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A PHYSIOLOGICAL, ANATOMICAL, AND PATHOLOGICAL STUDY OF THE GLOSSOPHARYNGEUS AND VAGUS NERVES IN A CASE OF FRACTURE OF THE BASE OF THE SKULL.[1]

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(From the William Pepper Laboratory of Clinical Medicine, Phœbe A. Hearst Foundation.)

The opportunity to study the effect on man of unilateral degeneration of the glossopharyngeus and vagus nerves from a lesion near the medulla oblongata is rarely offered, and the following case is reported in the hope that it may throw some light on the physiology and the anatomy of these nerves. H. R., aged about fifty-four years, on April 8, 1902, fell about eight feet from car, striking on the top of the head. There was no detectable fracture of the skull, and no paralysis of the limbs. He was unconscious fifteen or twenty minutes after the fall; he then got up and walked a short distance. He was not able to swallow at all after the accident. The tongue when protruded was said to deviate a little to the left. He had a small scalp wound over the right frontal bone. The man was sent to the University Hospital by Dr. D. P. Miller, of Huntingdon, Pa., and was referred to my service by Dr. James Tyson. My notes made May 6th are as follows:

"Sensation for touch and pain is intact in the limbs and trunk. The grasp of each hand is normal. No loss of motor power is detected in any of the limbs. The patellar reflex on the right

[1] Read before the College of Physicians of Philadelphia, March 4, 1903.

side is normal or slightly diminished, and on the left side it is present, but not very strong. Ankle clonus is not present on either side. The Babinski reflex is not obtained on either side. The Achilles jerk is normal on each side, but not quite so prompt on the right side as on the left. The station and gait are normal even with the eyes closed, but the man has a tendency to drag his feet slightly. The reflexes of the upper limbs are normal. He has no muscular atrophy. He has no hysterogenic zones. The tongue is protruded straight, and shows no atrophy and no fibrillary tremors. The soft palate is a little better innervated on the right side than on the left. The pharyngeal reflex is preserved on each side. Salt and sugar are tasted correctly and promptly on the anterior two-thirds of each side of the tongue. The ticking of a watch is not heard plainly in either ear, but he has always been a little hard of hearing. The facial muscles are not implicated. The movements of the eyeballs are normal in all directions. Slight nystagmus is present in looking to either side, and the left external rectus may be a little weak."

The nystagmus was probably the result of the injury of the left cerebellar lobe.

The report of the examination of his eyes by Dr. Mellor is as follows: "There are no evidences of injury in the eye-ground. The right eye is very highly myopic. A cataract is present in the left eye."

The report of the laryngeal examination by Dr. Grayson is as follows: "Complete paralysis of the left half of the larynx. Absolute immobility of the left vocal cord and arytenoid cartilage. Moderate amount of simple inflammatory infiltration."

The man was kept alive by nutrient enemata, but he became gradually weaker, and finally was unable to retain the enemata. Dr. D. L. Edsall, with great difficulty, succeeded in passing the stomach tube on May 23d, but after it had been passed twice the patient declined to permit it to be passed again, preferring to die rather than to undergo the discomfort caused by passing the tube. The tube seemed to lodge in a pocket of the œsophagus at the cardiac end of the stomach. The pocket was probably the result of paralysis of the œsophagus on the left side. The stomach tube was not passed until May 23d.

At 11.30 A.M., May 24th, the pulse became more rapid and the temperature subnormal, and at 1 P.M. the man died.

My diagnosis in this case had been fracture of the base of the skull, possibly with hemorrhage at the base of the brain, and the necropsy showed that the diagnosis was correct. The necropsy was made by Dr. W. F. Hendrickson. His notes are as follows:

"*Pathological Diagnosis.* Cerebellar hemorrhage and softening, with pressure upon adjoining nerves; multiple abscesses of lung (probably bronchopneumonic in origin); parenchymatous degeneration of the liver and kidneys; chronic interstitial splenitis.

"*Detailed Description of the Organs. External Appearance.* Body that of a fairly well-developed and fairly well-nourished white male. Slight rigor mortis. No œdema. Superficial abrasion over auricle of left ear, also on neck just below left ear.

"*Abdominal Cavity.* Normal.

"*Pleural Cavity.* Normal.

"*Pericardial Cavity.* Normal.

"*Heart.* Weight, 270 grammes. Normal.

"*Lungs.* Left lung voluminous, and on palpation numerous nodules of increased consistence and averaging 1.5 cm. in diameter can be felt. On section the general lung surface is congested, and corresponding to the nodules referred to above are quite a few small areas of consolidation, dark red in color, and with a granular surface. Most of these resemble the areas of bronchopneumonia, but others show distinct breaking down in the centre with abscess formation. The abscesses are little more than the size of a split pea.

"The right lung shows a similar condition throughout the middle lobe. Upper and lower lobes the seat of congestion.

"*Spleen.* Somewhat enlarged. Cut surface grayish-red. Consistence slightly increased. Trabeculæ prominent.

"*Gastro-intestinal Tract.* Slight hyperplasia of solitary follicles throughout gut.

"*Liver.* Weight, 1 kilo. Normal in size. Cut surface cloudy. Consistence slightly decreased.

"*Gall-bladder.* Moderately dilated, and found to contain from fifteen to twenty stones of light yellowish-white color, superficially dark brown in tint.

"*Pancreas.* Slight increase in consistence. Cut surface shows lobules more clearly than normal.

"*Adrenals.* Negative.

"*Kidneys.* Normal in size. Capsule strips readily. Surface markings indistinct and cloudy. Consistence slightly decreased. Weight, 290 grammes.

"*Genito-urinary Organs.* Negative.

"*Aorta.* Negative.

"*Brain.* Marked œdema of pia-arachnoid coat. Examination of the base of skull reveals a fracture of the left side of the occipital bone into the foramen magnum, with a spicule of bone projecting at least one-quarter inch upward. Corresponding to this projecting spicule of bone is discovered an area of hemorrhage and softening on under surface of the cerebellum. Area of cerebellar involvement measures 1.5 x 1 cm. in size. Bony projection undoubtedly pressed upon adjacent nerves coming off from the medulla."

The microscopic examination was made by me.

The left glossopharyngeus and vagus roots in teased preparations stained with 1 per cent. osmic acid appeared intensely degenerated. The left recurrent laryngeal nerve and portions of the left vagus below the cranium treated in the same way were greatly degenerated. The left facialis and hypoglossus, the roots of the left trigeminus and of the right glossopharyngeus were normal.

Fine black dots were found by the Marchi method along the intramedullary portion of the left hypoglossus, so that this nerve was slightly degenerated. The descending root of the left glossopharyngeus and vagus nerves was intensely degenerated by the Marchi method, as was also the transverse portion of the intramedullary part of the left glossopharyngeus and vagus roots, and the degeneration was found as far cephalad as there are fibres of these nerves. The fibres arising in the left nucleus ambiguus and passing toward the fourth ventricle were degenerated by the Marchi method. Degenerated fibres could be traced across the raphe to the right fillet, but were lost here. They crossed the raphe about midway between the ventral and dorsal surfaces of the medulla oblongata. It is impossible to say whether or not they were fibres of the glossopharyngeus and vagus nerves passing to the opposite

side of the medulla oblongata. Most of the degenerated fibres of the left glossopharyngeus and vagus roots entered the descending root of these nerves, but some passed this root on its median side in their course, apparently toward the posterior nucleus. The left facialis root at its exit from the pons was not degenerated by the Marchi method, and the fibres within the left facialis nucleus were not degenerated. The left cochlear branch of the acusticus nerve was not degenerated within the medulla oblongata by the Marchi method.

Some of the cells of the left hypoglossus nucleus were swollen, and in these the nuclei were eccentric. The cells of the left nucleus ambiguus were much degenerated, they had lost their dendritic processes, the nuclei were not distinct, and the cells did not stain well. The nuclei in most of the cells in the posterior nucleus of the left glossopharyngeus nerve were eccentric, whereas in the corresponding right nucleus they were central, with few exceptions.

A very few muscle fibres in the left side of the tongue in the region of the circumvallate papillæ were degenerated by the Marchi method, but the left laryngeal muscles were intensely degenerated. Sections of the left side of the pharynx at the level of the hyoid bone, stained by the Marchi method, contained some degenerated fibres, but not nearly so many as did the left laryngeal muscles. Sections from the middle of the arch of the left soft palate contained only a few degenerated muscle fibres.

