In the other two cases (Cases 66 and 67) no clinical history was available, but the histologic picture indicated a disease of long duration, so that these seem to be examples of chronic glomerulonephritis without cardiac hypertrophy. There is no notable enlargement of the heart in the subacute cases, but hypertension was found in the three cases in which the blood pressure was taken.

Anemia.—This is apparently a frequent complication in advanced chronic glomerulonephritis and it seems to increase in intensity toward the end of the illness. The hemoglobin was determined in ten chronic cases, and found to be below 50 per cent. in eight of them. One patient (Case 58) had a hemoglobin of 75 per cent. one month before death.

Urinary Changes.—Urinary examinations are recorded in thirty-four of the thirty-seven cases of this group. Albumin was found in every sample of urine from every patient. Usually a large amount was found but occasionally only a trace was present. When a large number of examinations are made on the urine of one patient the amount of albumin may vary from a trace in some samples to a heavy precipitate in others. We have no cases of glomerulonephritis with normal urine. Casts were found in thirty of thirty-four cases, and usually in large numbers. In the cases in which no casts were found only one sample of urine was examined. Casts may be rare in one sample and numerous in another sample of urine from the same patient. Bloody urine was recorded in one chronic and three subacute cases. Of course, only a small percentage of persons who have albumin and casts in the urine are suffering from Bright's disease. Brown [32] in a study

32. Brown, P. K.: A Study of the Etiology of Chornic Nephritis, J. A. M. A. **66**:793 (March 11) 1916.

of 7,000 hospital admissions found 594 with albumin and casts, of which only thirty-eight (6.4 per cent.) were considered to have Bright's disease.

Functional Tests.—Functional studies were made on sixteen patients. The tests were applied five months before death in two patients, and within the last two months of life in all the others. The phenolsulphonephthalein output was invariably greatly reduced, and in eleven patients in which it was determined shortly before death it varied from 0 to 20 per cent. In Case 69 the readings were higher but this patient died of lobar pneumonia before serious renal insufficiency had developed.

Marked retention of urea nitrogen and creatinin was usually observed. The exceptions are Case 36, in which the test was made very early in the attack, and Case 50, which is inconsistent with the phthalein excretion and probably an error. In Case 69, in which death was due to lobar pneumonia there was only slight retention. As is well known urea nitrogen begins to increase before there is any change in the amount of creatinin.

These tests usually run parallel and are of about equal value in estimating renal sufficiency. It is desirable to use both tests since each acts as a control on the other and both are entirely consistent with the structural changes found at necropsy. We have not seen any cases of marked inconsistency between these functional tests and the findings at necropsy. Functional tests are of no great value in acute glomerulonephritis since in these kidneys the damage is usually not permanent; but in chronic nephritis they give a fairly accurate measurement of the extent of the permanent injury. The difficulty with these tests is that they do not reveal the presence of nephritis until two-thirds or more of the renal filter has been closed, and they are therefore of no value in the recognition of the early stages of the disease when there might be some chance for successful therapy.

Functional tests are frequently useful in distinguishing a case of primary hypertension from one of chronic Bright's disease, and also in determining the extent of the renal injury in the arteriosclerotic kidney; but it is not often possible to distinguish this last named renal disease from chronic glomerulonephritis by functional tests. Occasionally patients may live a long time with a high degree of retention of metabolites in the blood and a very low phthalein excretion (O'Hare[33]), but, as a rule, such findings indicate that death will occur within a few months at most. In making a prognosis it is to be remembered that in acute nephritis and in acute exacerbations of a chronic

33. O'Hare, J. P.: Compatibility of Long Life with Low Renal Function, J. A. M. A. **73**:248 (July 26) 1919.

nephritis there is a temporary obstruction of many capillaries which open up again as the acute process subsides. Tests made during these acute stages indicate a more extensive destruction of renal tissue than actually exists.

Our data are not complete enough to warrant a statement as to the frequency of albuminuric retinitis.

Death in subacute and chronic glomerulonephritis seems to occur almost invariably as a direct result of renal insufficiency. A severe anemia is usually present in the terminal stages. Cardiac decompensation seems never to be the direct cause of death. Occasionally a seropurulent pleuritis or a bronchopneumonia of limited extent is found at necropsy. In only one case was death definitely due to a complication, viz., lobar pneumonia in Case 69.

Gross Changes in the Kidneys.—In subacute glomerulonephritis the kidneys may be of normal size but are usually enlarged. They are never contracted. In five out of eight adults the kidneys weighed more than 400 gm. In one instance the weight was 500 gm. and in another 630 gm. The external surfaces are smooth. The cortices are cloudy.

In the twenty-five chronic cases in which the weights are recorded the average was 248 gm. In ten cases the kidneys weighed less than 200 gm., in eight cases more than 300 gm., and in three cases more than 350 gm. The maximum weight was 405 gm. In a general way there is a relation between the duration of the disease and the size of the kidneys, the smaller kidneys being found in cases with histories of a long illness; but there are many exceptions. The external surfaces are almost invariably roughened and granular, a condition produced by an uneven atrophy of the cortex. The cortex is cloudy, reduced in thickness, and indistinctly marked off from the pyramids. Multiple small superficial cysts and adenomas do not seem to occur in uncomplicated glomerulonephritis but these structures are very common in arteriosclerotic kidneys.

Microscopic Appearances.—In chronic cases there are always a large number of hyalin glomeruli. These are smaller than normal and are of homogeneous structure. Their tubules may appear as small solid cords of cells, or they may have disappeared entirely. Roughly estimated, the number of hyalin glomeruli varies from one-third in some cases to three-fourths in others. These tubule systems are of course nonfunctional. The other glomeruli are practically all injured in varying degrees. Very few are entirely normal. The most important change is the permanent closure of various parts of the capillary network. Some glomeruli show closed portions here and there while others may show only an occasional permeable capillary

(Fig. 23). The size of the associated tubule depends on the permeability of its glomerulus. The tubular atrophy is pronounced when the capillaries are mainly closed. The work of the kidney is performed by damaged glomeruli (Figs. 17, 19, 23).

In the subacute kidneys the changes are not so far advanced. The glomeruli show closure of the capillaries by swollen endothelium with beginning hyaline degeneration, but very few glomeruli have become completely hyalinized. The subacute case differs from the chronic in the more uniform injury of all the glomeruli. Death in the subacute case occurs before any glomeruli have had time to reach the hyaline stage. In the chronic case the severely injured glomeruli become hyalin, while those less injured carry on the renal function.

The evidences of previous acute processes in chronic kidneys will be discussed later on.

ETIOLOGY OF SUBACUTE AND CHRONIC GLOMERULONEPHRITIS

The clinical and pathologic evidence that acute glomerulonephritis is due to bacterial infection is so convincing that this view has very few opponents at present; but there are many who do not believe that infection is the basis of the chronic form, and either attribute it to obscure metabolic disturbances or consider the etiology entirely unknown. The evidence as to the etiology of subacute and chronic glomerulonephritis will now be discussed.

1. *The Relation Between Acute and Chronic Glomerulonephritis.*—It is a common observation that acute glomerulonephritis does not often pass into the chronic form. Volhard and Fahr state that the majority of acute cases recover in days, weeks or months according to their severity, and that only the very severe die. Of their seventy-one acute cases three became chronic. One of their patients developed acute nephritis in 1903, fourteen days after an attack of tonsillitis. In 1906 edema of the legs developed and never completely disappeared. In 1910 he had a typical chronic nephritis. Death in 1913. Duration, ten years.

Aufrecht[34] gave a very thorough description of a case of twenty years' duration which began acutely six months after an attack of scarlet fever. Albumin was found in the urine almost constantly throughout the illness. The patient had seven attacks of hematuria, one or more years apart, usually following inflammations of the throat. During the last six months the symptoms were very severe. At necropsy contracted kidneys and an enlarged heart were found.

34. Aufrecht: Eine zwanzig Jahre dauernde Nephritis nach Scharlach, Deutsch. Arch. klin. Med. **42**:517, 1888.

Mann [35] described a very similar case of twenty-eight years' duration, which was under his observation the entire period. An acute nephritis began in 1866 at the age of 14 years, following an attack of scarlet fever. The acute symptoms subsided in a few weeks and the patient regained her health, except that albumin continued to be present in the urine. For seven or eight years after the original attack the patient had occasional subacute attacks some of which were accompanied by edema. Attacks usually followed exposure to cold and usually lasted two or three weeks. From 1880 on the urine became of lower specific gravity and increased in amount. Arterial tension gradually rose. Retinal hemorrhages and uremia preceded death in 1894. At necropsy the heart was found hypertrophied. The kidneys were contracted, each weighing about 2 ounces.

Löhlein had a case in which the acute attack occurred in 1894 at the age of 16 years. The patient spent 1897-99 in the army. In 1901 he developed symptoms of contracted kidneys and died with anuria, severe edema and uremic symptoms. Löhlein believes that a chronic nephritis "not very rarely" develops from an acute nephritis of scarlet fever or angina.

Eichhorst [36] reported two cases of intermittent albuminuria of several years' duration which followed scarlet fever. The patients finally recovered. Another of his patients developed a hemorrhagic nephritis on the fourth day of an acute tonsillitis. He still had blood, casts and albumin in the urine two years later.

Sorensen and Volhard and Fahr believe that scarlet fever is rarely responsible for a chronic nephritis. Reichel says "numerous observations show that a chronic nephritis may develop from a scarlatinal nephritis."

Ernberg [37] located forty of 106 adults who had had acute nephritis before the age of 15 years, and found normal urine in all. In sixteen of fifty adults who had had acute nephritis between the ages of 15 and 30 years he found normal urines in all but four.

Reports on soldiers who have had acute nephritis (war nephritis) show that many of them have not recovered completely (Robinson,[38] Patterson [39]). There are indications that some of these men will develop chronic nephritis.

35. Mann, J. D.: On Granular Kidneys Following Scarlatinal Nephritis, Lancet **2**:670, 1895.

36. Eichhorst, H.: Ueber chronische intermittierende Albumenurie als Nachkrankheit infektioser Nephritiden, Med. Klin., 1919.

37. Ernberg (cited from Hill): Boston M. & S. J. **177**:313, 1917.

38. Robinson, A. R.: The After History of War Nephritis, J. Roy. Army Med. Corps **30**:205, 1918.

39. Patterson, D. W.: British M. J. **2**:431, 1921.

Our Cases 48 to 51 are apparently examples of chronic glomerulonephritis developing from acute cases. It is possible that in Case 48 the sudden onset of symptoms was due to a severe exacerbation of a chronic nephritis and not to a primary acute attack. In Case 51 there is abundant microscopic evidence of an old attack of acute interstitial nephritis such as occurs in scarlet fever, and this observation is strong support for the assumption that his weakness after scarlet fever was due to nephritis. Cases 50 and 51 seem to be clean cut cases.

The evidence accumulated shows that a chronic nephritis may develop from a typical acute case but that such instances are rare. The great majority of acute cases do not terminate in chronic disease, and the great majority of chronic cases do not begin as clinical acute nephritis. But this does not exclude the origin of chronic nephritis from a "clinically veiled" acute case, as Löhlein has expressed it. It is conceivable and even probable that an infection of slow development may occur without producing intense clinical symptoms. If edema failed to develop there would be a striking change in the clinical picture.

The clearly established fact that an occasional case of chronic nephritis does develop from an acute case seems to prove that at least a few cases of chronic nephritis are due to infection, since the infectious nature of the acute type can hardly be denied.

2. *The Blending of the Different Clinical Types of Glomerulonephritis.*—It is maintained by some observers that chronic nephritis has very little clinical resemblance to the acute type and might therefore have a different etiology. But such a view encounters difficulties when a large series of cases is studied. Senator was impressed with the fact that the nephritides form a continuous group with numerous intermediate cases between the acute and chronic types. The recognition of a subacute type by most observers is a further support of this view.

Nine of our cases (Cases 33 to 41) have been classed as subacute, but some of these might be considered acute by other observers. Cases 42 to 45 show structural changes somewhat more advanced than the subacute group but much less advanced than the typical chronic case. Case 43 was of at least one year's duration. This group (Cases 33 to 45) seems to us to illustrate gradual transitions between acute and chronic nephritis.

3. *Associated Infections.*—In the subacute group there are several cases with evidence of a preliminary infection. Case 33 began with acute pericarditis, traces of which were found at necropsy. Case 38 followed a cold and bronchitis which was apparently due to wetting of the feet. Old healed endocardial lesions were found in Case 33. In Case 35 there was jaundice early in the disease and a seropurulent

pleuritis was found at necropsy. In Case 36 symptoms of nephritis appeared three days after an injection of neo-diarsenol. There was a severe attack of arthritis in Case 41 four months before death, and thrombosed pelvic veins were found in Case 37. Ophüls found in most of his subacute cases a comparatively recent history of tonsillitis, rheumatism or other streptococcic infection.

In the chronic group there were sixteen cases without history of a primary infection and without associated old infections at necropsy. The clinical data in some of these were, however, incomplete. In the other cases there was some evidence of a primary infection. Old healed mural or valvular lesions were found twice (Cases 45 and 63). One patient (Case 52) had a chronic purulent otitis media of many years' duration, as well as frequent attacks of tonsillitis. Two other patients (Cases 54 and 62) gave a history of frequent attacks of tonsillitis. A number of the patients had had scarlet fever, and microscopic evidence of scarlatinal interstitial nephritis was found twice (Cases 51 and 60). The high incidence of tonsillitis and scarlet fever among persons who do not develop nephritis of course detracts from the value of our data. Two patients had had acute articular rheumatism (Cases 42 and 63). Four cases apparently followed acute nephritis.

On the whole, it may be said that the evidence of associated streptococcic infections is very convincing in the acute group, fairly good in the subacute, but not at all satisfactory in the chronic group. It does not seem to us that these data exclude the primary infection in the chronic case. The clinical data are often incomplete, the patient having forgotten things that happened several years before; or the primary infection may have been comparatively mild and ignored by the patient. The primary infection may heal in a short time. Even in acute cases following tonsillitis, the throat is usually about normal when the renal symptoms appear.

4. *Microscopic Evidence.*—The strongest argument for the infectious origin of chronic glomerulonephritis is obtained from microscopic study of the kidneys. Every abnormal glomerulus in a chronic kidney is readily explainable as the outcome of one or more acute inflammatory processes. The various forms of acute glomerulonephritis are recognizable in their healing stages in the chronic kidney, and sometimes even acute glomerular lesions are seen along with the chronic changes.

The proliferative form of glomerulitis is the most important since it causes permanent closure of the capillaries. When there is complete closure of all the capillaries in the acute stage (Fig. 5) the tubule atrophies rapidly and the glomerulus soon becomes small and hyaline. If, however, some of the capillaries are not closed the glomerulus continues to function to some extent and undergoes hyaline degenera-

tion only in the closed portions (Figs. 19 and 17). In chronic nephritis practically all the glomeruli are damaged by closure of part of the capillary network.

The epithelial crescents which characterize the extracapillary type of glomerulitis are easily recognized in chronic nephritis. When first formed the crescents are composed of cells with distinct nuclei and well stained cytoplasm (Fig. 8). On long standing they gradually become homogeneous and hyaline. All intermediate stages are recognizable (Fig. 15). Extracapillary lesions were numerous in five of the subacute cases. In the chronic group old crescents were found in twelve of twenty-eight cases. They were numerous in four, frequent in three, and rare in five cases. Epithelial crescents have been produced experimentally by bacterial inoculations (Pernice and Scagliosi[40]). Their presence in chronic nephritis is a strong argument for the infectious nature of this disease.

Exudative glomerulitis is characterized by polymorphonuclears in the capillaries, and when this is combined with the proliferative type the leukocytes become imprisoned in the closed capillaries (Figs. 12, 13 and 14). Frequently masses of polymorphonuclears are retained for an indefinite time in the lumina of tubules or in the interstital tissues. This gives another form of evidence by which we may prove that a previous acute infection was present.

Polymorphonuclears in closed glomerular capillaries were found in six subacute and thirteen chronic cases, sometimes in large numbers. Masses of pus cells were found in the tubules in six chronic cases. There were only seven chronic cases that had no epithelial crescents and no pus cells in glomeruli or tubules.

The histologic evidence is convincing that the glomerular lesions in chronic kidneys are the healing stages of acute lesions, and if one admits that acute glomerulitis is due to infection it is difficult to escape the conclusion that chronic glomerulonephritis is due to the same cause.

Progressive Character of Chronic Glomerulonephritis.—It is known that patients with chronic nephritis may live many years. A duration of ten years is frequently seen and Mann's patient lived twenty-eight years. During the course of the disease there may be long intervals when the patient is in good condition with only a trace of albumin in the urine and fairly efficient kidneys as shown by functional tests. But at irregular intervals acute exacerbations occur, characterized by the usual symptoms of renal insufficiency. The patient improves after many of these acute attacks but finally develops a permanent renal insufficiency which soon ends in death. These exacerbations are well

40. Pernice and Scagliosi: Beitrag zur Aetiologie der Nephritis, etc., Virchows Arch. f. path. Anat. **138**:521, 1894.

illustrated in the excellent case records published by Mann and Aufrecht. They seemed to be due usually to exposure to cold in Mann's patient and to throat infection in Aufrecht's. Emerson [41] has recently emphasized the importance of these acute exacerbations in causing progressive destruction of the kidneys. He attributes these exacerbations to infections, chilling of skin, errors in diet, too much exercise, etc., and believes that chronic nephritis is not necessarily a progressive disease.

Our clinical data are not complete enough to warrant an extensive analysis of this topic, but there are records of acute exacerbations in eight patients (Cases 48, 49, 51, 52, 53, 57, 59 and 69). In Cases 49 and 51 the exacerbations followed attacks of sore throat.

In Case 51, in addition to the chronic changes, a number of fairly recent glomerular lesions were found, which were in all probability due to the severe throat infection which developed two months before death. In Case 52 a chronic purulent otitis media was present. The kidneys of this patient showed abundant evidence of a recent infection, viz., acute glomerulitis, fresh purulent exudate, etc. In these two patients at least there is convincing evidence that fresh infection contributed to the destruction of the renal tissue. Löhlein mentions rare instances in which acute glomerulitis is found in chronic kidneys.