The degeneration of the vagus on the left side in my case affords an opportunity to study the effect of injury of this nerve on the heart and lungs. This subject has received careful study by reliable observers. Bernhardt,[1] in his recent work on the nerves, says that according to some authors the inflammatory changes in the lungs of the character of bronchopneumonia, occurring after vagus lesions, are the result of paralysis of the bronchial musculature and of the vasoconstrictor fibres, which causes neuroparalytic hyperemia of the pulmonary tissue. He says, further, that, according to Deibel, it is not a fatal operation. Only division of both vagus nerves is fatal. Similar views were ex-

[1] Die Erkrankungen der peripherischen Nerven: Nothnagel's Specielle Pathologie und Therapie, vol. xi., part 1.

pressed by Demme and Mackenzie. The observations, however, of Demme and Stromeyer show that occasionally in man disquieting symptoms may result from unilateral division of the vagus; such as at first show deep respiration, hoarseness or almost loss of voice, diminished respiratory murmur on the injured side, dyspnœa, danger of suffocation, and small and rapid pulse. Stromeyer's case, however, is not altogether satisfactory.

According to Traumann,[1] pulmonary symptoms were present in all reported cases of bullet wound of the vagus except in his own case, as in all there was a weak respiratory sound, or even absence of respiratory sound on the side of the injury, or even pneumonia. Unilateral division of the vagus in experiments on animals, he says, has caused few pulmonary symptoms. Only rarely in dogs, never in rabbits, and after a considerable period has it caused any grave disease of the lungs. One vagus seems to be sufficient for the function of both lungs. Traumann says that in twenty cases known to him in which the vagus was resected during the removal of a tumor, no persisting impairment of respiration was observed. He points out that in Stromeyer's case of injury of the vagus both vagi were injured. Other cases, he thinks, are described too briefly or are too complicated to be of much service in determining whether or not lesion of one vagus causes pulmonary disease.

In another case reported by Traumann, one of injury of the hypoglossus and accessorius, bronchopneumonia developed on the second day after the injury occurred, and was attributed to particles entering the lungs. He believes this could not be explained by the unilateral paralysis of the accessorius alone, but was caused by this in association with hypoglossus paralysis. By the paralysis of the geniohyoid and thyrohyoid muscles on one side, the movement of the larynx upward and forward was disturbed.

Adolf Widmer,[2] in 1893, collected the reports of a large number of cases in which the vagus had been divided during operation. According to Widmer, Traube in 1871 showed that division of the vagus nerve in the neck caused pneumonia by paralysis of the larynx and œsophagus, this paralysis allowing saliva and food

[1] Deutsche Zeitschrift f. Chirurgie, 1893, vol. xxxvii. p. 161.
[2] Ibid., vol. xxxvi. p. 283.

to enter the lungs. O. Frey (1877) confirmed Traube's statements by numerous experiments, which seem to have been on both vagi. Widmer says that the results of unilateral vagotomy are contradictory; in some cases important pulmonary changes occurred, in others they were absent. The cases in which pulmonary changes occurred after unilateral vagotomy, as reported by Widmer, are of difficult interpretation.

Of nine cases in man in which the vagus was cut intentionally, no alteration of the character or frequency of the respiration was observed in seven; slight change of respiration was observed in one, and the respiration was deep and irregular in one case of difficult interpretation. Widmer concludes that aside from paralysis of the larynx and irritation causing coughing, unilateral vagotomy is a harmless operation so far as the lungs are concerned.

George W. Crile,[1] in his recent paper "On the Effect of Severing and of Mechanically Irritating the Vagi," remarks that in the literature of this object the clinical reports of the effects of mechanically irritating, dividing, or resecting the vagus are much at variance. His experiments showed that severing one vagus was attended by comparatively little effect upon either respiration or circulation. Usually there was a slight rise in the blood pressure, and a slight decrease in the frequency of respiration, with an increase in the amplitude. His reports of severing of the vagus in man seem to show that this operation is not usually followed by persisting serious results so long as only one vagus is injured.

The respiratory rate in my case was about normal, but the pathological findings in the lungs were exceedingly interesting in this connection. The left lung was voluminous, and on palpation numerous nodules of increased consistency and averaging 1.5 cm. in diameter were felt. The lung surface appeared congested on section, and small areas of consolidation, dark red in color, with a granular surface and corresponding to the nodules mentioned above, were found in the left lung. Most of these areas resembled the areas of bronchopneumonia, but others showed distinct breaking down in the centre, with abscess formation. The abscesses were about the size of a split pea. A similar condition was found

[1] American Journal of Medical Sciences, April, 1902, p. 652.

throughout the middle lobe of the right lung, and the right upper and lower lobes were congested. It seems improbable that this pulmonary condition was caused by the entrance of foreign bodies into the lungs, because the patient was entirely unable to swallow. Saliva, however, doubtless passed into the trachea and carried with it micro-organisms. I tested the patient once with a glass of water, and his choking was so alarming that the attempt was not repeated. He was nourished by rectal enemata, and the stomach tube was passed only on the day before his death. The choking was probably the result of impaired function of the epiglottis. It seems reasonable to attribute the pulmonary condition to the paralysis of the vagus nerve, but these pulmonary lesions were not recognized until a necropsy was obtained forty-six days after the accident. Recovery in some cases is probably reported before the cases have been observed sufficiently long.

Bernhardt[1] quotes Eichhorst as saying that the vagus is the trophic nerve of the heart, and that the lesion of one vagus may cause fatty change in the heart. He says that Masoin, in 1872, and Arloing and Tripier, in the same year, showed by experimentation that the two vagi do not exert the same inhibitory action on the heart, and that the right vagus exerts a more powerful inhibitory action than the left. Eichhorst has come to similar conclusions from experimentation. Bernhardt remarks that in seven cases of vagotomy that could be employed for a determination of the question, reported by Deibel, no remarkable cardiac phenomena were observed. In Traumann's case of injury of the vagus by a bullet, without necropsy, the pulse was 90 to 130 for weeks, although the patient was kept quiet, and after exertion it became 180. The increase in the rapidity of the pulse was not permanent. In the cases of bullet wound of the vagus reported by Demme and Schüller the pulse was rapid. Traumann says that in none of the cases of injury of the vagus by the removal of a tumor has any peculiarity in the beat of the heart been observed. In experiments on animals unilateral division of the vagus has not caused any change in the heart beat, but bilateral division has produced an increase in the rapidity of the beat.

[1] Loc. cit.

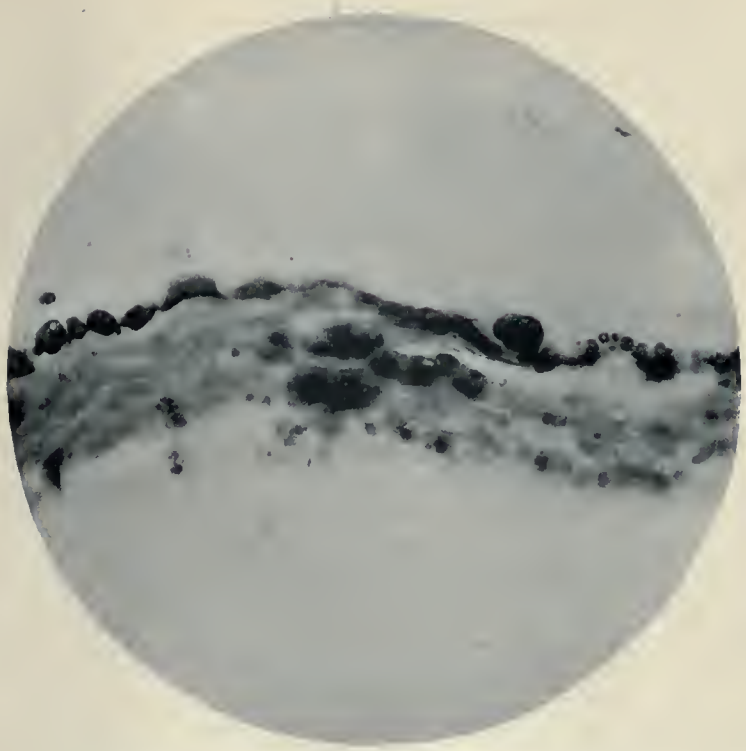


FIG. 1.—Photograph of degenerated root fibres of the glossopharyngeus and vagus nerves. Teased preparation stained with 1 per cent. osmic acid.

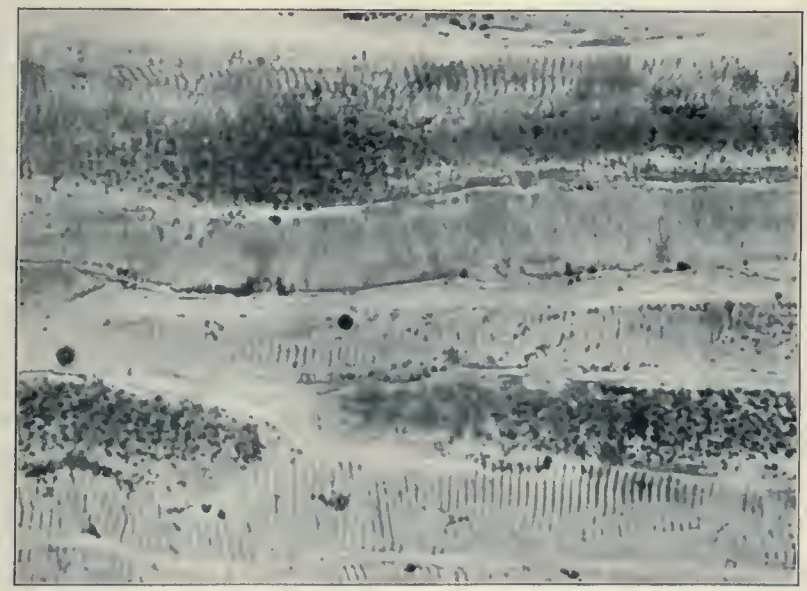
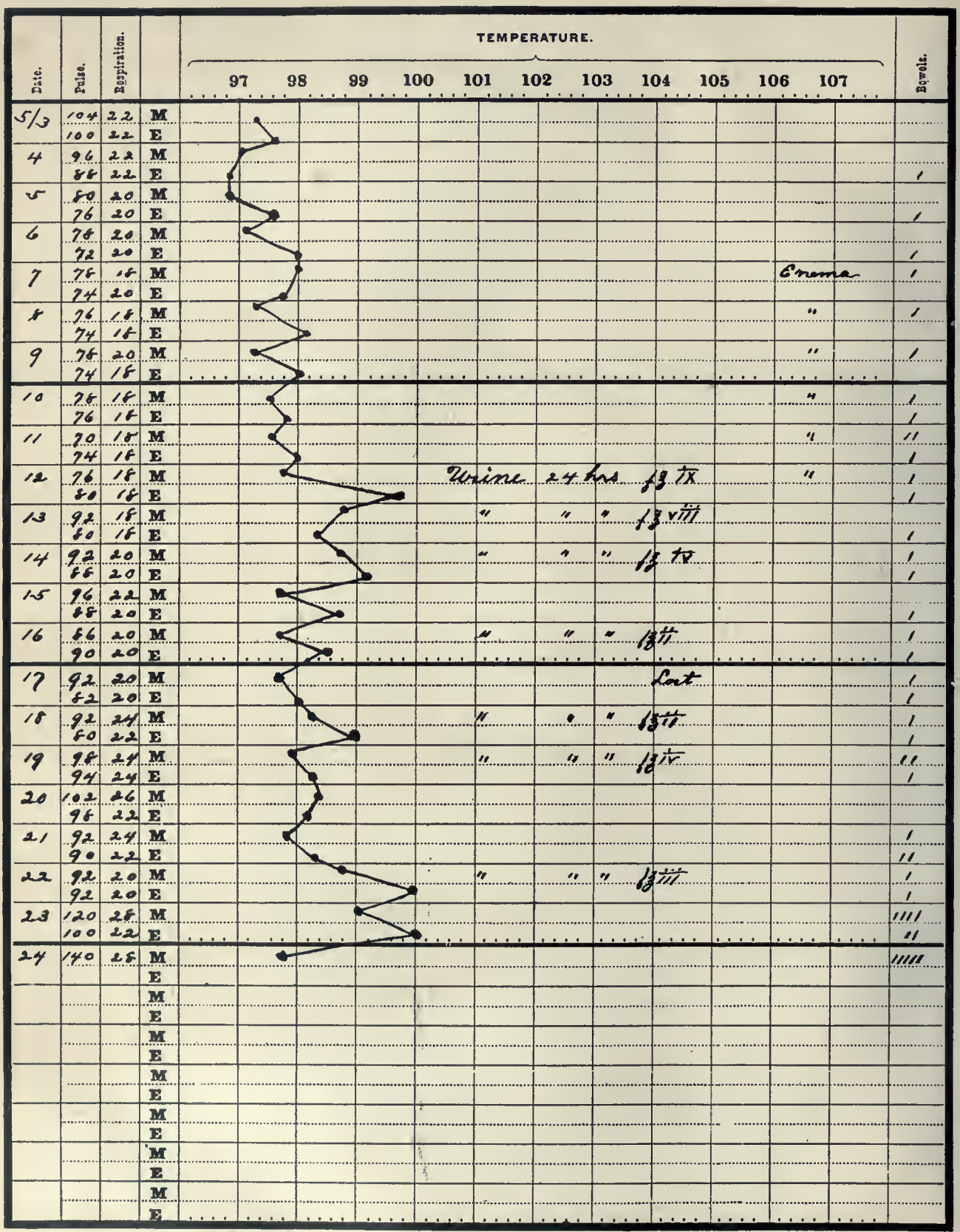


FIG. 2.—Photograph of the left laryngeal muscles, showing degeneration by the Marchi method.


TEMPERATURE.
97 98 99 100 101 102 103 104 105 106 107
Date.
Pulse.
Respiration.
Bowels.
5/3 104 22 M
100 E
4 96 22 M
88 22 E
5 80 20 M
76 20 E
6 78 20 M
72 20 E
7 76 18 M
74 20 E
Enema
8 76 18 M
74 18 E
"
9 76 20 M
74 18 E
"
10 76 18 M
76 18 E
"
11 70 18 M
74 18 E
"
12 76 18 M
80 18 E
Urine 24 hrs
"
13 92 18 M
80 18 E
"
14 92 20 M
88 20 E
"
15 96 22 M
88 20 E
16 86 20 M
90 20 E
"
17 92 20 M
82 20 E
Cast
18 92 24 M
80 22 E
"
19 98 24 M
94 24 E
"
20 102 26 M
96 22 E
21 92 24 M
90 22 E
22 92 20 M
92 20 E
"
23 120 28 M
100 22 E
24 140 28 M
E
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E
97 98 99 100 101 102 103 104 105 106 107
TEMPERATURE.

FIG. 3.—Chart.

Blanke regarded the pulse of 90 to 100 in his case of bullet wound of the vagus, hypoglossus, and glossopharyngeus as a vagus symptom, but this case was complicated with pneumonia, and fever existed.[1]

In my case the heart weighed 270 grammes, and on inspection appeared to be normal. The pulse, however, was a little accelerated. The man was kept very quiet, and yet the pulse at times was as high as 104, 96, or 92 when he came under my observation four weeks after the accident. It is a pity that the heart was not preserved for microscopic examination. Only on three occasions, except two days before death, did the temperature rise as high as 99° F., and on one of these occasions it was 99.8° F.

Vomiting was present in Traumann's case of bullet wound of the vagus during the first few days following the accident, and was attributed by Traumann to irritation of the vagus. Vomiting has been observed as a sign of injury of the vagus by Boinet also. It was not present in my case after the patient came under my care, and no mention was made of its having existed previously.

The influence of the vagus on the kidneys in man is not well known. In my case parenchymatous degeneration of the kidneys and liver was present, but it is questionable whether this was caused by the degeneration of the vagus nerve.

The distribution of taste fibres to the tongue is still a subject of much dispute. Recent critical studies of this subject are by C. K. Mills[2] and Frankl-Hochwart.[3] The former comes to the conclusion that the glossopharyngeus supplies all parts of the tongue with taste fibres, while the latter concludes that the trigeminus is the nerve of taste to the anterior two-thirds of the tongue in many persons, although not in all. The evidence that the glossopharyngeus supplies the part of the tongue behind the circumvallate papillæ, and including these papillæ, and that the chorda tympani supplies the part in front, seems very strong, but

[1] Eine Schussverletzung des linken Vagus. Dissertat., Göttingen, 1871. Cited by Traumann.

[2] The Nervous System and its Diseases. J. B. Lippincott Company, Philadelphia, 1898.