Both the clinical and the pathologic evidence, therefore, seem to support the view that the downward progress of chronic glomerulonephritis is largely due to recurring infection. These infections are probably not often focal in character, but it seems a reasonable inference that known foci of infection, such as diseased tonsils, abscessed teeth, etc., should receive attention. An effort should be made to protect the chronic nephritic against infection, but diseased glomeruli are abnormally sensitive to bacterial toxins and glomerular injury will probably occur no matter how careful the patient may be. Throat infections and exposure to cold are to be especially avoided. The influence of diet and excessive muscular effort in causing exacerbations is not well established.

In explaining the downward tendency of chronic nephritis after renal insufficiency has developed another factor should be considered. Dr. Hilding C. Anderson,[42] in some experiments carried on in this laboratory, has found that a permanent renal insufficiency may be produced by the surgical removal of about three-fourths of the renal tissue. In the course of a few weeks the kidney remnant undergoes degeneration which is not explainable on the basis of obstruction or infection and seems to be due to excessive functional strain. If these

41. Emerson, C. P.: The Acute Element in the Chronic Nephropathies, J. A. M. A. **77**:745 (Sept. 3) 1921.

42. This paper is being prepared for publication.

conclusions be correct they may be applied to the final stages of chronic nephritis in man.

Atrophy of the Renal Tubule.—Löhlein's interpretation of tubular atrophy as a disuse atrophy is in accord with our observations. From a study of serial sections it has been observed that the size of the tubule corresponds closely to the permeability of the glomerulus and that the tubule disappears when the glomerulus becomes completely hyalinized. It has been claimed that the atrophy of the tubule is due to inadequate blood supply because of the closure of the glomerular vessels; but one frequently sees atrophic tubules surrounded by well filled capillaries and there are free anastomoses between the capillaries of adjacent tubules. Besides, Dehoff [43] has shown that the terminal branches of the interlobular arteries pass directly to the capillary network of the tubules. Tubular atrophy occurs as readily at the surface of the kidney as elsewhere.

The evidence that chronic glomerulonephritis is due to infection may be summarized briefly as follows:

There is abundant clinical and pathologic evidence for the infectious origin of the acute type and good evidence for a similar origin of many subacute cases. When this is admitted there is no escape from the conclusion that the chronic type has a similar cause.

In our series there is a gradual transition from the acute through the subacute to the chronic type, and it is obvious that we are not dealing with different diseases. On clinical grounds alone a fundamental relationship between the different forms must be admitted.

An occasional acute case becomes chronic and it must be conceded that at least these chronic cases are due to infection. The structural changes in these kidneys are not different from those of other chronic cases.

The glomerular lesions in chronic kidneys are obviously healing and healed stages of acute glomerulitis. The old epithelial crescents and the closed capillary loops filled with disintegrated polymorphonuclears cannot be explained on any other basis.

Definite acute and subacute glomerular lesions are sometimes found in chronic kidneys. These cannot be satisfactorily explained except as exacerbations of an inflammatory process.

SUMMARY

Thirty-two cases of acute glomerulonephritis have been studied. In many of these cases death was due to extrarenal causes and early glomerular lesions are available for study.

43. Dehoff, E.: Die arteriellen Zuflüsse des Capillarsystems in der Nierenrinde des Menschen, Virchows Arch. f. path. Anat. **228**:134, 1920.

Degenerative, exudative and proliferative types of inflammation occur in the glomeruli. Proliferative changes are chiefly responsible for permanent glomerular damage.

Acute glomerulonephritis is nearly always due to some acute infectious process, usually a streptococcal infection. The bacteria gain access to the blood and it is probable that the injury is produced by the direct action of their bodies on the glomerular endothelium.

An occasional case of acute glomerulonephritis passes into the chronic form; but the great majority of chronic cases do not begin as frankly acute nephritis.

Acute glomerulonephritis is linked with the chronic form by numerous intermediate cases.

Glomerular lesions in chronic kidneys correspond to healing or healed stages of acute glomerulitis. Old epithelial crescents are common, and disintegrating polymorphonuclear leukocytes are frequently found in the closed glomerular capillaries and in the partially atrophied tubules. In a few chronic cases acute and subacute glomerular lesions were found, indicating acute exacerbations.

In chronic glomerulonephritis many glomeruli are obliterated completely and those persisting show permanent closure of a part of the capillary network. Function is carried on by damaged glomeruli, and is depressed not only because of reduction in the total number but also because of the reduced capillary network in those that persist.

The progressive nature of chronic glomerulonephritis is apparently due, in part, to repeated acute exacerbations.

All forms of glomerulonephritis are due directly to bacterial invasion of the glomeruli; and the various clinical and pathologic types depend on the degree and extent of the permanent glomerular injury.

BIOCHEMICAL STUDIES IN A FATAL CASE OF METHYL ALCOHOL POISONING*

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It is not sufficiently appreciated that methly alcohol is very toxic. For economic reasons, methyl (wood) alcohol is employed as a substitute for ethyl (grain) alcohol, in what may be termed comparatively innocent products, such as perfumes, hair tonics, skin lotions, polishes, varnishes, etc. Government analysts, not infrequently, find it employed in the manufacture of various extracts for the flavoring of food products. Since prohibition has come into force, pure methyl alcohol, being somewhat similar in odor and taste to ethyl alcohol, has been employed in the preparation of various alcoholic beverages. This in great part is due to ignorance and has resulted in many deaths.

The literature, both experimental and clinical, on this subject shows a preponderance of papers relative to the effects of this drug on the central nervous system, especially the brain and optic nerves, and little reference has been made to lesions elsewhere in the body. More recently the importance of an acidosis as the cause of the more general signs and symptoms in methyl alcohol poisoning has been emphasized.

Little consideration has, however, been given to the changes which may occur in the kidney and other functions which may be manifested by variations from the normal chemical composition of the blood. In the following case special attention was given to this.

REPORT OF CASE

History (Hosp. No. 4937 '21).—A female, aged 70 years, was admitted to the medical wards of the Montreal General Hospital, into the service of Dr. H. A. Lafleur, with a history of having taken, with suicidal intent, Oct. 24, 1921, one drinking-glassful of wood alcohol. There was a history of vomiting prior to admission, but no vomiting occurred while she was in the hospital, a period of five days. On admission, the patient was drowsy and very much confused, so that it was not possible to obtain a detailed history.

Physical Examination.—The patient was a white female apparently of the stated age. There was slight cyanosis. The right pupil was larger than the left. Both reacted to light and accommodation. The tongue protruded in the midline with a slight tremor at the edges. There was a slight sweetish (acetone) odor to the breath. Physical examination otherwise was negative, with the exception of the fundi oculi. There was a slight effusion into the retina.

Course.—From the time of admission the patient grew progressively weaker. The respirations, at first of the Kussmaul (acidosis) type, became very

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shallow during the last two days. October 29 the cyanosis became more marked and there was clinical evidence of bronchopneumonia.

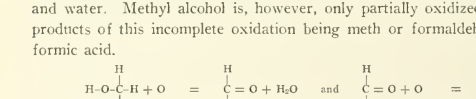
The patient was incontinent throughout her stay in the hospital, and it was not possible to obtain a specimen of urine at proper periods for chemical analysis. This was unfortunate as no examination could be made of the excretion of organic acids. A single specimen obtained by the house physician at the time of admission showed a clear urine, specific gravity 1.018, albumin 7.8 gm. per liter, many hyalin and granular casts, a few blood cells, and a trace of acetone. The accompanying table shows the combined results of the blood examination made every twelve hours during the patient's illness.

CHEMICAL ANALYSIS OF THE BLOOD

	Milligrams per 100 C.c.					CO_2	Per Cent.		Venous Oxygen		
Date	Uric Acid	Urea N	Creatinin	Sugar	Phosphorus	Volume	Hb.	mHb.	Content	Capacity	Unsaturation
Oct. 26, p.m.	3.1	42	1.6	...	....	46	..	..	...	....	....
Oct. 27, a.m.	5.3	102	2.3	...	....	39	..	..	...	....	....
p.m.	7.6	118	3.6	1822	8.8	39	..	..	...	....	....
Oct. 28, a.m.	8.4	130	4.0	225	11.2	34	..	..	...	....	....
p.m.	9.2	129	4.4	226	10.8	30	94	0	7.8	16.9	9.1
Oct. 29, a.m.	9.0	98	4.0	228	8.6	30	..	..	...	....	....
p.m. (3:30) 4 p.m. died	9.3	144	4.5	228	9.9	26	90	0	2.6	16.8	14.2

DISCUSSION

It has long ago been demonstrated[1] that the difference in the character and degree of intoxication between ethyl and methyl alcohol is due to the fate of these substances following their administration. Ethyl alcohol is oxidized into easily excreted products, carbon dioxid and water. Methyl alcohol is, however, only partially oxidized. The products of this incomplete oxidation being meth or formaldehyd and formic acid.



These partially oxidized substances are very toxic. It has been found[2] that formic acid is six times as toxic, and formaldehyd[1] is thirty-three times as toxic as methyl alcohol. Thus, from the oxidation of a toxic substance, products may result which are many times more toxic. This has an important bearing in the interpretation of the blood analysis.

1. Hunt, R.: The Toxicity of Methyl Alcohol, Johns Hopkins Hosp. Bull. **13**:2, 213, 1902.

2. Gettler, A. O., and George, A. V. St.: Wood Alcohol Poisoning, J. A. M. A. **70**:145 (Jan. 19) 1918.

KIDNEY FUNCTION

In experimental work with methyl alcohol changes in the kidney have been noted. Tyson and Schoenberg[3] in work on dogs found at necropsy dark purple and congested kidneys. Gettler[2] in one case, found marked parenchymatous degeneration of the kidneys. An analysis of the chemical findings of the blood in our case with reference to the urea nitrogen, uric acid, creatinin and phosphorus shows that rapid changes occurred in the kidney function. The uric acid content increased from 3.1 to 9.3 mg. per hundred c.c. in less than six days. The urea nitrogen content increased from 42 to 144 mg. per hundred c.c., and the creatinin content from 1.6 to 4.5 mg. per hundred c.c. blood in the same period. The acid soluble phosphorus varied from 8 to 11 mg. per hundred c.c. blood calculated as phosphorus (P). So far as we know only one other case has been studied from this viewpoint, that of Harrop and Benedict.[4] Their findings differ entirely from ours. These authors found that the urea content of the blood was normal at one period, but remarkably low at another, 0.091 gm. per liter. This would correspond to 4.2 mg. urea nitrogen per hundred c.c. blood, which is exceedingly low. The blood phosphorus in their case was normal (3 mg. per hundred c.c. blood). Their patient recovered.

The initial high findings in our case may have been due to a previously existant chronic nephritis. There can, however, be no doubt that the rapid changes noted daily were due to the action of the poison. Such findings suggest a complete "renal block," and correspond to those occasionally found in the acute retention as seen in hypertrophy of the prostate, or the anuria of mercuric chlorid poisoning. That the kidney function was practically nil is also supported by the rapid increase in the uric acid and creatinin content of the blood. The patient took no food during these few days of illness. It may, therefore, be assumed that all the uric acid found was of an endogenous origin. If it is assumed that the average daily excretion (endogenous) of uric acid is between 100 and 200 mg., and that this amount is not excreted but is distributed throughout the blood, it will account for the daily increase noted. The anatomic findings appear to corroborate this view.

BLOOD SUGAR

Hyperglycemia was present throughout the course of the disease. The lowest concentration of sugar, found at the first examination, was

3. Tyson, H. H., and Schoenberg, M. H.: Experimental Researches in Methyl Alcohol Inhalation, J. A. M. A. **63**:915 (Sept. 12) 1914.

4. Harrop, G. A., and Benedict, E. M.: Acute Methyl Alcohol Poisoning Associated with Acidosis, J. A. M. A. **74**:1 (Jan. 3) 1920.

0.182 per cent. This gradually increased to 0.228 per cent. These findings seem difficult to interpret. Apparently, they can be attributed to the impairment in the kidney function, for such findings are not infrequent in advanced cases of chronic nephritis. It might, however, be assumed that the figures do not represent glucose, for the reason that on theoretical grounds methyl alcohol is oxidized to formaldehyd, and the latter is a reducing agent. Part of the reduction of the cupric oxid in the test might therefore be attributed to the presence of this agent. Virtually, however, it does not seem that this occurred. The studies of Denis and Aldrich,[5] who employed liquor formaldehyd for the preservation of blood specimens, show that the addition of this drug in certain amounts does not alter the results obtained in blood sugar estimation. Even if we assume that all the methyl alcohol taken by this patient was completely oxidized to formaldehyd and distributed throughout the body, its concentration in the blood would not reach the percentage that these authors found could be added to blood without interfering with the chemical estimation of sugar. An interesting observation of these same authors is that liquor formaldehyd prevents glycolysis for at least ninety-six hours in vitro. That this should occur in vivo is only conjectural. The impairment of the kidney function seems sufficient to account for the hyperglycemia noted.

ACIDOSIS

The plasma carbon dioxid combining power on admission was 46 volumes per cent. It eventually fell to 26 volumes per cent. Other factors which may lower the carbon dioxid combining power of the blood, such as increased pulmonary ventilation having been excluded, it may be assumed that an acidosis existed. An acidosis has previously been demonstrated[4] in the study of methyl alcohol poisoning.[6] It has, however, been attributed to the failure of the body to completely oxidize methyl alcohol with the production of formic acid. The acidosis has been found[7] to be associated with an increase in the excretion of organic acids, lactic and formic. In our case the retention of phosphates in the blood would also explain part of the acidosis.

It does not appear to be unreasonable, on theoretical grounds, to suggest that the acidosis may, in large part, be due to the formation in the body of methylene derivatives, from the action of the formaldehyd on the amino-acids present. These derivatives are more

5. Denis, W., and Aldrich, M.: Note on the Preservation of Specimen of Blood Intended for Blood Sugar Estimation, J. Biol. Chem. **44**:203 (Oct.) 1920.

6. Haskell, C. C.; Hileman, S. P., and Gardner, W. R.: The Significance of the Acidosis of Methyl Alcohol Poisoning, Arch. Int. Med. **27**:71 (Jan.) 1921.

7. Van Slyke, D. D.: Studies of Acidosis, J. Biol. Chem. **41**:567 (April) 1920.

strongly acid in reaction owing to the destruction of the basic properties of the amino group, and, therefore, should effect the acid base equilibrium of the blood. Such a reaction is readily demonstrated in vitro. The Henriques-Sörensen formol titration of amino-acid nitrogen is based on this principle[8] as is shown in the following equation:

$$\begin{matrix} \mathrm{R.\ CH.\ NH_2} \\ \mathrm{COOH} \end{matrix} + \mathrm{6CH_2O} \rightarrow \begin{matrix} \mathrm{R{-}CH{-}N{:}\,CH_2} \\ \mathrm{COOH} \end{matrix} + \mathrm{H_2O}$$

Also the production of free acids from the action of liquor formaldehyd on neutral ammonium salts in the body does not seem unreasonable and may explain part of the acidosis, as is shown in the following equation:

$$4\ \mathrm{NH_4Cl} + 6\ \mathrm{CH_2O} = \mathrm{N_4(CH_2)_6} + 6\ \mathrm{H_2O} + 4\ \mathrm{HCl}$$

An interesting observation along these lines is that of Gregnolo who found after the injection of methyl alcohol there was an increase in the hydrogen ion concentration of the serum.

CYANOSIS

From the time of admission to the hospital the patient exhibited a definite cyanosis. This was very slight at first, but became more marked during the progress of the disease. Very little reference to biochemical studies could be found in the literature on the relation between methyl alcohol poisoning and cyanosis, although this relation has frequently been noted clinically. An effort was made to determine the cause in our case. An analysis was made of the oxygen content, oxygen capacity and oxygen unsaturation of the blood.

It might be recalled that the oxygen content represents the total oxygen combined with hemoglobin, and otherwise, circulating in the blood at the moment and site of withdrawal. The oxygen capacity represents the total oxygen the blood could hold if it were completely saturated with oxygen. The oxygen unsaturation[9] represents the difference between the oxygen capacity and content. The method employed for the estimation of the oxygen was that of Van Slyke.[10] It has been shown[11] that if the blood is completely saturated with oxygen in the lungs, the oxygen unsaturation of the venous blood may increase from 13 to 14 volumes per cent. before cyanosis appears. If it appears at less than this figure arterial unsaturation may be assumed. It will be noted in the chart that at the first estimation the oxygen

8. Hawk: Practical Physiological Chemistry, Ed. 6, Philadelphia, P. Blakistons Sons Co., p. 526.

9. Lundsgaard, C.: Studies of Oxygen in Venous Blood, J. Biol. Chem. **33**:133, 1918.

10. Van Slyke, D. D.: Gasometric Determination of the Oxygen and Hæmoglobin of Blood, J. Biol. Chem. **33**:127, 1918.

11. Lundsgaard, C.: Studies on Cyanosis, J. Exper. M. **30**:271 (Sept.) 1919.

unsaturation was 9 volumes per cent. Assuming, therefore, that arterial unsaturation may have existed, the cause of this under the circumstances (poisoning) was problematic.

An analysis of the daily clinical notes showed that no gross changes occurred in the respiratory or circulatory systems. Although no gross clinical changes need be evident, and still certain conditions may exist which prevent complete oxidation of the blood, it seemed important to determine whether any chemical alteration had occurred preventing the blood from taking up its normal load of oxygen. Stadie [12] pointed out that there are many substances which in vitro readily produce methemoglobin. These include certain oxidizing agents, reducing agents, organic bases, salts and bacteria. It will be noted in the chart that during the first examination of the blood for methemoglobin none could be found. The method employed was that of Stadie.[13]

The cyanosis gradually became more marked, and on the following day definite changes (bronchopneumonia) were found clinically in the lungs. The blood examination one half hour before death, at which period there was a very marked degree of cyanosis, also did not show the presence of methemoglobin. At this time the oxygen capacity was practically normal. It may, therefore, be assumed that in the case studied either no methemoglobin was formed, or that it was eliminated as rapidly as it was formed and played no important part in the production of the cyanosis.