[3] Nothnagel's Specielle Pathologie und Therapie, Band xi., II. Theil, IV. Abtheilung.

it is still uncertain in what way the taste fibres within the chorda tympani reach the brain. According to some writers (Schiff, Erb, Bernhardt) the taste fibres supplying the anterior portion of the tongue pass by the chorda tympani, the facialis, the petrosus superficialis major, the ganglion sphenopalatinum, the second branch of the trigeminus to the brain. Brücke and Carl (cited by Bernhardt) believe they pass by the ganglion oticum, the petrosus superficialis minor, the plexus tympanicus, the ganglion petrosum, the glossopharyngeus to the brain; still others believe that the portio intermedia, really a part of the glossopharyngeus, conveys the taste fibres from the facialis to the brain. Gowers[1] believes that the trigeminus is the nerve of taste to the entire tongue.

My case may throw some light on this subject. Salt and sugar were promptly recognized on both sides of the anterior two-thirds of the tongue. By some oversight the condition of taste in the posterior third of the tongue was not recorded, but it was probably tested. It is extremely difficult to determine accurately the condition of taste in the posterior portion of the tongue. I cannot determine whether in this case the taste fibres of the chorda tympani reached the brain through the portio intermedia or the trigeminus, as neither nerve was degenerated and taste in the anterior two-thirds of the tongue was normal. I may, however, assume that the taste fibres from the anterior portion of the tongue could not have reached the brain by the glossopharyngeus, as described by Brücke and Carl, inasmuch as the glossopharyngeus was intensely degenerated, and yet taste in the anterior part of the tongue was normal.

There has been some doubt concerning the condition of the taste buds of the circumvallate papillæ of the tongue after a lesion of the glossopharyngeus. The views of the different investigators are clearly set forth by Frankl-Hochwart.[2] Vintschgau and Hönigschmied found that the taste buds of these papillæ in the rabbit disappear soon after division of the glossopharyngeus, and that after three weeks no taste buds are found in the papillæ foliatæ or in the papillæ circumvallatæ. Their investigations were con-

[1] Journal of Physiology, July 21, 1902, No. 4.

[2] Loc. cit.

firmed by Ranvier, Drasch, Sandmeyer, and Rosenberg; while Benno Baginsky[1] alone has disputed their statements.

From his experiments on nine rabbits he concluded that after division of either the left or the right glossopharyngeus, in young or old animals, the taste buds were not affected, that they neither degenerated nor disappeared, no matter how long the animals lived after the operation. Rosenberg found degeneration of the taste buds in the circumvallate papillæ in a man in whom the glossopharyngeus had been destroyed by a tumor. The taste buds were degenerated on the side on which was the degenerated nerve, but the condition of the taste buds on the other side is not mentioned, although it seems to be implied that they were not degenerated. This is the only case in man that I know of, except my own, in which the taste buds of the circumvallate papillæ were found degenerated after a lesion of the glossopharyngeus nerve.

The taste buds in the circumvallate papillæ in my case had disappeared on the left side of the tongue, but were present though possibly not so numerous as normal on the right side of the tongue.

The taste buds probably are not so numerous nor so perfect in a person aged fifty-four years as in a child, but I have obtained for comparison the circumvallate papillæ from a man aged sixty-two years. I must believe, therefore, that the taste buds of the circumvallate papillæ are innervated by the glossopharyngeus. They are not nearly so numerous in man as in preparations from the rabbit loaned me by Dr. G. A. Piersol.

It is uncertain to what extent the trigeminus gives sensory fibres to the soft palate and pharynx. Inasmuch as in my case the pharyngeal reflex on the side of the degenerated glossopharyngeus was preserved, I believe that the sensory distribution of the pharynx cannot be confined to the glossopharyngeus.

The motor innervation of the soft palate has been supposed by many to be through the seventh nerve, and deviation of the uvula is described in facial palsy, but Hughlings Jackson, Gowers, and Frankl-Hochwart dispute the correctness of this opinion. In Traumann's case of bullet wound of the vagus the soft palate was

[1] Virchow's Archiv, 1894, vol. cxxxvii. p. 389.

paralyzed on one side, but as the superior laryngeal nerve escaped, the paralysis could not have been a vagus symptom. It was attributed by Traumann to injury of the palatine nerves from the sphenopalatine ganglion. In my case the soft palate was still innervated on the left side, and yet there was a distinct although slight difference between the two sides. A few degenerated muscle fibres also were found in the left side of the soft palate by the Marchi method. I conclude, therefore, that the innervation of the soft palate is, in part, by means of the glossopharyngeus or vagus.

The posterior nucleus of the vagus and glossopharyngeus is usually described as sensory, and yet strong evidence is offered that it is motor. Oppenheim[1] remarks that Forel, von Monakow, and Bruce regard it as a motor nucleus, or at least as the origin of centrifugal fibres. Marinesco has regarded it as a motor nucleus, and van Gehuchten by the silver stain has traced the axis-cylinder processes of the nerve cells of this nucleus toward the periphery of the medulla oblongata. In 1898 I[2] spoke of a case of amyotrophic lateral sclerosis, in which, in association with Dr. Dercum, I found degeneration of this posterior nucleus, and I remarked that the degeneration of this nucleus in amyotrophic lateral sclerosis suggested that the nucleus was motor in function, inasmuch as in this disease the degeneration is chiefly of the motor system. In my case described in the present paper the cells in the posterior nucleus on the left side were swollen and their nuclei were eccentric. As such alterations as these would not be likely to occur if the nucleus were sensory, because then these cells would not be an integral part of the peripheral fibres, it seems more probable that the posterior nucleus is motor.

There is much doubt concerning the origin of the accessorius. It is commonly spoken of in English and American works on anatomy as the spinal accessory nerve (nervus spinalis ad pneumogastricum accessorius), and the Germans describe it as the accessorius vagi. The nerve fibres innervating the larynx have been supposed to be derived from the accessorius, but Grossmann and Grabower have disputed this. The latter showed by experimenta-

[1] Lehrbuch der Nervenkrankheiten, third edition.

[2] Journal of Nervous and Mental Disease, 1898, p. 677, and February, 1899.

tion that the motor fibres of the larynx are contained in the lowest four or five root bundles of the vagus, and that these fibres have their origin in the nucleus ambiguus; whereas the accessorius has only a spinal nucleus. An accessorius vagi, according to Grabower, does not exist, as the ramus internus is a portion of the vagus. This view was held earlier by Holl, and seems to be accepted by most of the recent investigators. Bunzl-Federn, Roller, Darkschewitsch, and Dees believe the accessorius nucleus extends into the medulla oblongata and gives fibres to the vagus.[1] Inasmuch as the distal portion of the vagus roots is associated with the accessorius only for a small portion of its course and becomes a part of the vagus after its exit from the cranium, Obersteiner[2] suggests that it would be well to speak of it as distal vagus roots, and to describe the spinal portion alone as the accessorius.

This suggestion seems to me a proper one, but the name, accessorius, is then hardly suitable. My case shows that the fibres innervating the laryngeal muscles may be paralyzed by a fracture extending into the jugular foramen, when the fibres supplying the sternocleidomastoid and trapezius muscles escape, inasmuch as paralysis of these muscles was not observed. The nerve-root fibres that were degenerated could not be distinguished from those of the vagus, and it seems to me better to regard the nerve roots having their origin dorsal to the lower olive as belonging exclusively to the glossopharyngeus and the vagus. The association of the lower portion of these roots with the accessorius within the jugular foramen cannot be very intimate, as a fracture passing into this foramen may cause paralysis of the fibres innervating the larynx, while those to the sternocleidomastoid and trapezius muscles escape.

[1] See Oppenheimer. Loc. cit.

[2] Anleitung beim Studium des Baues der nervösen Centralorgane, fourth edition, p. 512.

TRAUMATIC LESIONS OF THE SPINAL CORD WITHOUT FRACTURE OF THE VERTEBRÆ.[1]

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

Injury of the spinal cord without fracture of the vertebræ is not of very rare occurrence, and it is important to know what is the pathological condition in these cases. Usually the symptoms are supposed to be produced by hæmatomyelia, and in some cases they undoubtedly are so produced, but in others they are the result of a traumatic myelitis. I have observed four very similar cases of severe traumatic lesions of the spinal cord without detectable fracture of the vertebræ within the past year, and two of these cases were with necropsy. Three of the patients died, and the fourth at the present time gives promise of recovery.

The case that forms the subject of study in this paper was in my service at the Philadelphia Hospital during the summer of 1901, and is interesting because of the dissociation of sensation that occurred, because of the difficulty in the diagnosis of the process and of the level of the lesion, because of the rapid restoration of power in the lower limbs notwithstanding the intense degeneration of the motor tracts, as shown by the Marchi method, because of the organic lesions of the spinal cord without compression of the cord or fracture of the vertebræ, and because of

[1] Read in abstract at the meeting of the American Neurological Association, June, 1902.

the diminution of the patellar reflex after partial transverse lesion of the spinal cord in the cervical region.

J. H., aged forty-six years, on August 10, 1901, fell out of a window about eight feet from the ground and struck on his face. His fall occurred during the night, and he was picked up the next morning and was carried into the house. He was unconscious after the fall for at least several hours. The exact period of unconsciousness was not known. He had not been drinking, and knew of no cause for his fall.

Present Condition, August 12, 1901. He is conscious and talks rationally, and has no peculiarity of speech. He has a recent scar on the right side of his chin and on the inner and right side of the lower lip. He has to be catheterized and has involuntary defecation. He is a well-developed, muscular man.

Lower Limbs. He can draw the left lower limb up freely, but there is diminution of voluntary power in the limb. Resistance to passive movement in this limb is much impaired.

Voluntary movement in the right lower limb is very much diminished at all parts. Resistance to passive movement in this limb is also very much diminished. Voluntary movement of the right toes is much impaired, while the voluntary movement of the left toes is better than that of the right.

Reflexes. The knee-jerk is prompt on each side, but not distinctly exaggerated. The Achilles-jerk is present on the right side, but diminished. The Babinski reflex is uncertain on the right side, but was distinct once or twice. The Babinski reflex on the left side is uncertain. No ankle clonus is obtained on either side. The plantar reflex on each side is prompt.

Sensation for touch in the lower limbs is normal. Sensation for pain is much diminished and equally in both lower limbs. Temperature sense in the lower limbs is very much altered. Priapism is not present.

Trunk. No deformity of the vertebral column is detected. Sensation for touch is normal in all parts of the trunk, back and front. Pain and temperature senses are very much altered as high as the base of the neck, over both back and front of the trunk.

Upper Limbs. Great loss of voluntary power is observed in both the upper limbs. He is unable to move the fingers of either hand. The movements are all more impaired in the distal ends of the upper limbs—*i. e.*, he can move his shoulders and elbow-joints better than his wrists or his fingers, but even at the shoulder and elbow of each side the movement is very much impaired.

Resistance to passive motion is almost *nil* in the upper limbs. No atrophy, no contractures, and no fibrillary tremors are seen anywhere. Sensation for touch is normal, for pain and temperature is diminished in each upper limb, but not so much so as over the trunk.

Head. The movements of the head from side to side, and from before backward, are free. The tongue is protruded in the median line, and is not atrophied, and moves freely. The movements of the lower jaw are free. The movements of the eyeballs are free in all directions.

Pupils. The left is decidedly larger than the right, but the dilatation in the left eye is not excessive, nor is the contraction in the right eye excessive.

The right palpebral fissure is narrower than the left, and some retraction of the right eyeball is observed. The movements of the facial muscles are normal.

Soreness is felt only in the face and arms, and is probably the result of bruising of these parts. No tenderness is felt along the vertebræ in the cervical region. He complains of a sense of smothering, and this has been present about twelve months.

No weakness of the diaphragm is found. He can shrug his shoulders fairly well.

August 17, 1901. The patient seems confused, and he does not recognize persons whom he has seen while in the hospital. No return of motor power is found in the upper limbs. Sensation cannot be tested carefully on account of the mental confusion, but when either hand is stuck with a pin, he says it hurts. He can pull up either lower limb at the hip and flex it at the knee. Voluntary power in the lower limbs is much diminished. The knee-jerk on the right side is feeble; on the left side it seems to be entirely absent. Achilles-jerk is absent on each side. The Babinski reflex, as shown by the extensor movement of the small

toes, is present on each side. The big toes are not moved distinctly in either direction.

When stuck deeply in the lower limbs the patient makes no attempt at defense, and shows no expression of discomfort. When stuck with a pin over the front part of the trunk he shows no discomfort until the pin approaches about two or three inches below each clavicle, so that pain sense is much impaired in these parts. It is preserved to some extent in the upper limbs. The left pupil is still larger than the right, but the reaction of the iris cannot be determined, because of the bad illumination and the exceeding dark color of the iris. There appears to be no contraction of the iris to light.

August 21, 1901. The right knee-jerk is present, but very much diminished. The left knee-jerk is present and prompt, although the movement of the leg is not very great. The Achilles-jerk is present on the right side, and is prompt; the same is true of Achilles-jerk on the left side. The Babinski reflex is present on each side.

August 24, 1901. The mental condition is much better than it has been during the past week, but he does not recall whether he had a fall or not. He answers questions correctly. He has a tendency to be rambling in his speech. The return of motor power in the lower limbs since the last examination is truly remarkable. He can draw up either lower limb at the hip or flex it at the knee, or move the foot at the ankle, and can move his toes quite freely on either side. The knee-jerk is present on each side, the right being a little prompter than the left, but neither is fully normal. The Babinski reflex is present on the right side, and also on the left in so far as the small toes are turned upward, but the movement of the big toe is not distinct on either side. The cremasteric reflex is present on each side. The abdominal and epigastric reflexes are uncertain.

Sensation. Tactile sense is present in all parts of the body. Temperature sense is altered throughout the body as high as the clavicles, and posteriorly as high as the level of the clavicles; above the line of the clavicles heat and cold are correctly distinguished, below this line hot and cold objects are called warm indiscriminately.

Pain sense is correctly felt in each lower limb, below the knee, and over the anterior surface of the right thigh. He is unable to distinguish correctly sharp and dull objects over the anterior surface of the left thigh, trunk, and upper limbs, but can distinguish them in the face. No distinct spasticity of the lower limbs is seen.

Upper Limbs. There seems to be a tendency to contracture at the right elbow, it is not very marked, and is easily overcome. He is unable to move his fingers on either side, or to move either hand at the wrist. He can flex the right upper limb at the elbow, but cannot extend it; he can both flex and extend the left upper limb at the elbow. He can shrug his shoulder well. Extension of the left forearm on the arm is very feeble. He has some power of elevation of the upper limbs at the shoulders. There is a suggestion of atrophy in the interossei muscles. He moves his head freely from side to side. There is no indication of fracture of cervical or thoracic vertebræ on inspection or palpation. The tongue is protruded in the median line, and is not atrophied. The masseters contract firmly The movements of the eyeballs. are normal. The left pupil is dilated, the right is contracted. Both irides are apparently immovable to light and in convergence.

Heart. A systolic murmur is heard at the apex. It is not very distinct and not transmitted into the axilla. The rhythm is very irregular. The second pulmonic sound is accentuated, and the action is feeble.

Lungs. Breathing is very superficial. Breath sounds back and front seem to be normal, although it is impossible to get the patient to take a deep breath. The breathing is chiefly abdominal. No paralysis of the diaphragm is detected. Examination seems to show that the lesion is chiefly in the seventh and eighth cervical and first thoracic segments.

September 9, 1901. The patient has feeble movements of flexion and extension in the fingers of each hand, and also feeble movements at each wrist.

He is said to have had a chancre thirty years previously.

Hyaline and granular casts and albumin have been found in the urine.

He died September 17, 1901.

The resident physician, Dr. Johnson, was present at the necropsy, and assures me that fracture of the vertebræ or compression of the cord was not found.

The results of the microscopic examination are as follows:

Uppermost Cervical Region. The degeneration as shown by the Marchi method is in the antero-lateral, direct cerebellar, and Gowers' tracts, the lateral limiting zone of Flechsig and the columns of Burdach and Goll. The crossed pyramidal tracts contain very few black dots.

Sections taken just above the sixth cervical segment, and, therefore, probably from the fourth and fifth cervical segments—although the location was not accurately determined—show a condition of degeneration implicating almost all the transverse area at this level. Several blocks of tissue were taken from the degenerated area, and numerous microscopic sections were made from these blocks. The separation of white and gray matter is sharp. The staining is imperfect even by the Weigert hæmatoxylin method, as sufficient time for some degeneration detectable by this method had elapsed. Numerous spaces from which nerve fibres have disappeared are found in the white matter. Swollen axones are seen here and there. Slight round-cell infiltration is found about the vessels of the cord, and proliferation of the neuroglia is distinct. A very few minute hemorrhages are present at this level and elsewhere in the cervical region, but the sections are chiefly remarkable on account of the absence of hemorrhages that can be detected with the naked eye. I would emphasize that the hemorrhages present are very minute, and are not numerous. Sections from this level stained by the Marchi method show numerous black dots scattered over the cord, but most numerous in the lateral columns, and these indicate that many of the myelin sheaths are in process of degeneration. The columns of Goll are less implicated than are the other columns of the cord.