REPORT OF POSTMORTEM EXAMINATION

Pathologic Report.—Acute parenchymatous nephritis; cloudy swelling of the heart and liver; bronchopneumonia.

DETECTION OF METHYL ALCOHOL IN THE BODY TISSUES

Experimentally it has been found that when methyl alcohol is given per rectum it is excreted by the stomach. It has also been demonstrated that the stomach may excrete methyl alcohol unchanged for a considerable time. It has been assumed [2] that the alcohol has a selective action for brain tissue. The brain in every one of six cases analyzed by this author was found to contain this alcohol. For these reasons both the brain and stomach tissues were analyzed in our case.

After a critical study of the fifty-eight methods proposed for detecting methyl alcohol, Gettler [14] classified them in order of their

12. Stadie, W. C.: Studies on Blood Changes in Pneumonoccic Infections, J. Exper. M. **33**:627 (May) 1921.

13. Stadie, W. C.: A Method for the Determination of Methaemoglobin in the Blood, J. Biol. Chem. **41**:237 (Feb.) 1920.

14. Gettler, A. O.: Critical Study of Methods for the Detection of Methyl Alcohol, J. Biol. Chem. **42**:311, 1920.

efficiency. Those accepted as reliable, extremely sensitive, and involving little technical difficulty were employed. The method employed in this case is based on the oxidation of the methyl alcohol into formaldehyd and the detection of the latter by various color reactions. Potassium bichromate and concentrated sulphuric acid was used as the oxidizing agent. In detail the method was as follows:

Method.—In order to preserve the stomach contents the stomach was tied off at the cardiac and pyloric ends and removed in toto This was then passed through a meat grinder and minced to a fine pulp. This pulp was then placed in an 800 c.c. Kjeldahl flask to which was added 400 c.c. water and sufficient concentrated sulphuric acid until a distinct acid reaction was obtained. This was then distilled and 200 c.c. of the distillate was neutralized to phenolphthalein with tenth normal sodium hydroxid and acidified with 5 c.c. of concentrated sulphuric acid, cooled, and 0.1 gm. potassium bichromate added and dissolved. This was then redistilled. To this final distillate the various color tests were applied.

1. To 3 c.c. distillate was added 5 c.c. concentrated sulphuric acid. This was cooled. The addition of a few milligrams morphin sulphate yielded a violet color. Test positive.

2. Test 1 was repeated with the morphin replaced by apomorphin. A violet color resulted. Test positive.

3. To 3 c.c. of the distillate were added two drops of a 2 per cent. solution of phenol. This was stratified on a layer of concentrated sulphuric acid. A red ring was noted at the junction of the two fluids. Test positive. Methyl alcohol was thus detected in the body tissues six days after its ingestion.

SUMMARY

In a fatal case of methyl alcohol poisoning changes had occurred in the renal and other functions as evidenced by variations from the normal chemical composition of the blood. These, in themselves, disregarding other well known factors, may account for the actual cause of death. Methemoglobin played no important part in the production of the cyanosis noted. Methyl alcohol could be detected in the tissues examined six days after the ingestion of the drug.

REVERSED RHYTHM OF THE HEART *

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I purpose, in this communication, to emphasize the distinction that should be made between the terms "reversed mechanism" and "reversed rhythm" of the heart.

The term "reversed mechanism" should be confined to express a reversal of the mechanism of impulse formation and conduction. Normally, the impulse originates in the sinus and traverses the auricles to be conducted through the auriculoventricular junctional tissues into both ventricles. In reversal of the mechanism, the impulse first originates in the auriculoventricular node, or the junctional tissues, or at a lower level in the heart and travels backward into the auricular musculature. Thus the term "reversed mechanism" implies a direction of stimulus conduction opposite to the normal.

Illustrative of such cases may be mentioned instances of auriculoventricular rhythm. In these cases, a ventriculo-auricular (R-P) interval may be exhibited with inversion or distortion of the auricular (P) wave. Williams and James,[1] Heard and Strauss,[2] White,[3] and Robinson and Draper [4] have recorded cases of this type. Cohen and Fraser [5] reported a case in which auricular contractions, represented by an inverted P wave, resulted from the mechanical stimulus received from the contracting ventricles. Wilson [6] reported a case of ventricular extrasystoles transmitted to the auricles.

From the experimental side, a great deal of work has been done on the subject by Lewis and his collaborators,[7] Eyster and Meek,[8] Meakins,[9] Wilson [10] and others.

The term "reversed rhythm," on the other hand, does not attempt to interpret the direction of stimulus conduction. It expresses only a time relationship between the ventricular and auricular contractions, i. e., the ventricular beat immediately precedes the auricular beat.

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* From the Department of Cardiovascular Diseases, Beth Israel Hospital.

1. Williams, H. B., and James, H.: Heart **5**:109, 1913.
2. Heard, J. D., and Strauss, A. E.: Am. J. M. Sc. **155**:238, 1918.
3. White, P. D.: Arch. Int. Med. **16**:517 (Nov.) 1915.
4. Robinson, G. C., and Draper, G.: Heart **4**:97, 1912.
5. Cohen, A. E., and Fraser, F. R.: Heart **5**:141, 1913.
6. Wilson, F. N.: Heart **6**:17, 1915.
7. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, Chapters XV and XIX, 1920, Paul B. Hoeber, New York; Lewis, White and Meakins: Heart **5**:289, 1913; Lewis and White: Heart **5**:335, 1913.
8. Eyster and Meek: Heart **5**:227, 119, 1913.
9. Meakins, J.: Heart **5**:281, 1913.
10. Wilson, F. N.: Arch. Int. Med. **16**:989 (Dec.) 1915.

This includes not only the cases of reversed mechanism, but also those cases in which the mechanism is normal, yet in which the ventricular contraction is delayed and, therefore, is grouped together with the following auricular contraction. In these cases, the auriculoventricular node discharges its impulse, in point of time, ahead of the sinus node, yet without reversal of the mechanism.

The case reported by Norrie and Bastedo [11] and entitled by them "reversed rhythm of the heart" is probably not, as they believed, a case of reversed mechanism. It is a case of heart block due to digitalis in which the beat of the auricle followed that of the ventricle. Their explanation that in their case, "the impulse to beat arises in the ventricle instead of at Keith's node and is conducted along the auriculoventricular bundle in a direction the reverse of normal" leaves room for question. Their published polygraphic curves might be interpreted as delayed P-R conduction, the auricular waves being related to the following ventricle. Thus their case is one of reversed rhythm, but probably not of reversed mechanism.

Lewis [12] described a case of premature beats arising in the a-v tissues in which the P wave was upright and of normal contour. From this fact, together with the varying P-R intervals, he concluded that the auricles were responding to the normal pacemaker while the ventricles were responding to an impulse arising low in the auriculoventricular bundle.

In Cushny's [13] earlier observation that reversed mechanism can be produced by injecting aconitin into the circulation of dogs, no electrocardiograms were recorded. In two instances, Cushny expressed the possibility that reversal of the rhythm may have occurred without reversal of the mechanism.

I desire now to give the observations in a case that presents periods of reversed rhythm without reversal of the mechanism and various features of interest associated with transitory partial heart block.

REPORT OF CASE

H. T., Russian, aged 46, gave a negative family history.

Past History.—He had measles and scarlet fever in childhood and occasional attacks of tonsillitis since. When he was 36 years old, he passed minute urinary calculi. The last attack occurred when he was 39 years old. His habits were good and he denied venereal disease.

Present Illness.—His present illness began when he was about 40 with a feeling of "heartburn" after meals which was relieved by sodium bicarbonate. For six months he had slight precordial pain which was worse with psychic depression. He had hunger pains during sleep and a pressing sensation in the

11. Norrie, V. H., and Bastedo, W. A.: St. Luke's Hosp. M. & S. Rep. No. 2
12. Lewis, T., and Allen: Am. J. M. Sc. **145**:667. 1913.
13. Cushny: Heart **1**:1. 1909.

chest. At times, he had a feeling of choking and a feeling of dizziness lasting fifteen minutes together with a tingling sensation, as he described it, in the precordium and below the angle of the left scapula.

Physical Examination.—He had large follicular tonsils. His heart showed no enlargement, and no murmurs or accentuations were audible. The muscular quality of the first sound was deficient at the apex. The apex beat and the

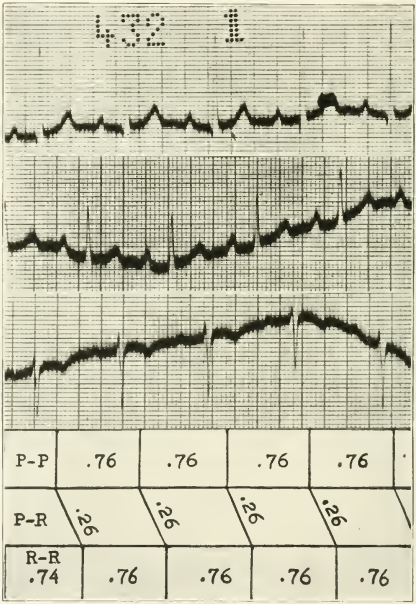

Fig. 1.—Showing a period of normal auricular and ventricular sequence and normal rhythm.

first sound, on the first examination, were distinctly and audibly alternans in character, and visibly so over the jugular. (This is explained later by the electrocardiograms.) Respiration increased the heart rate. Exercise increased it with some irregularity, the nature of which it seemed impossible to ascertain from physical signs alone and even from polygraphic tracings alone. Strenuous

exercise was tolerated without discomfort and produced no abnormal pulse or blood pressure reactions.

The urine was negative.

Cardiographic Studies.—The cardiograms show, at times, a regular heart with the normal auricular and ventricular sequence and normal rhythm (Fig. 1). The sinus rate is 79 a minute and the conduction

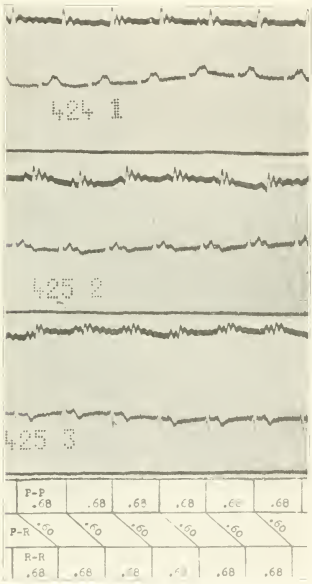

Fig. 2.—Showing delayed P-R conduction, with grouping of the R, P and T waves. Jugular tracing above and radial below.

between auricles and ventricles is 0.26 of a second. The only significant abnormality is the inversion of the T wave in Lead III.

The normal rhythm, however, is not permanent and can be easily disturbed by various influences which act on the circulation, on the myocardium and on the vagus nerves.

The conspicuous change that at times seems to occur spontaneously, and can easily be induced, consists of a moderate degree of sinus irregularity and a delay in conduction of the stimulus from the auricle to the ventricle. This is illustrated in the first cardiogram taken (Fig. 2). In this record, the action is regular. The auricular (P) wave is followed by the ventricular stimulus after a delayed conduction of 0.60 of a second. As the interval between beats is only slightly more than this (0.68 of a second), the P wave immediately succeeds the R and gives the picture of reversed rhythm where the R, P and T are grouped together in this respective order. The P wave is upright and normal in its contour.

The carotid wave is 0.18 of a second after the beginning of the Q R S wave. The auricular wave is seen 0.18 of a second after P and is very prominent because it contracts during ventricular systole and

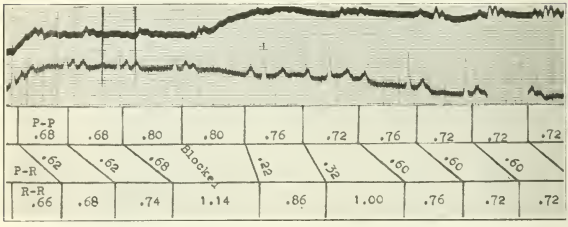

Fig. 3.—Showing the effect on the heart mechanism of taking a deep breath. The two vertical lines are the signal.

forces the blood back into the jugular veins. From the jugular tracing alone, the record could not be interpreted correctly. The carotid (c) wave would be thought to be the auricular wave and the following auricular wave would be considered ventricular because of the correct time relation between them and of their relative prominence. This record peculiarly demonstrates the indispensability of the electrocardiographic record in the interpretation of certain cases.

Effect of Vagus Stimulation.—The record following is a continuation and shows the effect on the heart mechanism of taking a deep breath indicated by the signal in Figure 3. The sinus is promptly slowed and there is a delay in conduction; the latter effect, on the junctional and bundle tissues, predominating and producing transient heart block. This is illustrated by the figures in the subjoined table showing the time relations between the various waves. The first

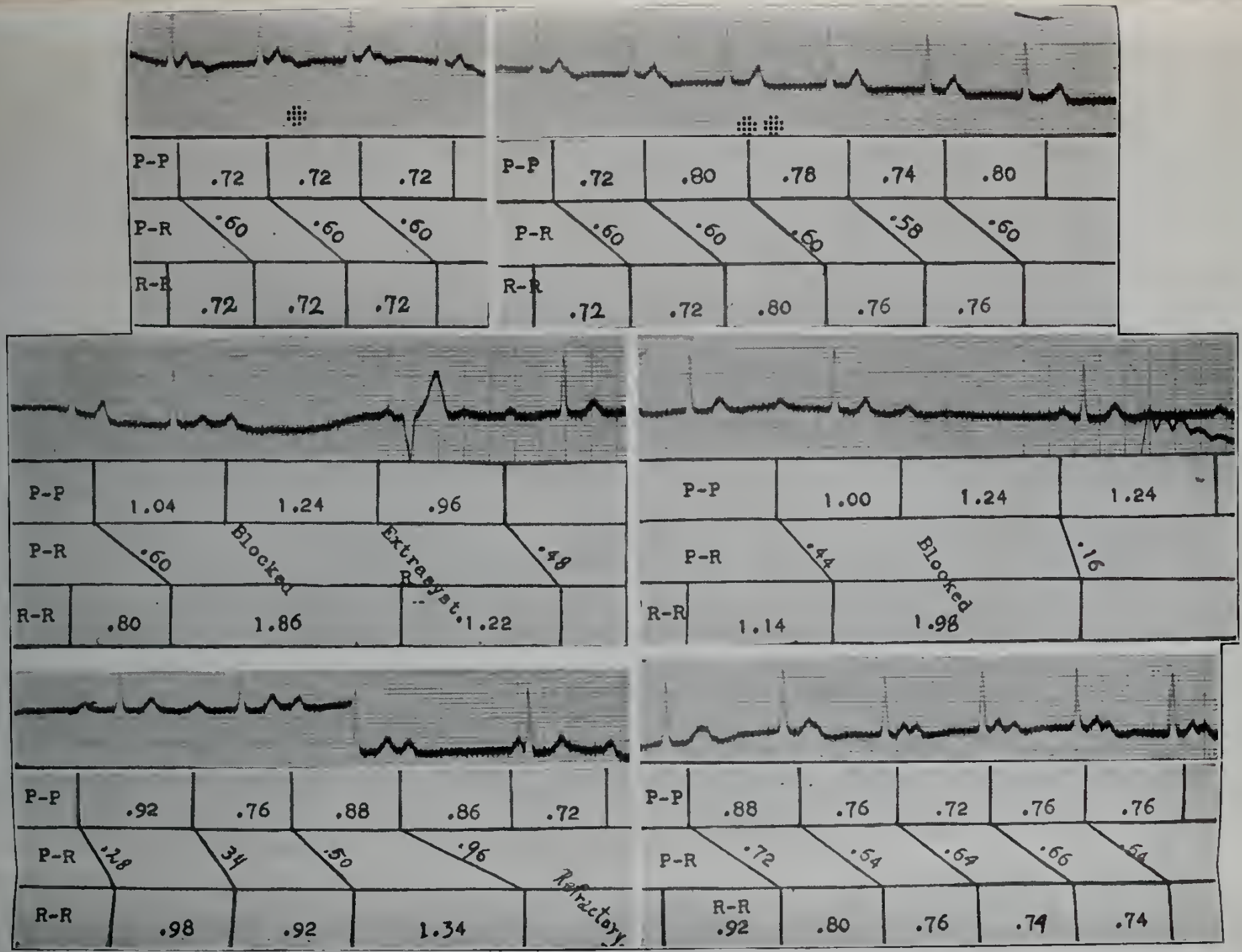

Fig. 4.—Showing the cycle of events during continued ocular pressure.

P wave after the signal is blocked, and in the following cycles, conduction, after having recovered, increases progressively until it is again 0.60 of a second.

Ocular pressure had a very similar, but much more marked effect. The sinus slowing and the heart block increased with the increase of pressure. One ectopic ventricular escape occurred after a period of block.

The cycle of events during continued ocular pressure is illustrated in the series of strips in Figure 4, the original reversal of rhythm returning after the effect of ocular pressure subsided.