Sixth Cervical Segment. There are no signs of softening of the cord at this level. Slight round-cell infiltration is present in one posterior root and in the pia. The intima of the anterior spinal artery is thickened. The anterior and posterior spinal roots are not degenerated. Some of the nerve cell-bodies of the anterior

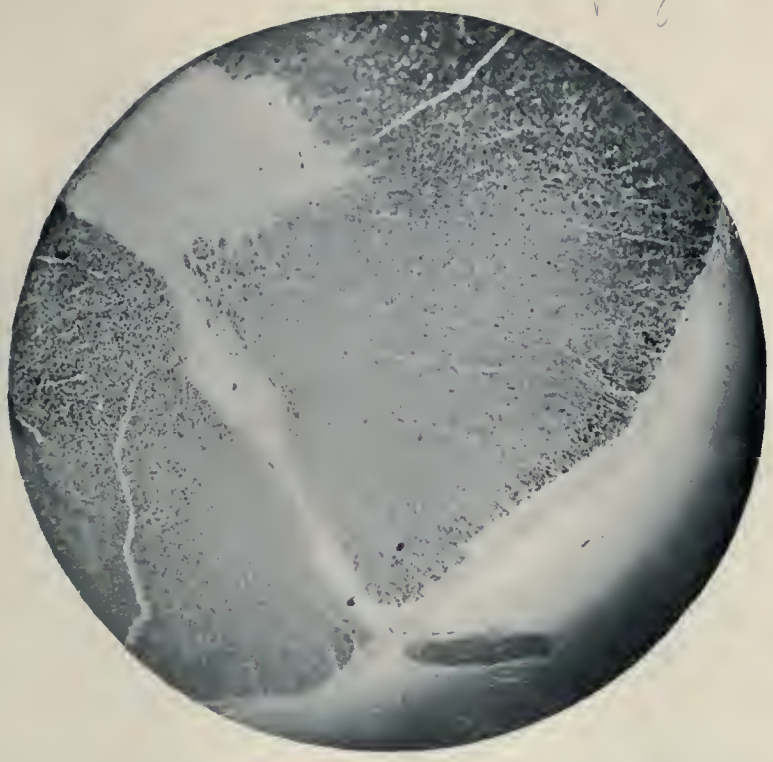

FIG. 1.—Photograph of a section from the upper cervical region, showing degeneration of the direct cerebellar and Gowers' tracts and of the posterior columns by the Marchi method. The crossed pyramidal tracts are not degenerated, as the section was taken above the area of traumatic myelitis.

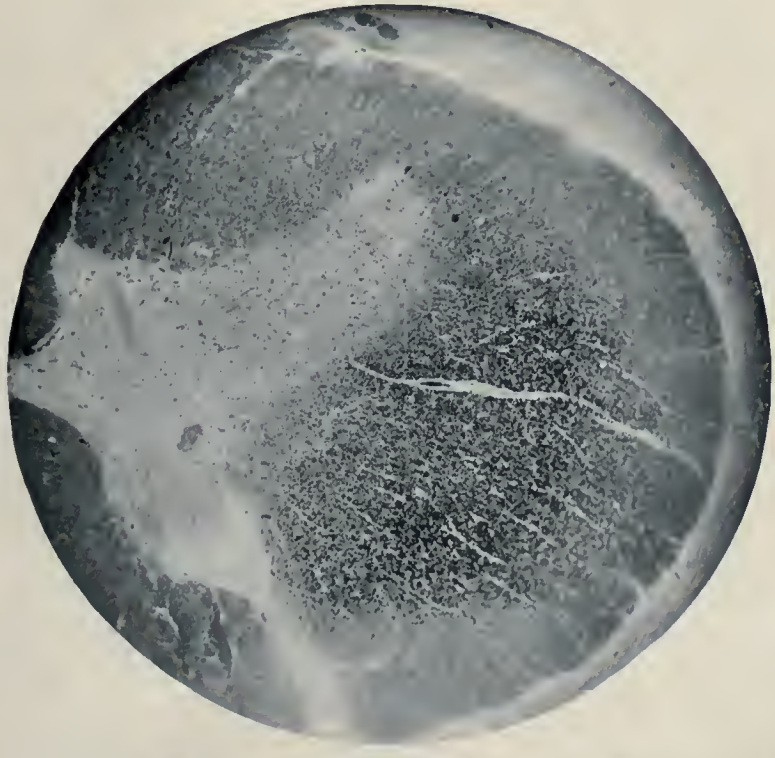

FIG. 2.—Photograph of a section from the eighth cervical segment, showing intense degeneration in the crossed pyramidal tract by the Marchi method.

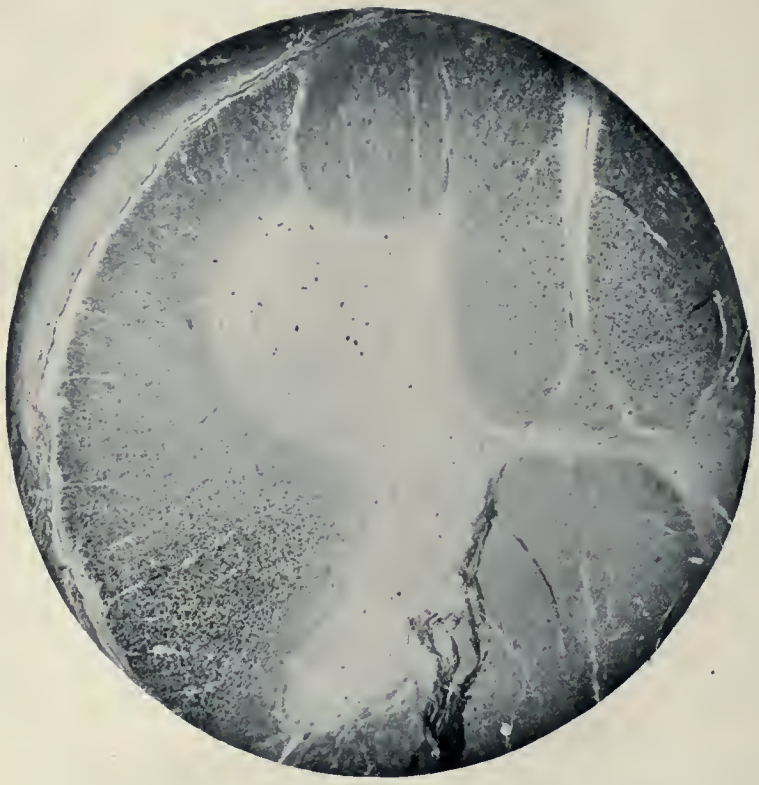

FIG. 3.—Photograph of a section from the lumbar region, showing intense degeneration in the crossed pyramidal tract by the Marchi method, and yet the recovery of voluntary power in the lower limbs was great.

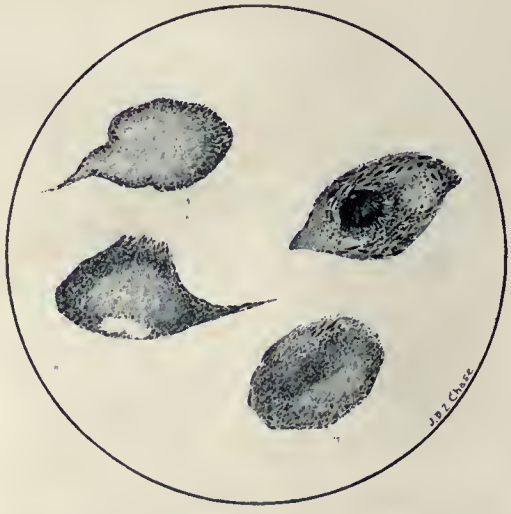

FIG. 4.—Degeneration of nerve-cell bodies in the anterior horns of the eighth cervical segment.

horns are much altered, in these the chromophilic elements have almost disappeared, and the cell-bodies have a greenish-yellow appearance. The alteration is much less intense than at the eighth cervical segment. The bloodvessels are congested. Degeneration is not distinctly shown by the Weigert hæmatoxylin method. *Seventh Cervical Segment.* The condition of this segment is very similar to that of the sixth cervical segment.