Effect of Exercise.—During a period of normal rhythm (Fig. 1), the patient was instructed to exercise, the exercise consisting of hopping on one foot one hundred times. After this, the electrocardiogram showed a slight increase in the rate of the beat. About three

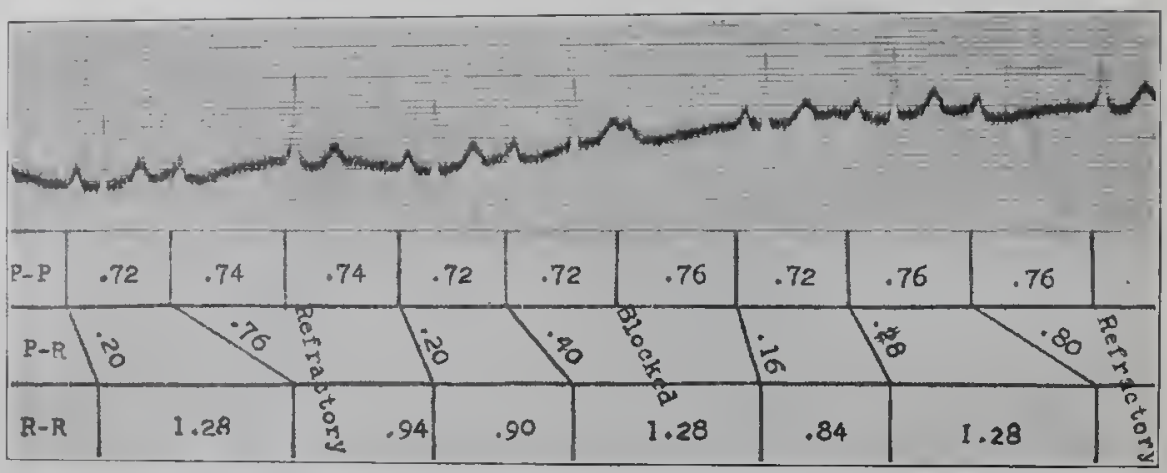

Fig. 5.—Showing the progressive increase of the block after exercise.

minutes after the exercise, while the patient was seated, the property of conduction suddenly began to show easy fatigue. A normal cycle took place with a normal P-R interval. The next cycle showed an increased P-R interval; the next might show a still further increase in the block and finally an auricular beat would be blocked or an auricular beat might occur simultaneously with a delayed ventricular beat; after this a repeated auricular beat would be promptly transmitted, conduction having recovered. This is illustrated in Figure 5.

Effect of Amyl Nitrite.—Amyl nitrite was administered by inhalation after a sufficient amount of rest following the exercise. A long record was taken during the entire period of inhalation. The rhythm just before inhalation was found to be normal and the amyl nitrite did not affect this rhythm. There was practically no increase in heart rate. As is usual, it depressed the height of the T wave. With the

elimination of its effect, the P wave returned to its previous height and a distinct U wave became evident. There was no evidence of difficult conduction.

Effect of Atropin.—When the effect of amyl nitrite had subsided and the rhythm was still normal, atropin, 1 150 grain, was given hypodermically. The first record was taken twenty-five minutes after this. There became evident a sinus irregularity and a marked difficulty of conduction, a normal conduction period being followed by a prolonged period or by a blocked cycle. No a-v nodal beats developed. Sixty minutes after the atropin was given, a record showed less difficulty in conduction than before. In Lead I, taken first, a normal cycle was followed by cycles in which conduction was progressively prolonged and every fourth cycle was blocked. In Leads II and III taken immediately after, the prolonged conduction became constant at 0.46 of a second, the heart rate being eighty-three a minute; i.e., the P-P and R-R intervals were 0.72 of a second.

This case is evidently an early case of heart block with periods of normal conduction and an instability of the normal rhythm. The important question to determine is whether the defect in conduction is due to nervous influences or is more definitely organic, due to disturbances in circulation or disease of the myocardium.

The features that incline one to the latter supposition are: (1) The stimulation of the vagus produces a temporary moderate, but not constant, increase of the block: i.e., the vagus influence superimposes itself on some other basis which continues to act after the vagus stimulation has subsided; (2) the depression or paralysis of the vagus by atropin does not completely relieve the difficulty in conduction; (3) exercise, accelerating the heart, seems to have a beneficial effect on conduction, perhaps by improving the cardiac circulation; (4) the electrocardiogram shows inversion of the T wave in Lead III.

The tracings and the record of this case emphasize the distinction that should be made between reversed mechanism and reversed rhythm and show the importance of electrocardiographic analyses.

SOME OBSERVATIONS ON PAROXYSMAL RAPID HEART ACTION WITH SPECIAL REFERENCE TO ROENTGEN-RAY MEASUREMENTS OF THE HEART IN AND OUT OF ATTACKS*

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With the application of the more accurate means of clinical investigation in the past decade, some of the views previously held concerning pathologic processes necessarily have needed revision. This has been true particularly with regard to the disturbed mechanism of the heart beat ever since the recent interest in cardiographic work. There must take place also a similar revision of our views concerning cardiac dilatation when one applies, as a check to findings from percussion and palpation, measurements determined by roentgen-ray examination. Any clinician, who has confirmed the results as to the size of the heart determined by percussion and palpation, with roentgen-ray measurements, must feel somewhat doubtful in detecting changes in the heart size of less than 1 cm., and not infrequently he will find that his bedside figures are at a considerably greater variance from the roentgenogram.

A further point that seems rather hazy in the minds of many students is the matter of dilatation of the heart. Possibly, the comparison to an elastic sac expanding and contracting unconsciously has led us to think of the heart in similar terms. For some reason there is a common belief that the heart frequently dilates, and as the clinical condition improves this dilatation disappears. The absolute proof that this is a common occurrence in cardiac patients is lacking, for most of the observations are made by the ordinary methods of inspection, palpation, percussion and auscultation and not confirmed by roentgen-ray examination. No doubt, the former methods are quite sufficient in the great majority of cases for the proper clinical management of the patient, but they are insufficient for the establishment of reliable scientific data on which to base our knowledge.

It is with this purpose in mind that roentgen-ray observations were made on eleven patients during attacks of paroxysmal rapid heart action and after the heart had returned to normal rhythm. These conditions have frequently been regarded as instances of acute dilatation

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of the heart, especially before cardiographic studies enabled us to classify and describe them properly. Mackenzie[1] says:

> Even more striking because more sudden and violent, are the changes (meaning dilatation) that take place in certain cases of paroxysmal tachycardia. . . . I have seen these cases on several occasions shortly before an attack and watched the steady progress of the change. The hearts were normal in size, but in three hours' time the transverse diameter had increased by two inches, the face had become livid and the lips swollen. . . . In the course of twenty-four hours edema of the legs appeared and the liver became large. After some days the dropsy extended up the legs, the abdomen became distended and the urine scanty. With the cessation of the attack of paroxysmal tachycardia, the patients at once experienced relief, and in a few hours every vestige of heart failure had disappeared, and the heart itself returned to a normal size and rhythm. . . . I have seen many cases in which the inception of the nodal rhythm was followed by these changes.

Lewis,[2] writing on the effect of paroxysms of fast heart on the circulation, says:

> When the heart commences to beat more rapidly it decreases in size. Where the acceleration is great the arterial pressure falls considerably while the venous pressure rises; but with lesser degrees of acceleration the arterial pressure may remain steady or may actually rise a little. . . . But in long continued paroxysms, especially where the reserve power of the ventricular muscle is imperfect, the heart dilates, the fall of pressure is more profound and the blood stagnates in the heart and venous systems.

In this study are included eleven patients with paroxysmal rapid heart action, the clinical data of which are appended. Five had paroxysmal auricular tachycardia, three had paroxysmal ventricular tachycardia, one had paroxysmal auricular flutter and two had paroxysmal auricular fibrillation. In all cases the diagnosis of the type of disturbance was confirmed by electrocardiographic tracings. In order to determine whether the hearts dilated during the various upsets, roentgen-ray examinations were made while the rapid heart action was in progress and while the heart was beating at a normal rate. Measurements of the transverse diameter of the heart shadows were made, which with other details are given in Table 1. These examinations were made after the attacks had lasted varying lengths of time, in some instances days after the onset, in others an hour or so (Table 2).

It is not the purpose here to discuss the technic and details of the roentgenological methods of heart examination. The method most used in this country at the present time for the measurement of the heart shadow is the teleroentgenogram, or the seven-foot plate. The determination of slight or moderate degrees of cardiac enlargement presents some difficulty even by the roentgenological method, because the shadow on the plate is merely a silhouette and because of individual variations associated with sex, height, weight, habitus, etc. The "cardio-

1. Mackenzie, J.: Diseases of the Heart, Oxford University Press, 1908, pp. 199-200.

2. Lewis, T.: Osler and McCrae's Modern Medicine, 1915, p. 87.

thoracic ratio" has been proposed by Danzer [3] as a convenient standard for determining whether the heart shadow is larger than it should be for the particular individual. In a study of more than five hundred cases he found that normal hearts cast a shadow the transverse diameter of which is 50 per cent. or less of the internal diameter of the chest shadow measured at its widest point, usually about the level of the fifth interspace anteriorly. This relation of the shadow of the heart to that of the thoracic cavity he terms the cardiothoracic ratio. Allowing

TABLE 1.—ROENTGEN-RAY MEASUREMENTS OF THE HEART SHADOW

Case	Diagnosis	Date	Approx. Target-Plate Dist.	Before, During, After Attack	Measurements in Cm.					Change in Mm. with Attack
					M R	M L	T D	I D C	C-T R	
1	Paroxysmal auricular tachycardia	12/23/14	30 in.	During	5.4	10.2	15.6	30.5	54%	
		1/ 8/15	30 in.	After	2.8	10.0	12.8	32.0	40%	28
2	Paroxysmal auricular tachycardia	7/ 6/16	84 in.	During	5.9	9.2	15.1	26.0	58%	
		7/ 8/16	84 in.	After	5.6	10.1	15.7	26.0	60%	—6
3	Paroxysmal auricular tachycardia	12/13/16	84 in.	During	5.1	11.1	16.2	27.5	59%	
		12/13/16	84 in.	After	4.4	10.8	15.2	27.5	55%	10
4	Paroxysmal auricular tachycardia	11/ 6/19	84 in.	Before	3.8	5.5	9.3	20.5	45%	
		11/ 7/19	84 in.	During	3.5	6.3	9.8	20.5	48%	5
		11/10/19	84 in.	After	3.9	5.6	9.5	20.5	46%	3
5	Paroxysmal auricular tachycardia	6/ 9/20	84 in.	During	6.8	9.0	15.8	23.0	69%	
		6/12/20	84 in.	After	5.9	10.0	15.9	23.0	69%	—1
6	Paroxysmal ventricular tachycardia	9/ 5/15	30 in.	During	3.3	6.7	9.9	28.0	35%	
		12/ 2/15	30 in.	After	3.0	7.6	10.6	30.0	35%	—7(?)
7	Paroxysmal ventricular tachycardia	11/ 3/16	30 in.	During	5.0	11.4	16.4	31.5	52%	
		11/ 9/16	30 in.	After	3.8	11.9	15.7	30.5	51%	7
8	Paroxysmal ventricular tachycardia	1/ 5/20	84 in.	During	4.8	13.1	17.9	27.0	66%	
		3/ 9/20	84 in.	After	5.2	11.3	16.5	27.0	61%	14
9	Paroxysmal auricular flutter	10/21/14	30 in.	During	7.3	9.6	16.9	32.0	53%	
		10/29/14	30 in.	After	7.1	9.4	16.5	32.0	52%	4
		2/ 5/15	30 in.	During	6.5	9.3	15.8	30.5	52%	
		2/ 8/15	30 in.	After	6.4	9.3	15.7	30.5	51%	1
10	Paroxysmal auricular fibrillation	3/12/20	84 in.	During	4.5	8.6	13.1	21.5	61%	
		3/15/20	84 in.	After	4.0	8.6	12.6	21.5	59%	5
11	Paroxysmal auricular fibrillation	12/14/20	84 in.	During	4.9	9.4	14.3	24.5	58%	
		12/16/20	84 in.	After	5.1	9.7	14.8	24.5	60%	—5

Measurements: M R = distance from the median line to the point of the heart shadow farthest to the right; M L = distance from the median line to the point of the heart shadow farthest to the left; T D = transverse diameter of the heart shadow, i. e. M R plus M L; I D C = Internal diameter of the chest shadow at about the level of the left diaphragm; C-T R = cardiothoracic ratio = T D divided by I D C.

a margin of 2 per cent. for error, he believes the heart to be enlarged when this ratio is more than 52 per cent., but points out that enlargement cannot be ruled out when the figure is less than 52 per cent., particularly in the ptotic habitus. As both the size and shape of the chest and the size and position of the heart vary with the above mentioned factors, especially with the habitus, this seems to be the best

3. Danzer, C. S.: Cardiothoracic Ratio, An Index of Cardiac Enlargement, Am. J. M. Sc. **157**:513, 1919.

method at hand for the determination of slight or moderate degrees of enlargement. It has been used in this study as a check on the actual measurements in centimeters of the heart shadow, especially in those cases taken at a distance of about thirty inches, in three of which there was apparently enough variation in the distance to make a difference of 1 or 2 cm. in the internal diameter of the chest. In Case 6, for example (Table 1), the heart shadow itself measured 0.7 cm. more

TABLE 2.—Clinical Data

Case	Med. No.	Age	Sex	Diagnosis	Wassermann	Symptoms of Heart Failure During Attack	Rate in Attack	Duration of Attack	Duration at Time of Roentgenoscopy	Dilatation
1	2092	38	M	Paroxysmal auricular tachycardia	—	Severe Severe	250 242	5 days 8 hrs.	3 days	Marked
2	4940	50	F	Paroxysmal auricular tachycardia, syphilis	++	Moderate	220	4½ da.	4 da.	None
3	5742	21	M	Paroxysmal auricular tachycardia, aortic insufficiency, mitral insufficiency, chronic myocarditis	—	Severe	162	Several hours	Few hours	Slight
4	12207	24	F	Paroxysmal auricular tachycardia, mitral stenosis	—	Moderate	233	2 hrs.	½ hr.	?
5	13577	50	F	Paroxysmal auricular tachycardia, chronic infectious arthritis	—	None	171	Several hours	2 hrs.	None
6	3324	64	F	Paroxysmal ventricular tachycardia, chronic myocarditis	—	Moderate	160	Several hours	Few hours	None
7	5593	50	M	Paroxysmal ventricular tachycardia, chronic myocarditis	—	Severe	160	Few hours	1 hr.	None
8	12646	64	M	Paroxysmal ventricular tachycardia, chronic myocarditis	—	Severe	165	36 hrs.	12 hrs.	Slight
9	1791	35	M	Paroxysmal auricular flutter, aortic stenosis and insufficiency	—	Slight Slight	178 178	12 da.+ 4 da.	11 da. 3 da.	None None
10	13074	38	F	Paroxysmal auricular fibrillation, mitral stenosis and insufficiency	—	Moderate	135	Several hours	1 hr.	None
11	*	26	M	Paroxysmal auricular fibrillation	..	Slight	120	2 da.	18 hrs.	None

* This was a private case of Dr. Paul D. White, Boston, who kindly offered it for use in this series, for which we wish to express our appreciation.

after than during the attack; but as the internal diameter of the chest shadow also was larger in the second plate, the cardiothoracic ratio was the same in both, showing that no definite change in the size of the heart shadow had taken place.

In the estimation of the size of the heart from its shadow on the plate three sources of error are to be considered: (1) magnification due to the divergence of the rays; (2) changes in the position of the

heart during the respiratory cycle, and (3) changes in the profile of the heart due to the fact that the chest is not pressed symmetrically against the plate during the exposure and spoken of as "rotation." It seems advisable to discuss these points very briefly.

The magnification due to the divergence of the rays is practically compensated for by increasing the distance between the target of the roentgen tube and the plate to approximately seven feet. The mathematically figured correction for the transverse diameter of the heart shadow taken at a target-plate distance of two meters, as given by LeWald and Turrell,[4] is 4 per cent., i. e., the true transverse diameter is 96 per cent. of that of the silhouette.

During ordinary quiet respiration the position of the heart changes very slightly, if at all. With full inspiration or forced expiration, however, there is a very marked change in the relation of the heart to the chest wall and in the physical axis of the heart, and consequently in the form and size of its silhouette. The transverse diameter of the heart shadow of one of us taken during quiet respiration at approximately 7 feet measured 14.3 cm., while that taken at the same distance but with full inspiration measured only 12.8 cm. At a thirty-inch distance with full inspiration the shadow was 14.1 cm. in diameter. Here the change in the heart shadow due to the descent of the diaphragm was slightly greater than that due to the magnification from the divergence of the rays. For this reason the standard teleroentgenogram is made during quiet respiration. Unfortunately the plates made in four of the cases in 1914-1916 were taken at a thirty-inch distance at full inspiration, the technic used for the study of the lung fields. This study, however, is not concerned so much with the exact size of the heart as with an estimation of the possible changes in its size which might occur during the course of paroxysmal rapid heart action. Therefore, we believe that two plates taken at approximately the same distance at the same period in the respiratory cycle will furnish data sufficiently accurate for this purpose, i. e., the comparison of the relative sizes of the heart shadow in the same patient on two different occasions.

The presence of rotation can very easily be determined by observation of the relation of the shadows of the sternoclavicular joints to that of the spine. Very slight degrees of rotation produce errors which are insignificant and which do not vitiate the observation. In this series it occurred in very few plates and in such slight degrees that it has been ignored.

4. LeWald, L. T., and Turrell, G. H.: The Aviator's Heart. Roentgen Ray Studies Under Conditions Simulating High Altitudes, Am. J. Roentgenol. **7**:67, 1920.

It is generally accepted that changes in the measurements of the heart shadow up to 0.5 cm. and in the cardiothoracic ratio of 2 per cent. are within the limits of error and may be discounted.

In estimating the change in the heart shadow we have used the actual difference in the transverse diameters and the difference in the cardiothoracic ratios. In a review of Table 1, one is readily impressed by the absence of any distinct dilatation in most of the cases. When it is remembered that changes of 0.5 cm. or less in the transverse diameter of the heart shadow and of 2 per cent. in the cardiothoracic ratio are within the limits of error, there remain only three cases in which an appreciable dilatation of the heart occurred. Case 1 shows the most marked change in the series. Here the heart dilated sufficiently to produce an increase of 2.8 cm. in the transverse diameter and of 14 per cent. in the cardiothoracic ratio. This patient was also seen in a similar attack some months later and a dilatation was again observed with an increase of 2.5 cm. in the heart shadow. Unfortunately, one of these plates was lost. The marked dilatation in this case probably was the result of the extremely rapid heart rate and the comparatively long duration, for nothing abnormal in the heart itself could be detected between attacks. Case 3 was a patient with severe valvular disease who showed clinical evidence of a markedly damaged myocardium. In this case there was an increase of 1 cm. in the transverse diameter and of 4 per cent. in the cardiothoracic ratio. Despite the short duration and the rather low heart rate during tachycardia (162), distinct dilatation occurred and may be explained by the poor condition of the heart that was evident when the rate was normal. Case 8 was an elderly colored man with a severe chronic myocarditis who had attacks of ventricular tachycardia. A roentgenogram taken during an attack, twelve hours after the onset, while the rate was 165, showed an increase of 1.4 cm. in the transverse diameter of the heart shadow and of 5 per cent. in the cardiothoracic ratio over the measurements made after the heart had returned to normal rate. This dilatation may be explained as in the previous case. In seven of the remaining eight cases the changes did not exceed the limit of error. In Case 4 questionable increase in the size of the heart occurred, the cardiothoracic ratio being 3 per cent. larger during than before the attack, and 2 per cent. larger during than after the attack. It is interesting that this patient, who had mitral stenosis, had considerable dilatation of the left auricle during the attack as is shown in Figure 1. In Cases 2 and 11 there was an apparent decrease in the size of the heart shadow during the attack.

The main interest in these roentgen-ray findings is the absence of definite dilatation in the majority of the cases. It is fair to say that, with the exception of Case 1, and possibly of Case 8, it would be impossible

to detect by percussion and palpation any of the changes that occurred in this series. For it must be appreciated that when a change in the transverse diameter of the heart shadow occurs, it may be divided into two portions, one to the right and one to the left of the midline. For example, in Case 3, to detect the difference of 1 cm. that occurred, it would be necessary to percuss an increase of 7 mm. to the right and 3 mm. to the left. It must not be understood that even the slight dilatation that escapes clinical detection is not significant, for if the transverse diameter of the heart increase 0.5 cm. it would mean considerable stretching of the muscle fibers and likewise a considerable increase in the heart volume. But the important point is that the dilatation is so slight in most cases that it cannot be detected on ordinary bedside examination, and that only in isolated cases is it very appreciable even when roentgen-ray examinations are made. It appears to us that the three factors that determine whether dilatation will occur are the duration of the attack, the rapidity of the ventricular rate during the attack and the general health of the heart. The longer the attack, the more rapid the heart rate and the more severely damaged the heart, the more apt it is to dilate.

Observations on the systolic, diastolic and pulse pressures were made on seven of the patients during the course of rapid heart action and again while the heart mechanism was normal. Our interest was aroused by Case 1. The patient, who had suffered serious accidents with three attacks, always showed a remarkably small pulse pressure during those in which he was observed. With such a sluggish circulation, it is not surprising that he developed gangrene of an arm, hemiplegia and aphasia.

In Case 1 (Table 3) the systolic pressure fell and the diastolic rose, resulting in a pulse pressure of 8 mm. as soon as eight hours after the onset of the attack although the patient had no demonstrable heart disease. This occurred because the rate was extremely fast, about 250 to the minute. Case 2, on the other hand, showed a very low pulse pressure of 10 mm. when the attack had lasted three days, but the change was only slight during another attack when the readings were made after it had lasted only sixteen hours. Case 4 illustrates the rapid development of a small pulse pressure, for within fifteen minutes after the onset of a rate of 233 it was only 12 mm., while nine minutes after the attack had ended the pulse pressure had risen to 18 mm. and three hours later to 24 mm. This rapid change took place because of the very fast heart rate and because the patient was already suffering from mitral stenosis. Similarly Case 7 showed a decrease in the pulse pressure from 31 mm. to 18 mm. and from 46 mm. to 14 mm. only a few hours after the onset of two attacks, although the heart rate was only 160. This is explained by the fact

that the patient was already suffering from chronic myocarditis. Likewise in Case 8, a chronic myocarditis, a small pulse pressure developed within one hour after the onset of tachycardia, although the heart rate rose to only 165. The last patient (Case 9), who had aortic stenosis and a low systolic pressure of about 90 mm., when the heart was beating normally, showed a pulse pressure of only 12 mm. three days after the attack of auricular flutter had begun, while the ventricular rate was

TABLE 3.—Blood Pressure Readings

Case	Diagnosis	Date	Heart Rate	Blood Pressure			Time of Blood Pressure Readings in Relation to Attacks
				Systolic	Diastolic	Pulse	
1	Paroxysmal auricular tachycardia	12/28/14	270	94	86	8	4 days after onset
		1/3/15	82	109	66	34	3 days after end
		7/14/15	242	84	76	8	8 hours after onset
2	Paroxysmal auricular tachycardia, syphilis (positive Wassermann)	7/ 9/16	217	134	114	10	3 days after onset
		7/ 7/16	80	110	75	35	1 day after end
		7/10/16	86	148	116	32	1 day after end
		7/14/16	192	98	65	30	16 hours after onset
		7/15/16	68	135	95	40	1 day after end
3	Paroxysmal auricular tachycardia, aortic and mitral insufficiency, chronic myocarditis	12/ 9/16	162	148	30	118	10 hours after onset
		12/13/16	90	200	[illegible]	200	1 day after end
4	Paroxysmal auricular tachycardia, mitral stenosis	11/ 5/16	130	129	95	34	2 days before attack
		11/ 7/16	203	176	124	52	15 minutes after onset
		11/ 7/16	258	158	129	29	17 minutes after onset
		11/ 7/16	225	134	122	12	19 minutes after onset
		11/ 7/16	140	156	108	48	9 minutes after end
		11/ 7/16	142	132	108	24	3 hrs. 22 min. after end
7	Paroxysmal ventricular tachycardia, chronic myocarditis	10/25/16	160	98	80	18	2 hours after onset
		10/30/16	90	103	72	31	3 days after end
		11/ 3/16	160	97	83	14	Few hours after onset
		11/ 7/16	86	114	68	46	3 days after end
8	Paroxysmal ventricular tachycardia, chronic myocarditis	1/ 3/20	84	145	95	50	1 day before onset
		1/ 4/20	164	115	94	21	1 hour after onset
		1/ 5/20	165	112	94	18	24 hours after onset
		1/ 5/20	163	110	80	30	5 hours after onset
		1/ 8/20	165	110	92	18	12 hours after onset
		1/19/20	82	124	92	32	12 hours after end
9	Paroxysmal auricular flutter, aortic stenosis and insufficiency	2/ 5/17	176	92	80	12	3 days after onset, average of 6 readings
		2/ 6/17	74	90	69	21	6 hours after end, average of 3 readings
	Averages.....	In....	164.7	113.5	90.4	22.1	
		Out....	94.2	126.7	81.4	45.3	

176; six hours after the attack had stopped the pulse pressure had risen to 21 mm.

This discussion, although it includes only seven cases with a comparatively small number of blood pressure readings, indicates that during attacks of rapid heart action there is a tendency for the pulse pressure to decrease. The extent of this diminution, like the occurrence of dilatation, will depend on the duration of the attack, the rapidity of the heart and the state of health of the heart muscle. It also shows that the pulse pressure may occasionally become dangerously low when

these three factors are sufficiently antagonistic to an efficient circulation. The figures at the bottom of Table 3 indicate that the decrease in pulse pressure is brought about by a fall in systolic pressure and an increase in diastolic pressure, for although there are some variations in the isolated observations, the average of all readings shows a fall of systolic pressure from 126.7 mm. to 112.5 mm., and a rise of diastolic pressure from 81.4 mm. to 90.4 mm. during attacks. Readings made on other patients with paroxysmal rapid heart action, not included in this study because no roentgen-ray observations were made, showed similar changes.

In addition to the roentgen ray and blood pressure determinations, a study of these cases showed that a leukocytosis and slight fever were not uncommon findings during the attacks of rapid heart action. In some instances they were quite striking, the temperature and leukocyte count falling to normal promptly after the attack was over. Six of the patients had a leukocytosis of from 13,000 to 22,000 during the upsets and two had a temperature of over 100 F. It does not seem likely that an actual infection had taken place which brought on the tachycardia, but rather that the fever and leukocytosis were the result of the cardiac upset.

SUMMARY

Roentgen-ray examinations and blood pressure studies were made on eleven patients with paroxysmal rapid heart action. Five had paroxysmal auricular tachycardia, three had paroxysmal ventricular tachycardia, one had paroxysmal auricular flutter and two had paroxysmal auricular fibrillation. Observations were made during the attacks and while the heart was beating normally.

It was found that in eight cases no appreciable dilatation of the heart occurred, in two it was definite but slight and in one it was considerable. These results indicated that in ten out of eleven cases it would have been impossible to detect with any certainty by percussion and palpation a change in the size of the heart.

In seven of the cases blood pressure readings showed that the systolic pressure was apt to fall and the diastolic pressure to rise, resulting in a low pulse pressure which in rare instances became very small, i. e., 8mm. This low pulse pressure may explain some of the symptoms that occur during the severe attacks.

It is suggested that the amount of dilatation and the decrease in pulse pressure are dependent on three factors; the duration of the attack, the rapidity of the ventricles during the attack and the state of health of the heart before the attack occurs.

In several cases a leukocytosis, even as high as 20,000, and a temperature of 100 F. developed with the attacks and quickly subsided as the heart returned to normal.

REPORT OF CASES

CASE 1 (Med. No. 2092).—*History.*—A baker, age 38, was seen at the hospital on numerous occasions for attacks of palpitation. The first attack occurred about four years before his first admission to the hospital. It lasted four days and during it he suddenly developed loss of memory which lasted for a year. The second attack occurred about one year later and continued for eight and one-half days. During the seventh day he developed a right hemiplegia which cleared up after six months, leaving a slight weakness of that side of the body. Two and a half years before the first admission he had the third attack. This lasted ten days, but on the eighth day he developed dry gangrene of the left arm which required amputation just below the shoulder. Dec. 26, 1914, following a fall downstairs, he noticed his heart beating irregularly and later rapidly. At times there were sharp gripping pains over the heart and a feeling of dizziness. He was short of breath after the onset but had no orthopnea, cough or edema. All the previous attacks began and ended suddenly. He entered the hospital Dec. 28, 1914.

Physical Examination.—This showed a well developed man with a very anxious expression on his face. His skin was covered with a profuse perspiration. Very rapid oscillatory pulsations were seen over the jugular bulbs. Heart examination showed an extremely rapid regular rate, 250 to the minute. No murmurs were heard. The second heart sound could not be heard. Lungs were negative, liver edge not felt, no edema of the legs. The fingers and lips were distinctly cyanosed.

The urine was negative. The blood showed 21,300 leukocytes, with 80 per cent. polymorphonuclears during the attack, and 7,700 two days later during normal rate. The temperature ranged around 101 F. during the attack and then fell to normal. The blood Wassermann was negative. Electrocardiograms taken during the attack showed paroxysmal tachycardia of auricular origin.

Course.—Numerous attempts to stop this attack by ocular and direct vagal pressure were unsuccessful. It stopped spontaneously two and a half days after admission. During the following two years the patient was observed in several similar attacks all of which were successfully ended by pressure over the carotid artery. During one of these further blood counts were made and a leukocytosis of 25,400 was found; there was no fever. The following day when the heart rate was normal the white count was 6,000. Between attacks examination showed the heart to be normal.

Blood pressure readings on the first admission to the hospital were: during tachycardia, systolic, 94; diastolic, 86; five and seven days later during normal rate: systolic, 100; diastolic, 66, and systolic, 114, diastolic, 84, respectively. Several months later during an attack: systolic, 84; diastolic, 76; one-half hour after the attack was ended by vagal pressure: systolic, 100; diastolic, 86. The following morning: systolic, 130; diastolic, 90. Roentgenograms were taken at a distance of about thirty inches during and after two attacks, and showed an increase in the transverse diameter of about an inch while the tachycardia was in progress. During recent years the patient has had occasional attacks which he has been able to stop by vagal pressure or holding a deep inspiration.

Diagnosis.—Paroxysmal auricular tachycardia.

CASE 2 (Med. No. 4940).—*History.*—A woman, 50 years old, entered the hospital June 5, 1916, complaining of palpitation. Twenty-five years previously she had typical rheumatic fever. Thirty-five years previously, while stooping to pick up something from the floor, her heart suddenly began to beat very rapidly. This attack lasted five minutes. Similar attacks recurred every eight or twelve months, gradually becoming more frequent and of longer duration. Things would become black before her eyes at the beginning and end of each attack. She would always lie down during the attacks. The longest attack

was of seven days' duration. Recently she had been having an "aura" of indigestion, a heavy feeling in the abdomen, nausea, gas and nervousness for two or three days ending with precordial pain just preceding the attack. Riding in a buggy on a rough road used to stop the attacks, later running up and down stairs and applying ice to the precordium were successful, but now the only thing that works is vomiting for which she uses ipecac. During the attacks she had dyspnea on slight exertion, a tight sensation in the chest and tremendous palpitation. The upset which brought her to the hospital began June 2, 1916.

Physical Examination.—This showed a somewhat enlarged heart with an extremely rapid and regular rhythm but no murmurs. There was an area of hyperesthesia in the right hypochondrium and a palpable and very tender liver edge. Vagal pressure was tried without success. The attack stopped spontaneously the night following admission, i. e., four days after the onset. During her stay she had several other shorter attacks, some stopping spontaneously while others were ended by vomiting induced by ipecac.

Thee white count was from 18,000 to 21,000. The urine showed a large trace of albumin on admission which later completely disappeared. The phenolsulphonepthalein output in two hours was 48 per cent. Wassermann reaction was strongly positive. The basal metabolism during the attack was + 27 per cent.: during normal rate, + 6 per cent. Electrocardiograms showed paroxysmal tachycardia of auricular origin with a rate of 217.4. There was typical alternation of the ventricular complexes. Blood pressure readings were: during first attack, July 6: systolic, 124; diastolic, 114; July 7, normal rate: systolic, 110; diastolic, 75; July 13, during the third attack (duration one day): systolic, 95; diastolic, 65; two days later with normal rate, systolic, 135, diastolic, 95. Roentgenograms taken at seven feet during and after the attack showed no appreciable change in the transverse diameter of the heart.

Course.—She was discharged July 26 improved.

Diagnosis.—Paroxysmal auricular tachycardia: syphilis (positive Wassermann).

Case 3 (Med. No. 5742).—*History.*—A man, aged 21, entered the hospital Dec. 9, 1916, complaining of pain in the heart and palpitation. He had rheumatic fever in 1913 and was quite sick for four months, after which he had frequent attacks of sore throat. For four years he noticed shortness of breath, and in 1915, after climbing a flight of stairs, he had severe palpitation. He had numerous attacks of palpitation since then, at first coming on about once a month but more recently every day. Generally, the attacks were of short duration, sometimes lasting minutes or a few hours, but one attack continued for twenty-four hours. Patient stated that at the commencement of an attack the heart became irregular, weak beats and forceful thumps interspersed with pauses and then the heart would finally "start its race." At the time of admission and for several days afterward he had frequent short paroxysms of tachycardia causing marked subjective discomfort.

Physical Examination.—This showed an enlarged heart with signs of aortic and mitral insufficiency. There was no congestion of the lungs or edema of the legs. The liver was not enlarged. The pulse rate generally was around 100 or 120, and would suddenly rise to 160 during attacks.

Electrocardiograms showed paroxysmal tachycardia of auricular origin. Pulse tracings showed pulsus alternans during attacks. The urine was negative. Blood Wassermann was negative. There was a leukocytosis varying from 15,400 to 22,400. The temperature was essentially normal throughout. During attacks systolic blood pressure was 148 while at other times it ranged around 200; the diastolic figure could not be obtained. Roentgenograms were taken at a distance of seven feet during and after an attack on December 13. The plate taken during the attack showed the transverse diameter of the heart shadow to be 1 cm. greater than that of the plate taken after the attack.

Course.—During his stay in the hospital the patient was extremely sick, suffering with severe precordial pain, and having frequent paroxysms of tachycardia which were generally stopped by vagal or ocular pressure. One day he had an attack of unconsciousness with gasping respirations. The general condition gave the impression of severe myocardial damage in addition to the valve defects. He gradually improved so that during the last two weeks of his stay in the hospital he was absolutely free from attacks. He was discharged improved Jan. 4, 1917.

Diagnosis.—Aortic and mitral insufficiency; chronic myocarditis, paroxysmal auricular tachycardia.

The patient died about one year later

CASE 4 (Med. No. 12207).—*History.*—A seamstress, aged 24, came to the hospital Dec. 5, 1919, complaining of "heart spells." She had the ordinary children's diseases, frequent sore throats and typical rheumatic fever lasting one month at the age of 10. One year later, while jumping rope, she suddenly had a queer sensation in her throat "as if her heart had jumped up." She felt faint and found that her heart was beating very rapidly. She remained in bed two weeks, at the end of which time she vomited and the heart slowed down as suddenly as the attack had begun. Following that similar attacks recurred about twice a year, always ending with a vomiting spell which was not voluntarily induced. Later the attacks were much shorter in duration and more frequent, appearing every few weeks and lasting about twelve hours; generally the heart rate was around 200. She thought that her upsets were brought on by dietary indiscretions, excitement or exertion.

Physical Examination.—At the time of admission the patient was not having an attack, but came in to be studied. She had typical signs of mitral stenosis, with a pulse rate of 120, but without evidence of decompensation. Otherwise the physical examination was negative.

The urine and blood Wassermann were negative. White blood count on admission was 13,200.

Course.—Two days after admission the patient developed one of her attacks of rapid heart action, the rate jumping from 90 to 233. Electrocardiograms confirmed the diagnosis of paroxysmal auricular tachycardia. After numerous attempts to stop the attack by having the patient hold a forced inspiration and by pressure over the eyeballs and over the carotids, left vagal pressure finally ended the attack, the heart rate returning to its previous level. Blood pressure readings were made as follows: before the attack: systolic, 120, diastolic, 95; during the attack: systolic, 136, diastolic, 124; nine minutes after the attack: systolic, 126; diastolic, 108; three hours later: systolic, 132; diastolic, 108; five days later: systolic, 125; diastolic, 85. Roentgenograms were taken before, during and after the attack, and showed a definite dilatation of the left auricle during the paroxysm but no appreciable increase in the transverse diameter of the heart shadow. She had no further attacks in the hospital and was discharged on Nov. 15.

Diagnosis.—Mitral stenosis, rheumatic in origin, paroxysmal auricular tachycardia.