Eighth Cervical Segment. A section at this level stained by the Marchi method shows intense degeneration in the pyramidal tract of each side, and some degeneration—less intense—in each antero-lateral column. Degeneration is also seen in the column of Burdach of each side near the posterior horn. Numerous degenerated fibres are found in the anterior commissure and in the anterior horns. The direct cerebellar and Gowers' tracts are not degenerated. The columns of Goll are not degenerated. The anterior roots cut separately from the cord are not degenerated. The nerve cell-bodies of the anterior horns at this level are very much altered. They are rounded, and some have lost their dendritic processes, and in many the chromophilic elements have disappeared.

Mid-thoracic Region. The degeneration is chiefly in the pyramidal tracts, but is found also in the antero-lateral columns. The posterior columns are almost entirely free from black dots. The direct cerebellar and Gowers' tracts are not degenerated.

Lumbar Region. The nerve cell-bodies of the anterior horns are not distinctly degenerated, although here and there a cell-body is found that is not perfect. The condition is such as might be expected in a spinal cord from a normal person of about the same age. The degeneration in the pyramidal tracts extends into the lumbar region, as shown by the Marchi method, but not by the Weigert hæmatoxylin method. A slight round-cell infiltration is found in the pia of the lumbar region.

Summary. A man fell out of a window, a distance of eight feet, and struck on his face. His fall occurred during the night, and he was picked up the next morning. He was unconscious after the fall for several hours. His condition on the second day after the fall, when he was seen by me, was as follows: He was

perfectly rational. He had no control over the bladder or rectum. He could draw the lower limbs up, but movement was much impaired in these limbs. The patellar reflex was not exaggerated but was present. Babinski's reflex was uncertain on each side. Voluntary movement was much impaired in the upper limbs, and the fingers of each hand could not be moved voluntarily at all. The limbs at the shoulders and elbows could be moved imperfectly. Sensation for touch was normal in all parts of the body. Sensation for temperature and pain was much impaired in the lower limbs, and over the trunk anteriorly and posteriorly as high as the base of the neck, and in the upper limbs, but not as much here as in the lower limbs. Movements of the head were not impaired.

On the seventh day after the fall the knee-jerk on the right side was feeble, and on the left side absent. This Babinski reflex was present on each side.

On the fourteenth day the restoration of power in the lower limbs was recorded as remarkable. He could move the lower limbs and toes freely while in bed. The knee-jerks were still diminished. Tactile sensation was normal in all parts of the body. Temperature sense was much diminished as high as a line through the clavicles, pain sense was much diminished in the same region, except in each lower limb below the knee and on the anterior surface of the right thigh. He was still unable to move his fingers or hand on either side, but had partial return of power at the elbows, and still more at the shoulders. He could shrug his shoulders well.

On the thirtieth day after the fall he had feeble movements of extension and flexion in the fingers of each hand and at each wrist. He died thirty-eight days after the accident.

The Dissociation of Sensation. At one time that form of dissociation of sensation in which tactile sense is preserved or only slightly diminished, while pain sense and temperature sense are lost, was regarded as pathognomonic of syringomyelia. We now recognize that this is not a positive sign of this disease, and that it may occur in other forms of intramedullary as well as in extramedullary affections. Edsall, for example, has reported dissociation of sensation in Pott's disease, and other cases are on

record. More rarely it may be found in peripheral nerve lesions, or it may even be a sign of hysteria. It is, however, much more common in syringomyelia than in any other affection, and when associated with wasting of the muscles of the hands and trophic disturbances of these parts, becomes a sign of much value.

This case of traumatic myelitis shows how careful we must be in attributing certain sensory functions to certain tracts. The transverse area of the cord seemed to be equally degenerated in the upper cervical region, and yet touch sense had been normal in all parts of the body, while temperature and pain senses below the neck had been much altered. A similar condition was observed in the case of syphilitic myelitis reported by Mills and Spiller[1] at the meeting of the American Neurological Association. It seems impossible from cases such as these to confine the tactile sense to certain definite tracts, and we are almost forced to accept the view of those who hold that all sensory fibres may transmit tactile impressions, while certain more sharply-differentiated fibres convey temperature and pain sensations. This view would explain the phenomena of the two cases referred to, and would also explain why in cases of Brown-Séquard paralysis or hæmatomyelia tactile sense is often preserved when temperature and pain senses are much impaired From the clinical aspect there is much to be said in favor of this view. Tactile sense is closely associated with pain sense or temperature sense, and yet not always associated with either one. We may experience the heat of a fire, or suffer pain from severe cold, but it is undeniable that touch sense is closely associated with the other forms, and the functional association may be indicative of a close anatomical association.

The Diagnosis of the Process. In four cases of trauma of the spinal column, Minor[2] believed he could diagnose *with certainty* hæmatomyelia (zweifellos um Hämatomyelie handelt), although the cases were without necropsy. The peculiar disturbance of sensation—intense analgesia and thermo-anæsthesia, with preservation of tactile sensation—in these four cases, Minor said, had scarcely been known in hæmatomyelia, but he believed that when

[1] Mills and Spiller. Journal of Nervous and Mental Disease, January, 1903.
[2] Minor. Archiv für Psychiatrie, 1892, vol. xxiv. p. 693.

this syringomyelic form of dissociation of sensation occurred within a short time after trauma to the vertebral column, we should be justified in diagnosing central hæmatomyelia. It is true that he mentions that central softening of the cord could produce such a symptom-complex, but he lays far greater stress on central hæmatomyelia as a cause. He refers to cases reported by Krafft-Ebing as cases of hæmatomyelia, in one of which this dissociation of sensation was present.

Traumatic myelitis—by which I mean nerve cell-body and nerve fibre degeneration, round-cell infiltration, proliferation of neuroglia, congestion of bloodvessels, and miliary hemorrhages—may cause exactly the same symptoms as hæmatomyelia, in which the blood that has escaped from the vessels may be seen by the naked eye. I believe this case justifies me in saying that it is impossible to make a positive diagnosis between hæmatomyelia and traumatic myelitis, even when the myelitis implicates the whole transverse area of the cord. The dissociation of sensation in this case was very distinct, and the pathological condition was neither hæmatomyelia nor central softening, but transverse myelitis. It seems probable that the diagnosis of hæmatomyelia is made often with a certainty not warranted by microscopic examination of lesions.

The Level of the Lesion. From the symptoms the lesion would probably have been diagnosed as situated chiefly in the lower cervical region, seventh and eighth cervical, and first thoracic segments, and as extending to the upper part of the cervical enlargement, but in much less intensity. The seat of the transverse myelitis in reality was at the fourth and fifth cervical segments, and did not extend below the sixth cervical segment. The greater implication of the distal portion of the upper extremities is explained by the degenerative changes in the cell-bodies of the anterior horns, much greater at the eighth cervical segment than elsewhere. The symptoms caused by these lesions were added to those caused by the transverse myelitis higher up. There were, therefore, two distinct foci of disease.

The Rapid Restoration of Power in the Lower Limbs. This was truly remarkable in view of the great degeneration of the pyramidal tracts, as shown by the Marchi method. Many of the

motor fibres must nevertheless have escaped degeneration and have assumed a vicarious action. The case is important as showing how a limited number of nerve fibres may assume the function formerly discharged by many fibres.

The Organic Lesions without Vertebral Lesions. I was not able to be present at the necropsy, but my resident physician, at that time Dr. Johnson, who is a thoroughly reliable observer, informed me positively that no fracture of the vertebræ and no compression of the spinal cord could be detected at the necropsy. The degenerative changes within the spinal cord were very intense, and they were not caused by compression or by intramedullary hemorrhage. This disorganization was the result of the severe trauma, and is what is meant by concussion of the spinal cord, although the lesions of concussion are not always so intense. It is impossible to determine the exact method by which a severe blow leads to degenerative changes in the nerve fibres and nerve cell-bodies, but there can be no doubt that it does. I have discussed concussion of the spinal cord elsewhere,[1] but I take this opportunity to repeat that it is well to remember that in some cases severe symptoms following trauma of the brain or cord are the result of organic changes within the nervous tissues, and are not always evidence of hysteria, although often they point unmistakably to the latter. The diminution of the patellar reflex from incomplete transverse lesion of the cord in the cervical region is important, because the case shows that this diminution was not the result of alteration in the lumbar region of the spinal cord, and there was no reason to believe that the peripheral nerves of the lower limbs were diseased.

The loss of the patellar reflex from lesions situated high in the spinal cord, and therefore much above the lumbar segment containing this reflex arc, is recognized, but the method in which this loss is produced is unknown, although there are many theories.