CASE 5 (Med. No. 13577).—*History.*—A woman, aged 50, entered the hospital, May 18, 1920, complaining of painful swelling of the hands and feet. Seven weeks before admission she suddenly noticed painless swelling of the sole of the left foot. Three weeks later a similar swelling appeared in the right foot. Each lasted about a week. In the meantime, the joints of both hands and feet began to ache and swell.

Course.—During her stay of four months in the hospital she ran a typical course of chronic infectious arthritis. Blood pressure on admission was: systolic, 180; diastolic, 115. At times she had a fever, and her urine showed many pus cells which were thought to be due to a pyelitis. The leukocyte count, except on one occasion, was normal. Blood Wassermann was negative.

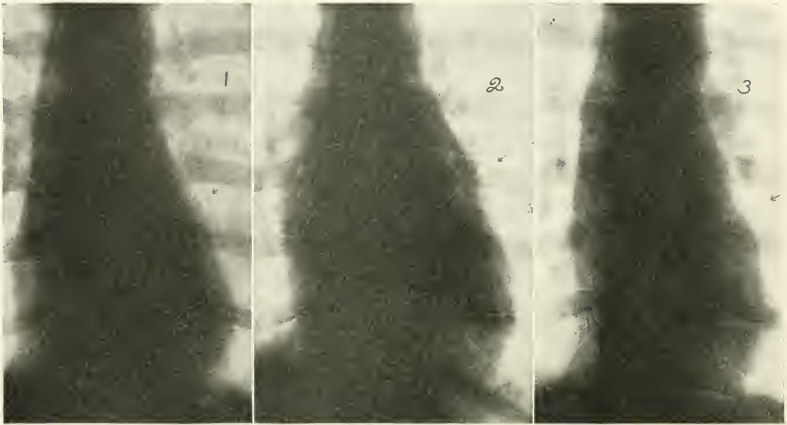

Fig. 1.—"Seven-foot" roentgenograms taken in Case 4 (paroxysmal auricular tachycardia; mitral stenosis) (1) November 6 before; (2) November 7 during, and (3) November 10 after the attack. Arrow points to left auricle. Note prominence of auricular shadow during attack. No appreciable increase in transverse diameter of heart shadow.

Incidental to her main illness, on two days she had transient attacks of tachycardia lasting a few hours. These caused no inconvenience to the patient, and in fact were discovered on routine examination. During the attacks the heart rate was 175 to 180. One was observed to end spontaneously and the other was stopped by vagal pressure. No observations on blood pressure or leukocyte counts were made during these attacks. Electrocardiograms showed paroxysmal auricular tachycardia. Pulse tracings during the attacks showed pulsus alternans. Examination of the heart during the slow rate showed definite enlargement. Roentgenograms taken at seven feet during and after one of the paroxysms showed no change in the size of the heart. She was discharged Sept. 19, 1920, with her joint condition unimproved.

Diagnosis.—Chronic infectious arthritis; paroxysmal auricular tachycardia.

Case 6 (Med. No. 3324).—*History.*—A woman, age 64, entered the hospital Sept. 10, 1915, complaining of palpitation. Her father died at 51 of apoplexy. Her mother died suddenly at 34 presumably of heart disease. Two brothers died of heart disease (one suddenly). Patient had been a school teacher for forty years and had never missed a day's work until the week before admission. During April, 1915, she began to have palpitation and oppression in the chest. She kept at work but often had to lie down during attacks of palpitation. For a year she noticed slight shortness of breath and swelling of the ankles at night. For three months walking would bring on a feeling of faintness and palpitation. She took tincture of digitalis and some strychin off and on during the month before admission. The morning of entry to the hospital she awoke with a sense of oppression in the chest and a rapid heart.

Physical Examination.—Negative, except for rapid heart action and poor heart sounds. The rate was 160 per minute and regular. Electrocardiograms showed paroxysmal tachycardia of ventricular origin. After the resumption of the normal rate the heart examination was also negative.

The urine and the leukocyte count were essentially normal. The blood Wassermann was negative. Temperature remained normal throughout.

Course.—The patient had numerous attacks of tachycardia lasting from a few minutes to several hours, and although frequent attempts were made to stop the attacks by ocular and vagal pressure none were successful. In addition there were times when the heart mechanism showed transient auricular fibrillation. The admission blood pressure, which was the only one obtained, was: systolic, 116; diastolic, 70. Roentgenograms taken at a distance of about thirty inches during tachycardia and during normal rate showed no appreciable change in the size or outline of the heart. She gradually improved with rest in bed and small doses of digitalis and was finally discharged Dec. 16, 1915, improved.

Diagnosis.—Chronic myocarditis; paroxysmal ventricular tachycardia.

Patient died suddenly Oct. 1, 1916.

Case 7 (Med. No. 3503) *History.*—A machinist, 50 years old, entered the hospital Oct. 25, 1916, complaining of indigestion and palpitation. He had consumed large amounts of tobacco and was a moderate drinker. One year previously he had an attack of indigestion lasting ten days. He belched a great deal of gas, vomited after meals and was constipated. During this time he had dull pains down both arms, palpitation and rapid heart. One and a half months before admission he had a similar attack. Since then attacks of palpitation have been the most troublesome complaint. A few days before entering the hospital he thought he was going to die during an attack. These attacks lasted about fifteen minutes and occurred daily for three weeks. For one month he had increasing dyspnea and orthopnea. There was no edema, cough or precordial pain. For a few days he had dizzy spells requiring him to hold on to nearby objects for support.

Physical Examination.—This showed a very sick-looking, orthopneic man, with a pasty yellowish appearance to his face. The lips were cyanosed. The

heart was considerably enlarged, the sounds distant, rapid and regular, rate 160, and no murmurs. The lungs were negative. The liver edge was felt 4 cm. below the costal margin and was tender. There was slight edema of the ankles.

The urine showed a very slight trace of albumin and a few granular casts. Subsequently the urine became normal. There was a leukocytosis of 19,000. The Wassermann reaction was negative. There was a temperature of about 100 F. for a few days. Electrocardiograms taken during the attack showed paroxysmal ventricular tachycardia.

Course.—The attack which brought the patient to the hospital continued for about three days. Numerous attempts at vagal and ocular pressure failed to produce any slowing of the heart rate. Three grams of digitalis leaves were given during the course of the first eight days in the hospital. Shortly before the attack ended the patient had a spell of hiccoughing. During the second week in the hospital he had another attack lasting about twenty-four hours. Blood pressure readings were made at various intervals during and after attacks. October 25, the heart rate was 160; systolic pressure, 98; diastolic, 80. October 30, with the heart rate normal, systolic pressure was 103; diastolic, 72. November 3, the heart rate was 160; systolic pressure, 97; diastolic, 83. November 7, with a normal heart rate, systolic pressure was 114; diastolic, 68. Roentgenograms taken at a distance of about thirty inches during and after the second attack showed no appreciable change in the shape or in the transverse diameter of the heart. Discharged November 16, improved.

Diagnosis.—Chronic myocarditis; paroxysmal ventricular tachycardia.

Case 8 (Med. No. 12646).—*History.*—A colored man, aged 64, entered the hospital Jan. 3, 1920, complaining of dizziness. During the previous year he had five or six spells of dizziness and fainting, in which he fell to the ground and lost consciousness for five or ten minutes. After this he felt weak and unsteady. For the previous five or six weeks he had shooting pains in his legs, and for one week there was increasing dyspnea and weakness so that he was compelled to remain in bed.

Physical Examination.—This showed cyanosis of the lips and finger tips. The heart was considerably enlarged and there was a blowing systolic murmur at the apex. The heart rate on admission was 90. There was some congestion at the base of the left lung. The liver edge was just felt below the right costal margin. There was no edema of the legs.

The urine on admission showed a trace of albumin which cleared up subsequently. There were no casts. The leukocyte count on admission was 13,600; the temperature was 99.6 F. The Wassermann reaction was negative.

Course.—The day after entry his heart rate jumped from 74 to 160 and electrocardiograms showed paroxysmal tachycardia of ventricular origin. Pulse tracings at this time showed pulsus alternans. This attack lasted thirty hours. During his stay in the hospital he had several such attacks lasting generally two hours. Numerous attempts to stop the paroxysms by ocular and vagal pressure were unsuccessful; they always ended spontaneously. The blood pressure on admission with a normal heart rate was: systolic, 145; diastolic, 95. The next day during tachycardia it was: systolic, 115; diastolic, 94. On two other days during tachycardia three readings were obtained as follows: (1) systolic, 112; diastolic, 94; (2) systolic, 110; diastolic, 90; (3) systolic, 110; diastolic, 92. Jan. 19, 1920, during normal heart rate, the readings were: systolic, 124; diastolic, 92. Roentgenograms were taken at a seven-foot distance during and after one attack. The transverse diameter of the heart shadow was slightly but definitely increased during the attack.

Course.—During the first two weeks, the patient was dangerously ill, but with rest in bed and digitalis therapy he gradually improved and became free from attacks. He was discharged March 10, 1920, improved.

Diagnosis: Chronic myocarditis; paroxysmal ventricular tachycardia.

Case 9 (Med. No. 1791).—*History.*—A man, age 35, entered the hospital Oct. 21, 1914, complaining of shortness of breath. Two years previously he had an attack of acute tonsillitis with some stiffness of the elbows. On October 9 he began to have pain in his shoulders and arms and on the following day he felt that his heart was beating rapidly. He kept about his work but on the sixteenth he began to feel short of breath. After staying two days in the hospital the patient was displeased with his treatment and left. His course, however, was followed in the Outpatient Department from time to time. The attack of rapid heart action and shortness of breath ended some time between October 22 and 29. After this he was well for three weeks when a similar attack occurred lasting three weeks. He remained in good health until Feb. 2, 1915, when the third attack began, associated with pain in the left ankle and both shoulders.

Physical Examination.—During the two attacks which were observed the physical findings were essentially the same. The heart was definitely enlarged and the action rapid and regular, 176 to the minute. No murmurs were heard. There were prominent pulsations in the veins of the neck. During the first attack the urine was negative, the white count was normal, the temperature was 99.2 F. and the blood Wassermann was negative. During the second attack the temperature was 99.4 F. At this time he was given 1 gm. sodium salicylate, every three hours, and digitalis leaves, 0.1 gm., three times a day. Electrocardiograms taken during both attacks showed that the auricles were fluttering with a rate of about 350 and the ventricles were contracting regularly to every other auricular impulse. February 6 he awoke and found that his heart was beating normally. Examination during this normal rhythm disclosed signs of aortic stenosis and slight aortic insufficiency, i. e., there was a prominent systolic thrill in the aortic area, a loud systolic murmur and a faint but definite diastolic murmur. The blood pressure February 2, during an attack, was systolic, 92; diastolic, 80; February 6, during normal rate: systolic, 90; diastolic, 69. Roentgenograms taken at about thirty inches during and after both the first and third attacks showed no appreciable change in the outline or in the transverse diameter of the heart shadow. The first plate was taken when the attack had lasted twelve days. The roentgenogram during the other attack was taken when it had been in progress three days.

Course.—The patient returned to Bulgaria, his native country, and was reported to have joined the army and to have died during the succeeding year or so.

Diagnosis.—Aortic stenosis, slight aortic insufficiency; paroxysmal auricular flutter.

Case 10 (Med. No. 13074).—*History.*—A woman, aged 38, entered the hospital March 2, 1920, complaining of pain in the heart and stomach. Following curettage two years previously she developed precordial pain and palpitation. This passed away and she had no further trouble until five weeks before admission when she began to have severe epigastric and precordial pain, palpitation, nocturnal dyspnea and orthopnea.

Physical Examination.—This showed an enlarged heart with an absolutely irregular rhythm and a loud blowing systolic murmur at the apex. There was a pulse deficit of 20 beats. A tender liver edge was felt. There was no edema of the legs.

The urine on admission showed a trace of albumin which cleared up subsequently. The leukocyte count was normal. The Wassermann reaction was negative. The basal metabolism was plus 39 per cent. The temperature was normal throughout. The day following admission the cardiac rhythm became regular.

Course.—During her stay in the hospital she had several attacks of paroxysmal auricular fibrillation, which diagnosis was confirmed by electrocardiograms.

Roentgenograms were taken at a distance of seven feet during and after an attack of fibrillation and showed no definite change in the size or contour of the heart shadow. There was evidence of cardiac hypertrophy. The patient improved slowly with rest in bed and with digitalis. She impressed some of those who saw her as suffering from hyperthyroidism and others thought she had mitral stenosis. She was discharged May 17, 1920, improved.

Diagnosis.—Mitral stenosis and regurgitation; paroxysmal auricular fibrillation.

Case 11.—*History.*—A man, aged 26, came to Dr. Paul D. White at the Massachusetts General Hospital Dec. 14, 1920, complaining of palpitation. The first attack occurred during the spring of 1916 while he was playing tennis. For one hour his heart beat very tumultuously, rapidly and irregularly. Two or three months later there was a second attack. He had numerous similar attacks after this and the usual interval between them was two or three months, except while he was driving a motor cycle in France, when they came weekly. He was sent home as a case of effort syndrome. These upsets started and stopped suddenly and lasted from one hour to more than a day. During the attack he had slight dyspnea, weakness and marked palpitation, but he never had to stop work.

Physical Examination.—The attack which brought him to Dr. White began the previous day about 11 p. m. Electrocardiograms showed auricular fibrillation with a ventricular rate of from 110 to 130.

Course.—No effect was produced by right or left vagal or right ocular pressure. December 16 he was seen again after the attack had stopped. Examination of the heart disclosed no evidence of valvular disease. Roentgenograms were taken at a distance of seven feet during and after the attack and showed no appreciable change, although there was evidence of hypertrophy.

Diagnosis.—Paroxysmal auricular fibrillation.

A STUDY IN EXPERIMENTAL DIABETES

THE EFFECT OF INTRAVENOUS INJECTION OF PANCREATIC PERFUSATES ON THE D/N RATIO FOLLOWING PANCREATECTOMY *

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The relation of the pancreas to diabetes mellitus was proved in 1889 when Von Mering and Minkowski discovered that fatal diabetes always followed complete pancreatectomy. Two principal hypotheses have been advanced to explain how the pancreas is linked with carbohydrate metabolism, viz., the detoxication and the internal secretion theories. In the former the pancreas is supposed to remove a toxic substance from the blood stream, the presence of which interferes with the oxidation of carbohydrates by the tissues; in the latter the pancreas is said to contribute something to the blood stream which acts as a necessary link in the process of carbohydrate assimilation. Attempts to establish either of these theories have met with little success although the preponderance of evidence to date seems to favor the theory of an internal secretion. Notwithstanding a vast amount of experimentation the exact role of the pancreas in carbohydrate metabolism remains unknown.

The parabiosis experiments by Forschbach,[1] the transplantation and cross circulation experiments by Hedon,[2] pancreas feeding experiments and many others have yielded results either negative or else contributory alike to the detoxication and the internal secretion theories.

The blood transfusion experiments by Carlson and Ginsberg;[3] and by Drennan; the study of experimental diabetes in pregnant dogs by Carlson [4] and the experiments by Clark [5] in which the surviving mammalian heart and pancreas were perfused in circuit, all support the theory of an internal secretion. These conclusions are also supported by the in vitro studies carried out by Cohnheim [6] and Levene.[7]

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* From the Hull Laboratories of Physiological Chemistry and Pharmacology, University of Chicago.

1. Forschbach: Arch. f. exper. Path. u. Pharm. **9**:131, 1908.
2. Hedon: Arch. intern. di. Physiol. **13**:4. p. 255, 1913.
3. Carlson and Ginsberg: Am. J. Physiol. **36**:280, 1915.
4. Carlson: Am. J. Physiol. **28**:391, 1911.
5. Clark, A. H.: J. Exper. Med. **24**:621, 1916.
6. Cohnheim: Ztschr. f. Physiol. Chem. **39**:, 1903.
7. Levene, P. A., and Meyer, G. M.: J. Biol. Chem. [illegible]

Of these methods of attack, perfusion experiments seem most promising, for if it can be shown that the pancreas contributes something to a physiologically inert solution passing through its vessels by which utilization of sugar by the tissues is augmented, the theory of an internal secretion would be made tenable. Besides the perfusion experiments of Clark already mentioned, only two references to the direct perfusion of the pancreas could be found. Hustin perfused the pancreas in a study of its external secretion and de Meyer found that by adding a solution previously perfused through a pancreas to one subsequently perfused through a liver there was an increase in liver glycogen.

In the experiments reported herewith an attempt has been made to determine the effect of pancreatic perfusates upon dextrose utilization in depancreatized dogs.

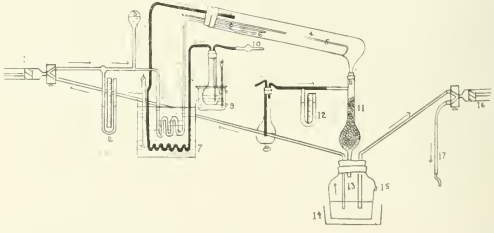

Fig. 1.—1. Woodyatt pump. 2. Mercury manometer for measuring the pressure of the perfusate. 3. Air cushion. 4. Perfusion chamber. 5. Supporting rod to which the pancreas is fastened. 6. Cannula for the pancreaticoduodenal artery. 7. Water bath maintained at 42 C. 8. Water bottle for saturating air with moisture. 9. Bath for maintaining second water bottle at 75 C. In this way the air entering the chamber was heated to from 30 to 35 C. 10. Cotton filter for air entering apparatus. 11. Artificial lung composed of glass beads. 12. Small manometer for registering negative pressure in perfusion chamber. 13. Receiving bottle containing 150 c.c. of perfusion medium. 14. Vessel containing warm water used to warm the perfusate to body temperature previous to injection. 15. Attachment for vacuum pump. 16. Woodyatt pump by which perfusate was injected. 17. Cannula for the saphenous vein. The black tubing carries air.

Method of Procedure.—The D/N ratio was taken as a criterion for the carbohydrate consuming power of the animal. Dogs were depancreatized and the D/N ratios were determined daily. When these figures became rather constant for each animal, it was the plan to inject intravenously a quantity of pure dextrose dissolved in Tyrode's solution. Subsequent determinations of the D/N ratio

should show the amount of dextrose retained after such injections. It was then proposed to perfuse the pancreas of a normal animal with Tyrode's solution containing dextrose, and to inject this perfusate intravenously, at the same rate, into an experimentally diabetic animal, with the expectation that the subsequent D/N ratios would show some change in dextrose utilization.

Females under morphin-ether anesthesia were used for removal of the pancreas. The technic of pancreatectomy was developed so that the complete extirpation of the gland could be assured. Asepsis was given particular attention. The postoperative recovery of the animals was satisfactory and they survived from five days to five weeks.

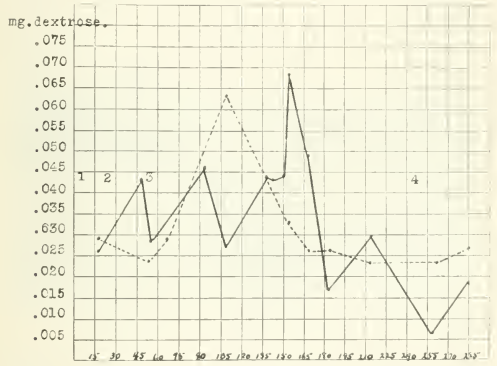

Fig. 2.—Showing the effect on the sugar and nitrogen excretions of repeated injections of pancreatic perfusates. Black line indicates dextrose. Dotted line indicates nitrogen. Figures represent time of injection of perfusate.

Immediately following pancreatectomy the animals were placed in clean metabolism cages and the urine was collected every twenty-four hours. The dogs were kept on a constant daily diet of 480 gm. raw lean meat. Water was given freely. The urine was collected at the same time every day, alcoholic thymol being used as a preservative. The volume was measured and the sugar and nitrogen determinations were made. The total nitrogen was determined by the Kjeldahl-

Gunning procedure. The Munson-Walker-Bertrand method was used for the determination of the urine sugars.

The perfusion medium used in all experiments was Tyrode's solution modified so that it contained no dextrose. The formula was as follows: Sodium chlorid, 0.7 per cent.; potassium chlorid, 0.02 per cent.; magnesium chlorid, 0.02 per cent.; calcium chlorid, 0.02 per cent.; sodium bicarbonate, 0.01 per cent., and monobasic sodium phosphate, 0.005 per cent. Fresh solutions were always used.

The pancreas was perfused as follows: The peritoneal cavity of a dog under morphin-ether anesthesia was opened aseptically by a right rectus incision so as to expose the pancreas. The superior pancreatico-duodenal artery and vein were isolated and ligated close to the origin of the former. The vessels were then cannulated so as to send the perfusion medium through the pancreas in the direction of the blood flow. To render the subsequent steps of the experiment practically bloodless, the thorax was rapidly opened, the aorta clamped

Fig. 3.—Showing effect of the intravenous injection of 1 c.c. of the freshly prepared perfusate on the blood pressure of an etherized animal.

above the diaphragm and the chest cavity quickly closed. The apparatus for maintaining the circulation through the gland was designed so that it could be sterilized in an autoclave. It consisted of a motor driven syringe (Woodyatt transfusion pump) connected through a manometer to the cannula in the pancreatico-duodenal artery. The solution as it came from the pancreatico-duodenal vein poured over glass beads through which a current of moist air was being drawn. The perfusate then flowed into a closed bottle from which it was drawn by the syringe and again sent through the gland. During the procedure the dog was kept under light anesthesia. The perfusate was maintained at 37 C. and a pressure of 120 mm. of mercury. The gland at first became mottled and later white in color as the perfusate continued to pass through its vessels. After fifteen or

twenty minutes moisture was noticed, due to the escape of the perfusate from the surface of the pancreas, and in this way a few cubic centimeters of the solution were lost. By the addition of small quantities of Tyrode's solution at intervals to compensate for this loss on the surface of the gland, a continuous flow of Tyrode's solution through the vessels could be maintained indefinitely.

One hundred and fifty cubic centimeters of Tyrode's solution containing 10 gm. dextrose was allowed to pass through the gland for one hour. At the end of this period a small sample was withdrawn for analysis and the remaining portion injected by means of a Woodyatt apparatus at the rate of 10 c.c. per minute, directly into the saphenous vein of a diabetic animal. Local anesthesia was used to cannulate the vein. The concentration of dextrose in the perfusate was determined in the sample withdrawn for that purpose, and the

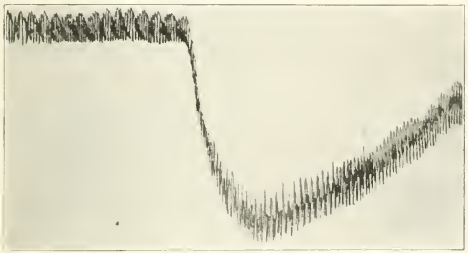

Fig. 4.—Showing effect of the intravenous injection of 1 c.c. of the perfusate allowed to stand for forty hours at room temperature on the blood pressure of an etherized animal.

quantity of sugar injected into the diabetic animal calculated. It was the plan that dogs so treated should show a fairly constant D:N ratio for a period of at least three days preceding the injection. Also the quantity of sugar excreted in the urine following injections of known quantities of pure dextrose was to be determined before injection with the perfusate containing dextrose. It was thought that the pancreatic factor found present by Clark in his perfusates might enable the diabetic animal to utilize all or a portion of the injected dextrose.

Such experiments were attempted on a series of about fifteen depancreatized dogs. Necropsy on these animals revealed complete

removal of the pancreas in almost every instance. Death in a large percentage of cases was caused by pneumonia. Table 1 shows that Dog 8 was injected with 3.27 gm. pure dextrose seventeen days following pancreatectomy. For some unknown reason the daily sugar excretion, preceding the day the animal was injected, rose from 10.54 gm. to 20.35 gm. The following day only 15.15 gm. sugar were excreted in spite of the injection of 3.27 gm. dextrose. In no instance did we feel justified in drawing conclusions as to dextrose utilization from such fluctuating figures.

Having found this procedure useless in the solution of the problem, it was decided to attempt to influence the onset and course of experimental diabetes by the intravenous injection of pancreatic perfusates alone. Such an experiment, if successful, might also throw some light on the hypothetical internal secretion of the pancreas.

TABLE 1.—Experimental Results from Observation of Dog 8, Receiving 480 Gm. Raw Meat per Day. Plenty of Water

Date*	Time	Amount of Urine	Sugar, per Cent.	Sugar Total	Total Nitrogen	D/N
April 3	10:00 a.m.	350	4.70	16.15	.....	....
April 4	10:00 a.m.	470	2.30	11.28	6.063	1.86
April 5	10:00 a.m.	490	2.40	11.76	11.270	1.05
April 6	10:00 a.m.	527	2.00	10.54	12.648	0.83
April 7	10:00 a.m.	260	Contaminated urine			
April 8†	10:00 a.m.	370	5.50	20.35	9.250	2.20
April 9	10:00 a.m.	505	3.00	15.15	9.595	1.56
April 10	10:00 a.m.	265	4.80	12.72	7.950	1.60
April 11	10:00 a.m.	200	4.80	9.60	6.000	1.60
April 12	10:00 a.m.	185	4.60	7.79	7.326	1.06

* Complete pancreatectomy March 22.
† Intravenous injection at 3:00 p. m. of 3.27 gm. pure dextrose dissolved in 100 c.c. of Tyrode's solution. Fifteen minutes was required for the injection. The saphenous vein was cannulated under local anesthesia.

Clarke's work as previously quoted, indicates the existence of such secretion in pancreatic perfusates.

The first line of experiments were conducted as follows: Proceeding on the theory that the animal would most likely respond to treatment while the cells were in a normal physiologic state rather than after they became altered by an abnormal carbohydrate metabolism, intravenous injections of pancreatic perfusates were made immediately following pancreatectomy. In this way the onset of experimental diabetes might be delayed.

The following technic was used in preparing these perfusates. The abdomen was opened by an upper right rectus incision. The splenic end of the pancreas was first liberated as far as the pylorus. The duodenal end was then cut from the mesentery up to the point of its attachment to the bowel wall. The superior pancreatico-duodenal artery was isolated and ligated close to its origin. The thorax was opened and the aorta clamped immediately above the diaphragm so

as to make the subsequent steps practically bloodless. The gland with the attached piece of duodenum, 8 cm. in length, was quickly extirpated and washed in a warm, glucose-free, Tyrode's solution. The pancreatico-duodenal artery was then cannulated and the gland suspended by passing the supporting rod of the perfusion chamber through the lumen of the attached bowel. The splenic end of the pancreas was then tied by a thread to a loop in the supporting rod, and the gland placed in the perfusion chamber. The cannula was connected and the perfusion started. This procedure was carried out in from five to seven minutes. A pressure not to exceed 120 mm. of mercury was maintained and about 15 c.c. fluid was passed through the gland per minute. The perfusate was maintained at 37 C.

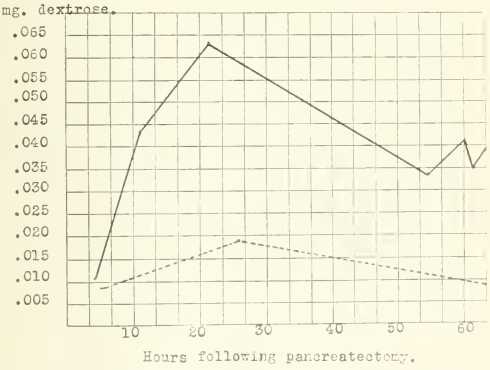

Fig. 5.—Curve showing dextrose and nitrogen excretion for a period of sixty-two hours following the injection of 175 c.c. pancreatic perfusate. The perfusate was prepared by allowing the solution to flow through the gland once. It was injected immediately into the animal following pancreatectomy. Solid lines indicates dextrose. Broken line indicates nitrogen.

For these experiments a special effort was made to devise a perfusion apparatus which would approximate, as nearly as possible, physiologic conditions. A diagram of this is shown and explained in Figure 1. Following each experiment the apparatus was carefully washed and filled with 75 per cent. alcohol. Immediately preceding each experiment the alcohol was removed and repeated washings of Tyrode's solution were pumped through the system. One hundred

and fifty cubic centimeters of fresh, glucose-free Tyrode's solution were then placed in the receiving bottle.

Twenty-seven dogs were used in this series of experiments. None of the animals were fed after operation. The perfusate was allowed to pass through the vessels of the pancreas for one hour. Small, white areas appeared on the surface of the gland almost immediately after the perfusion fluid had entered its vessels. These regions gradually enlarged as the perfusion proceeded until the body and head of the pancreas became white. Aside from this whiteness, due to the washing out of the blood, the tissue remained entirely normal in gross

Fig. 6.—Curve showing dextrose and nitrogen excretion for a period of seventy-six hours following injection of 100 c.c. pancreatic perfusate, prepared as described below. Solid line indicates dextrose. Dotted line indicates nitrogen. The perfusate was prepared by passing once through a pancreas 100 c.c. of defibrinated blood drawn from a diabetic dog. It was injected intravenously into a second animal immediately following pancreatectomy.

appearance. Peristaltic waves were often observed traveling along the attached bowel, and these persisted throughout the time of perfusion. While the gland was being perfused, a pancreatectomy was completed. The perfusate was then injected, intravenously, into the depancreatized dog by the Woodyatt apparatus at the rate of 10 c.c. per minute. This operation was done aseptically while the dog was still under ether

anesthesia. Following this the animal was at once placed in a metabolism cage and the urine collected as soon as possible after being voided. The time of the appearance of glycosuria was noted and quantitative sugar and nitrogen determinations were made from this point until the death of the animal.

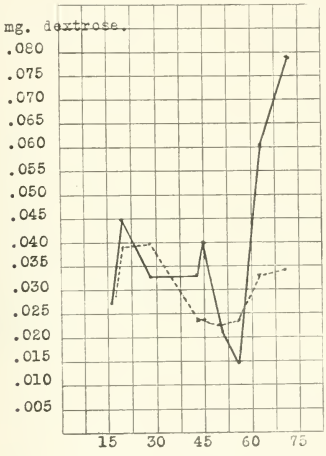

Fig. 7.—Curve showing the dextrose and nitrogen excretion for a period of ninety-two hours following injection with 150 c.c. pancreatic perfusate. The perfusate was allowed to circulate through the gland for one hour and injected immediately following the completion of pancreatectomy. Solid line indicates dextrose. Dotted line indicates nitrogen.

It was found that the course of diabetes following complete removal of the pancreas was fairly constant. Sugar invariably appeared in the urine from six to eighteen hours after complete pancreatectomy and reached its maximum (from 5 to 8 per cent.) in from twenty-four to forty-eight hours. Aside from the glycosuria, the usual diabetic syndrome was noted, viz.: excessive thirst, polyphagia, polyuria, failure of wounds to heal, rapid loss of weight, progressive weakness, and death from complications or extreme inanition.[8]

8. Drennan, F. M.: Am. J. Physiol. **28**:396, 1911.

Dogs injected immediately following pancreatectomy with 150 c.c. of perfusate prepared as described, showed no delay in the onset of glycosuria. There were, however, two exceptions in which sugar did not appear in the urine of animals so injected until forty and fifty-eight hours, respectively, following complete removal of the pancreas. Glycosuria, on appearing, followed its usual course until a few days later when the dogs died of pneumonia. Necropsy on these animals revealed the duodenum to be smooth and free from bits of pancreas visible to the naked eye. Both dogs were in early pregnancy, fetuses measuring from 1 to 1.5 cm. being found.

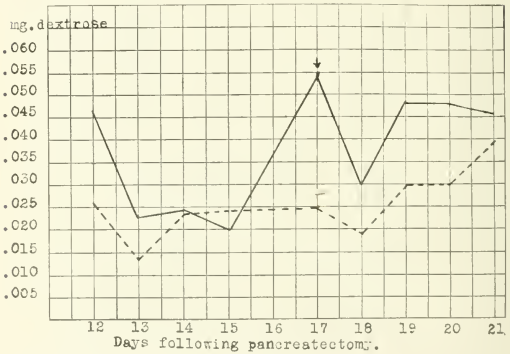

Fig. 8.—Showing glucose and nitrogen output per twenty-four hours on a constant protein diet. Solid line indicates dextrose. Dotted line indicates nitrogen. Arrow indicates intravenous injection of 3.27 gm. pure dextrose.

Glycosuria developed within from six to eighteen hours following pancreatectomy in the remaining ten dogs of this series. As is noticed in Table 2, subsequent injections after glycosuria had developed produced no consistent change in the D/N ratio. Figure 2 shows that the urine sugar did not reach its maximum until 138 hours following pancreatectomy. During this period the dog was injected three times with pancreatic perfusates. The result is typical of those obtained in this series. The delayed sugar excretion is probably apparent rather than real, since it is always followed by a compensatory rise lasting through a period of several hours. The total quantity of glucose excreted for the given period remains unchanged.

This interpretation seems justified by examination of the tracing (Fig. 3) which shows the action of these perfusates on the blood pressure of an etherized animal. Their marked vasodilator effect indicates that they are in this respect similar to tissue extracts. It is known that a fall in blood pressure resulting from the injection of tissue extracts into experimentally diabetic animals is usually accompanied by a decrease in glycosuria followed by a compensatory rise.

TABLE 2.—EXPERIMENTAL RESULTS FROM OBSERVATION OF DOG 20*

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Nitrogen, Gm.	Total Nitrogen	D/N
July 6–7†	9:00 a.m.	175	2.61	4.568	4.568	5.0225	5.0225	0.91
July 7–8‡	8:45 a.m.	170	4.29	7.293	.....	4.875	.....	....
	12:55 p.m.	30	2.83	0.849	8.142	0.843	5.718	1.42
July 8–9	8:30 a.m.	75	3.31	2.483	2.483	2.160	2.160	1.15
July 9-10	10:45 p.m.	118	4.64	5.475	.....	7.434	.....	....
	6:00 p.m.	50	5.74	1.570	6.845	3.150	10.584	0.65
July 10-11	No urine							
July 11-12	8:35 a.m.	65	4.42	2.873	.....	3.152	.....	....
	11:00 a.m.	105	4.33	4.547	.....	3.476	.....	....
	7:45 p.m.	85	4.42	3.757	.....	2.814	.....	....
	9:00 p.m.	50	6.72	3.360	14.337	1.655	10.097	1.44
July 12-13	7:30 a.m.	80	4.80	3.84	3.84	3.176	3.176	1.77
July 13-14	8:00 a.m.	65	1.69	1.099	1.099	1.768	1.768	0.62
July 14-15	12:00 n.	215	2.96	6.364	6.364	5.354	3.354	1.39
July 15-16	8:00 p.m.	180	1.60	2.880	2.880	4.446	4.446	0.64
July 16-17§	8:00 a.m.	85	0.70	0.595	0.595	1.394	1.394	0.43
July 17-18	10:00 a.m.	70	1.91	1.337	1.337	1.890	1.890	0.71

* Pancreatectomy complete 12:45 p. m. July 5, 1919. Injected immediately following pancreatectomy with 150 c.c. pancreatic perfusate prepared as described.
† Second injection 12:50 p. m. July 6.
‡ Third injection 12:45 p. m. July 7.
§ Fourth injection 9:00 p. m. July 16.

TABLE 3.—EXPERIMENTAL RESULTS FROM OBSERVATION OF DOG 26*

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Total Nitrogen	D/N
July 17	10:00 p.m.	450	1.30	5.896	5.896	4.138	1.42
July 18	7:10 a.m.	395	4.33	17.104	.....	.....	....
	8:35 p.m.	185	6.40	11.840	28.944	10.759	2.68
July 19	8.45 a.m.	340	3.67	12.478	.....	.....	....
July 19	11:00 a.m.	45	4.60	2.070	.....	.....	....
July 19	4:00 p.m.	50	4.51	2.255	18.224	6.777	2.69
July 19	1:30 p.m.	35	4.06	1.421	.....	.....	....

* Operated on 4 p. m. July 17; injected with 175 c.c. pancreatic perfusate directly as it came from the gland.

The marked depressor action of the perfusates may be a factor in explaining their apparent influence on glycosuria (E. G. Kirk).[9] Figure 4 shows an increase in this property if the perfusate is allowed to stand thirty hours, probably a result of autolysis caused by pancreatic digestive enzymes present in the solution. However, throughout the experiments no rise in temperature or visible signs of toxemia or depression were noted.

9. Kirk, E. G.: Arch. Int. Med. **15**:39 (Jan.) 1915.

It was suggested that the apparent negative results were due to a decomposition of the internal secretion contained in the perfusate, and that decomposition rather than concentration resulted from an hour's perfusion of the gland. The findings of Clark as to the stability of the secretion made this theory probable. Consequently, the solution

TABLE 4.—Experimental Results from Observation of Dog 30*

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Total Nitrogen	D/N
July 23	9:30 a.m.	90	4.87	4.183	4.183	3.384	1.26
July 24	7:30 a.m.	120	6.17	8.124	.....	.....	....
July 24	9:15 p.m.	115	4.64	5.336	13.460	9.823	1.37
July 25	9:30 a.m.	80	6.68	5.344	.....	.....	....
July 25	8:15 p.m.	40	2.61	1.044	6.388	4.392	1.45

* Pancreatectomy on Dog 30 was completed at 3:45 p. m., July 22, 1919, and the animal immediately injected with a perfusate prepared by passing defibrinated blood of a diabetic dog through the normal gland once.

TABLE 5.—Experimental Results from Observation of Dog 22*

Date	Time	Amount of Urine	Sugar, per Cent.	Sugar, Gm.	Total Sugar	Nitrogen, Gm.	Total Nitrogen	D/N
July 11-12	7:00 a.m.	80	2.70	2.160	.....	2.296	.....	....
	8:35 a.m.	98	4.47	4.380	.....	3.900	.....	....
	7:45 p.m.	255	3.27	8.338	14.818	10.276	16.472	0.89
July 12-13	7:30 a.m.	210	3.27	6.867	.....	4.767	.....	....
	1:00 p.m.	35	3.89	1.362	.....	0.795	.....	....
	3:30 p.m.	55	2.09	1.150	.....	1.249	.....	....
	6:55 p.m.	50	1.52	0.760	10.139	1.135	7.946	1.28
July 13-14	8:30 a.m.	20	6.04	1.208	.....	0.67	.....	....
	12:30 p.m.	20	7.88	1.576	2.784	0.67	1.340	2.07

* Pancreatectomy on Dog 22 was complete at 3:30 p. m., July 10, 1919. The animal was injected immediately following pancreatectomy with 150 c.c. pancreatic perfusate as described.

TABLE 6.—Dog 2 Was Fed 480 Gm. Raw, Lean Meat per Day, and Received Plenty of Water*

Date	Time	Amount of Urine	Sugar, per Cent.	Total Sugar	Total Nitrogen	D/N
April 26	10:00 a.m.	645	2.60	16.77	12.90	1.30
April 27	10:00 a.m.	427	Spilled by accident			
April 28	10:00 a.m.	250	3.66	9.11	5.950	1.54
April 29	10:00 a.m.	227	2.30	5.22	4.984	1.05
April 30	10:00 a.m.	270	3.10	8.37	5.670	1.48
May 1	10:00 a.m.	70	2.92	2.04	1.680	1.22
May 2	10:00 a.m.	240	3.20	7.68	5.280	1.45

* Complete pancreatectomy April 16.

was passed once through the gland and injected immediately into the depancreatized animal. The same technic and precautions were observed as previously described.

Figure 5 shows the typical curve from such an experiment. Glycosuria appeared six hours following pancreatectomy and rose to its maximum within thirty hours. As will be seen in Table 3, the

D/N ratios rose from 1.42 to 2.69 during the sixty hour period immediately following pancreatectomy.

A third series of experiments was then attempted in which defibrinated blood from a depancreatized animal was used instead of Tyrode's solution. It was hoped that this would be a better medium for collecting the internal secretion from the gland. Defibrinated blood from depancreatized animals had been previously shown by Drennan to have no effect on the D/N ratio in experimental diabetes.

Under light anesthesia, blood was drawn aseptically from the jugular vein of an animal depancreatized three days previously. The animal was diabetic, having a glycosuria of 3.36 per cent and a hyperglycemia of 1.22 mg. dextrose per c.c. of blood. The Munson-Walker method for blood sugar determination was used. One hundred cubic centimeters of this blood, after being defibrinated, was passed through a normal pancreas and then injected into an animal immediately following pancreatectomy.

Figure 6 shows the dextrose nitrogen curves for this experiment. There was apparently no effect on the onset of glycosuria. Table 4 shows a uniform rise of the D/N from 1.26 to 1.45 during a period of seventy-five hours following injection.

CONCLUSIONS

1. As compared with the figures reported in the literature, especially by Lusk, the D/N ratios are uniformly low.

2. The percentage of sugar in the urine and the total sugar excretion per day show wide variations both on a constant diet and during starvation.

3. Although the total nitrogen excretion in some animals was relatively constant, others under identical conditions showed marked variations.

4. All factors within our control, such as diet, water, etc., did not maintain a D/N ratio sufficiently constant to be of use in carrying out the first series of experiments.

5. Perfusates prepared by passing glucose-free Tyrode's solution for one hour through the blood vessels of a normal pancreas did not delay the onset of diabetes.

6. Two exceptions to the above conclusion are recorded. It seems unlikely, in view of the work of A. J. Carlson and co-workers on the Control of Diabetes in Pregnancy, that the fetuses described in these animals could have altered the course of diabetes. Since we were unable subsequently to confirm these results, they are merely of suggestive value.

7. Maximum elevation of glycosuria is delayed by injection of pancreatic perfusates.

8. The influence on glycosuria is probably apparent and not real, since it is followed by a compensatory rise. This effect may be explained by the action of depressor substances shown to be present in the perfusates.

9. Solutions passed once through the gland when injected intravenously showed no effect either on the onset or course of experimental diabetes.

10. Defibrinated blood drawn from pancreatectomized animals and passed once through the normal pancreas had no effect on experimental diabetes.

11. The internal secretion of the pancreas, if it can be obtained by the perfusion experiments described, may be too labile or in too low concentration to influence the sugar metabolism of the diabetic animal.

We wish to record our thanks to Dr. F. C. Koch for his many valuable suggestions and his untiring interest in our work.

BOOK REVIEWS

THE EVOLUTION OF MODERN MEDICINE. A Series of Lectures Delivered at Yale University on the Silliman Foundation in April, 1912, by Sir William Osler, Bt., M.D., F.R.S.

Nearly ready for publication, the proofs partially corrected by Sir William, the great war interrupted the final correction and completion of this volume. The work was completed by Fielding H. Garrison, Harvey Cushing, Edward P. Streeter, and Leonard L. Mackall, who have carried out the author's plans and wishes in every respect. The volume represents Osler at his best—not only as a physician but as a scholar, a man of letters and an historian—while the publishers have achieved a setting worthy of the content. Composed originally for a lay audience and popular consumption, it will furnish inspiration to physicians as well, tracing as it does the devious course of medical progress and struggle to the present, and one needs no medical knowledge to follow the golden thread. In the introduction he considers Egyptian, Assyrian, Babylonian and Oriental medicine, with evidence of early operative and therapeutic procedures and directions. Then Greek medicine with the contributions of both mythology and the philosophers—medieval medicine with the isolated centers in universities throughout Europe—the renaissance and development of anatomy and physiology —modern medicine, and the rise of preventive medicine. Osler himself called it "an aeroplane flight over the progress of medicine through the ages." But, in spite of the necessary brevity, one gets an amazingly clear picture of the individuals and the events, due partly to the numerous cuts and engravings, themselves, the author's choice from an enormous bulk of extant material.

The volume is a delightful addition to the physician's library. With it he can journey for a time away from his twentieth century setting to bygone times and other places, returning with a happier perspective and a clearer understanding of his own position in the evolution of medicine.

HUMAN PARASITOLOGY. By Damaso Rivas. Philadelphia and London: W. B. Saunders Co., 1920.

This book is written primarily as a textbook of the animal forms parasitic in man, and while a large part is devoted to the classification and description of these parasites, the author has added brief chapters on certain phases of bacteriology, serology and laboratory diagnosis. These are not especially attractive, as they, in themselves, are sufficiently comprehensive to be considered in separate texts rather than as addenda to a textbook of the animal parasites of man.

The first chapters of the book deal with the historical features of animal parasitology, the relation of parasite to host and the effect of animal parasitism on a host. Descriptions of the parasitic forms are complete. The classification is strictly zoologic, and somewhat confusing, at least for the average physician. However, it is readily understood by those with a broad zoologic training, and the book, therefore, will appeal more to such physicians. The literature references of a book now being offered to physicians as a text of the animal parasites of man should include recent work in parasitology, especially as such a book is intended for more than a laboratory guide.

PRECIS DE PARASITOLOGIE, par le Pr Guiart, professeur à la Faculté de médecine de Lyon et à la Faculté de médecine de Cluj. Ed. 2, 1922, 575 pages, with 462 illustrations. (*Bibliothèque du Doctorat en Médecine*, Gilbert et Fournier) (*Librairie J.-B. Baillière et fils, 19, rue Hautefeuille, Paris*).

This volume is one of the thirty-five composing the "Bibliothèque du Doctorate en Médecine" collected under the supervision of Gilbert and Fournier.

In undertaking the work the editors state their reasons frankly. The sum of the knowledge required today of the student and practitioner of medicine is large, and increasing daily, and in the relatively short time devoted to the acquisition of the knowledge necessary, there is a large amount of information which can neither be covered in the classes nor remembered afterward, especially the minutiae and less essential details of the subdivisions or specialties of medicine. In undertaking to present the series, the editors have endeavored to obtain the outstanding authorities in each division. The present second edition is the volume on parasitology, the result of twenty-four years' specialization by the author, Professor Guiart. It is written for the student and physician, contains only material useful to them, and retains the medical point of view in the study of the parasites, followed by concise descriptions of the diseases produced by them. The volume is profusely and clearly illustrated, well indexed, and in every respect attains the editors' desire to present all that is indispensable in the knowledge of parasitology in a clear, concise volume.

ZUR THERAPIE DES KARZINOMS MITT RONTGENSTRAHLEN. Vorlesungen Ueber Die Physikalischen Grundlagen Der Tiefentherapie. Von Prof. Dr. Fr. Dessauer, Direktor Des Instituts Für Physikalische Grundlagen Der Medizin An Der Universität Frankfurt A. M. 30 Illustrations. Dresden and Leipzig: Theodor Steinkopff, 1922.

In the form of four lectures the author outlines the roentgen-ray therapy of deep lying cancer by the use of the Roentgen rays of extremely short wave length combined with copper filters, large areas and increased distance, so as to obtain a high dose quotient at the depth of the disease. Only by this means is an adequate dosage of rays administered to the cancer cells without injuring the overlying tissues. The depth of ten cm. is used as a standard for computing ray absorption, and in order to generate a beam rich in the rays of high penetrating character a larger capacity tube must be used combined with an electrical transformer delivering a current of much higher potential than has been the practice in the past. Two hundred thousand volts excites the tube, and the beam is filtered through a copper filter of a thickness the major fraction of a millimeter. This absorbs much of the heterogeneous discharge and allows the passage of short wave lengths only. To obtain a sufficient dose the time must be prolonged. Scattered radiation within the tissues is taken advantage of by increasing the area of tissue treated. It is found that multiple small portals of entry and many angles of cross-fire are not necessary. Much attention must be paid to the percentage of rays absorbed at various levels, however, so that when cross fire dosage is given the proper summation of effects is obtained throughout the pathologic mass. In malignancies located in the middle of the body a heavy exposure is made from the front, back and sides to build up in the center a combined dosage sufficient to destroy carcinoma. The ratio of skin to depth dose, or dose quotient, is further increased by increasing the tube-skin distance. The physics underlying these technical considerations is explained and illustrated by many cuts, tables and graphs. Abstracts of numerous other articles relating to deep therapy are appended.

THE LETHAL WAR GASES: PHYSIOLOGY AND EXPERIMENTAL TREATMENT. Frank P. Underhill, Ph.D., New Haven, Yale University Press, 1920.

This octavo volume of 310 pages embodies a report of work conducted during the late war under the author's direction by the section on Intermediary Metabolism of the Medical Division of the Chemical Warfare Service, organized originally by the Bureau of Mines. The work of this section consisted largely in exposing dogs during single or repeated periods of different time lengths to chlorin, phosgene or chlorpicrin in known and varying concentrations. Thorough and systematic examinations were made of the gassed animals under exactly specified conditions as to the clinical symptoms and their course, of the mor-

phologic and volume changes in the tissues and blood, the chemical changes in the blood and urine, the respiratory function, the acid base balance, etc. The findings are tabulated in detail together with the writer's analysis and interpretation. Having established a standard for control, experiments were performed with different therapeutic procedures.

One gathers from the data that the most notable gross changes observed consisted of edemas, especially of the lungs, with a fall in the volume of the blood, a rise in the blood concentration, and a failing circulation, this accounting, according to Underhill, for those observed changes of the respiratory function referable to oxygen starvation of the tissues with a fall of temperature and finally suspension of vital activities. The immediate cause of death must, he believes, be assigned to blood concentration. Acidosis, as measured by the methods selected, was missed except in the later stages of the picture. The therapeutic measures that yielded the most favorable results were those directed toward increasing the blood volume and dilution, namely, bleeding properly carried out and followed by a restoration of water, with alkali administration when acidosis was demonstrable. The work is notable for its thoroughness and accuracy. Apart from the value that it would have in the case of future warfare with gases it represents a piece of inductive research of exceptionally high order, and contains a mass of data and the description of methods that may well find their application in the study of toxicology in general.

THE MECHANICS OF THE DIGESTIVE TRACT. By WALTER C. ALVAREZ, M.D., Assistant Professor of Research Medicine University of California Medical School. Pp. 200. 22 Illustrations. Paul B. Hoeber, New York City.

This monograph is written to defend or establish the following theses from experimental and clinical data: (1) The normal and pathologic activities of the intestine are due to a polarized gradient in the intestinal musculature. There are no local reflex actions in the intestine itself. Auerbach's ganglionic plexus functions only in connection with the extrinsic nerves. All the local variations in action shown in different regions of the intestine are due to change in the rhythmicity of the muscular gradient. (2) That many, if not all, of the symptoms usually referred to a disordered intestine are caused by reversal of the gastro-intestinal peristalsis.

The first seven chapters deal with the facts and speculations on which the theory of muscular gradient of intestine action is based. Chapter IX deals with the practical application of this theory to conditions of gastro-intestinal disease in man. Chapter X deals with the supposed symptoms of reversed peristalsis. Chapter XI contains a critique of the current notions of "vagotonia" and "sympatheticotonia." The last chapter deals briefly with experimental methods, and the volume ends with a good bibliography of 450 titles.

The author is both a clinician and a laboratory worker. He has enthusiasm, and a good knowledge of the literature. The book is, therefore, a valuable compilation and treatise on the intestine, and is of interest to all medical men and physiologists. While, in general, the author is scientific in the analysis of facts and theories, in a few cases he becomes a special pleader and misconstrues facts in favor of his two main theses. He speaks of pieces of the stomach and intestine as "strips of muscle," when, as a matter of fact, they are strips of muscle, ganglia and nerves. On page 4 he says: "Most of us think of the pupillary response to light as a complicated cerebral reflex." That view may be held by the ignorant; the others know that in the mammal it is a midbrain, not a cerebral reflex.

On page 14 he says: "Another function of the Auerbach's plexus is probably to make the intestinal muscles respond properly to stimuli coming from the underlying mucous membrane. These stimuli are taken up by Meissner's plexus and transmitted to Auerbach's by connecting fibres." This is in all essentials a reflex act, and yet the author devotes a large part of the book to disprove reflex action in the intestine itself

Alvarez's recurring objection to local reflexes and the nervous action in the motor activities of the intestine is that "nervous action is not really understood." Granted! But is muscle contraction, or cell growth, or, in fact, any fundamental physiologic phenomenon really understood today? We do not understand the mechanism of memory, but must we, therefore, exclude memory as a factor in animal behavior? Nobody denies today that visceral as well as skeletal muscles, placed in certain artificial solutions in vitro, may be made to contract rhythmically. But these activities of dying tissues in artificial mediums have probably no relation to the normal activities of these tissues in the intact animal. Theories built on such nonphysiologic experimentation may help to explain, e. g., paralysis agitans or St. Vitus dance, but not normal neuromuscular coordination.

The following symptoms, according to the author, are due to reverse peristalsis in the intestine: vomiting, regurgitation, heart burn, belching, nausea, biliousness, coated tongue, foul breath, feeling of fulness soon after beginning a meal, globus, hiccough. The interested reader must judge for himself how successful the author is in these explanations. How is nausea and vomiting started by the smell or sight of disgusting objects to be explained by reverse peristalsis in the gut without admitting that the reversal of the peristalsis is itself a nervous action? In the paragraph on "Globus," the author offers this bit of physiologic speculation: "A few times in my life I have happened to swallow while a wave of regurgitation was on its way up the esophagus, and when the two waves met there was a painful tearing feeling. It may be that globus is brought about in that way." Alvarez meets the objection that reverse peristalsis is rarely seen even in marked gastro-intestinal motor disturbance by the assumption that such peristalsis, too feeble to move the intestinal content toward the stomach, or to be detected by the Roentgen ray, still produces nausea and allied mental states. He fails to make clear why reversal of peristalsis should cause central symptoms, while normal peristalsis does not, or why the reversed peristalsis which is normal (colon; duodenum) fails to cause untoward effects. The medical practitioner will probably be most interested in the "practical application" in Chapter IX. At the end of this chapter we read: "Some one may ask: In what way does the idea of a gradient altered by disease influence our method of treatment? The answer is that so far little has been done because therapeutists have not been thinking along these lines." The author hopes for drugs to restore the normal gradient, but at present can suggest only a smooth diet, a remedy that helps or fails, irrespective of the theories of intestine mechanism.

INDEX TO VOLUME 29