In some cases there is alteration of the lumbar region or of the nerves arising from or entering this portion of the spinal cord, but all cases cannot be explained in this way.

[1] Spiller. American Journal of the Medical Sciences, 1899.

THE PATHOLOGICAL CHANGES IN THE NERVOUS SYSTEM IN A CASE OF LEAD POISONING

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(From the William Pepper Clinical Laboratory, Phœbe A. Hearst Foundation)

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Although paralysis occurring in lead poisoning has been recognized many years, the pathology of lead palsy and lead encephalopathy has not been fully determined. A case with very positive symptoms has occurred in the service of Dr. F. P. Henry, at the Philadelphia Hospital, and the material obtained from this case at necropsy very kindly has been given to me for study by Dr. Henry. The clinical notes are his.

P.S., a man, aged forty-eight years, was admitted to the Philadelphia Hospital, Jan. 16, 1902, complaining of abdominal pain and weakness in the extremities. He had been working in lead about twenty years, and had had attacks of lead colic.

During the four weeks previous to admission he had had pain in the abdomen and back, which had become gradually worse, and weakness had been increasing during this time. On admission he was poorly nourished. The irides reacted to light and in accommodation. The conjunctiva was inflamed, and there was a muco-purulent discharge from the eyelids; the tongue was protruded in the median line. A characteristic blue line was found on the gums. The pulse was regular and of fair volume. The arteries were moderately sclerotic. The abdomen was scaphoid. The cardiac impulse was felt in the fifth interspace. The dulness was normal in extent. The valvular sounds were well defined, and the second aortic was accentuated. The lungs appeared to be normal. The liver was diminished in size and the spleen was not palpable. Slight wrist-drop was present. The patient could supinate and pronate the hand to a limited extent; the grip was feeble and he could not lift the arms. The reflexes were absent. The lower limbs were completely paralyzed. The plantar reflexes alone were retained. The Babinski reflex was not obtained. Sensation generally was preserved.

* Read at the meeting of the American Association of Pathologists and Bacteriologists, May, 1903. Received for publication, June 1, 1903.

On January 19 the paralysis in the upper limbs was more complete than on admission.

On January 21 a note was made that the man was delirious at times, especially at night, and on January 30 the delirium was still very great.

The urine contained much albumin and casts.

On February 5 it was noted that he had incontinence of urine. He was still delirious at night and occasionally during the day. The paralysis had largely disappeared in the lower limbs, but marked wrist-drop was present.

The blood count during the height of the disease was as follows: white cells, twenty-one thousand, red cells two million five hundred thousand, hemoglobin forty per cent. Red cells in staining gave the degenerative granular change.

The report of Dr. C. A. Oliver regarding the ocular condition was as follows: "Feb. 4, 1902, Marked catarrh from the left conjunctiva. The pupils are 3 mm. in diameter. The irides are very sluggish, especially the right. There is rather high grade retinitis without any hemorrhages, more pronounced in the right eye."

On March 15 the paralysis in the upper limbs was unaltered. The lower limbs could be moved at will. Diarrhea existed.

The patient died March 19, 1902.

At the necropsy fibrosis of liver and spleen was found. The kidneys were small and there was considerable interstitial change. The myocardium appeared degenerated, but the cardiac valves were not markedly altered,

Right Paracentral Lobule: The blood vessels in the pia and in the substance of the brain are much congested. Within the cortex there seems to be an increase of neuroglia cells. Small accumulations of round nuclei are found about some of the blood vessels of the cortex, and amyloid bodies are found within the cortex just below the pia. The pia in some places is intimately adherent to the cortex. Recent hemorrhages are found within the pia and between the pia and the cortex. Considerable round-cell infiltration is found within the pia.

Sections from the left paracentral lobule resemble closely those from the right paracentral lobule. The cells of Betz, even by the thionin stain, are not intensely altered, although in some there is displacement of the nucleus and partial disintegration of the chromophilic elements, but, as compared with the

cell-bodies of the anterior horns of the spinal cord, they are remarkably well preserved. Most striking is the proliferation of the endothelial cells at places on the outer surface of the pia, with the formation of masses or long rows of cells upon the surface of the pia. This proliferation of endothelial cells is most pronounced in the motor region of the cortex, but is distinct also in sections from the right frontal lobe, right parietal and right occipital lobes.

Sections from the right optic thalamus do not present any proliferation of the ependymal cells.

Sections from one of the cerebellar lobes do not show distinct pathological changes.

Marchi sections from the cervical and lumbar regions of the spinal cord present no degeneration of the white matter, but accumulations of black dots are found along the intramedullary portion of the anterior roots. These accumulations are not very pronounced, but they are possibly indicative of degeneration of the medullary sheaths. The anterior and the posterior roots of the lower cervical region, even when cut separately from the spinal cord and stained, do not appear to be degenerated. The nerve cell-bodies of the anterior horns in the cervical and lumbar regions are intensely degenerated; the alteration consisting of displacement of the nucleus, chromatolysis, vacuolation of some of the cell-bodies, and pigmentation. The alteration is fully as intense in the lumbar region as in the cervical, and all the groups of cell-bodies are affected. The posterior roots of the lumbar region show little alteration.

A portion of one of the peripheral nerves (median) stained by the Marchi method presents intense degeneration. Stained by the Weigert hematoxylin stain, the same nerve shows considerable degeneration. Pieces of the median and sciatic nerves alone were saved for examination.

The sciatic, by the Weigert hematoxylin stain, does not present much alteration.

Sections from a muscle on the anterior surface of the forearm, and from the pronator radii teres, show a considerable increase in the number of nuclei between the muscle fibers,

giving the appearance of interstitial myositis. The muscle fibers are not much atrophied, and black dots within the muscle fibers, showing fatty degeneration, are not found by the Marchi method. Nerve bundles within the muscles are much degenerated. Here and there an unusually large muscle fiber may be found.

Sections from one of the lumbar or sacral spinal ganglia show proliferation of the endothelial cells of the capsules, without much interstitial round-cell infiltration. The condition resembles closely that seen in rabies.

The views entertained regarding the pathological changes in lead palsy are clearly presented by Remak and Flatau in their monograph on neuritis. According to them, only a few investigators (Hitzig, Harnack, Friedländer) believe that the muscles are primarily diseased, and most investigators hold that the lesions are primarily in the peripheral motor nerve fibers, but it is uncertain whether the lesions are primarily in the peripheral nerve fibers, or in the cell-bodies of these nerve fibers. The supporters of the peripheral theory (Westphal, Charcot, v. Leyden, Schultze, Eisenlohr, and others) advance as an argument the occurrence of degenerative changes in the peripheral nerves, while the anterior spinal roots and the spinal cord remain intact. Erb and Remak have suggested that lead may cause a functional disturbance of the nerve cell-bodies, not detectable by the microscope, and that this in turn may cause the degenerative changes in the peripheral nerves. Pathological changes, however, have been detected in the spinal cord and anterior roots, but not in the majority of cases.

The degenerative changes are said to be usually most pronounced in the posterior interosseous nerve, though not confined to this nerve, and they diminish in intensity toward the proximal end of the nerves.

The only investigators who have found changes in the spinal cord of man in lead paralysis, mentioned by Remak and Flatau, are Vulpian, Oppenheim, v. Monakow, Oeller, Zunker, and Goldflam. Such changes, however, in experimentation by

Stieglitz, by Schaffer, and by Nissl are referred to by them. In the thesis of Mme. Dejerine-Klumpke on polyneuritis and lead palsy in particular, published in 1889, changes in the spinal cord occurring in lead palsy are said to have been found only in five cases (Vulpian, v. Monokow, Zunker, Oeller, Oppenheim), so that the only additional name mentioned by Remak and Flatau is Goldflam. Mme. Dejerine-Klumpke remarked that the existence of lesions in the muscles and peripheral motor nerves in lead palsy was well known and beyond all dispute, while it was very different as regards spinal lesions. In Vulpian's case, some of the nerve cells of the spinal cord had a colloid or vitreous appearance; in von Monakow's case, in the spinal cord were foci of sclerosis, alteration of the walls of the vessels, small hemorrhages and accumulations of lymphatic cells in the pericellular spaces, and the lesions as well at the symptoms resembled those of paretic dementia; in Zunker's case, the number of nerve cells was diminished; in Oeller's case, foci of hemorrhage and softening were found, and the nerve cells were small and stained badly; and in Oppenheim's case, many of the nerve cells had disappeared. This last case, according to Mme. Dejerine-Klumpke, is the only one of the five in which the lesions of the cells of the anterior horns were very positive. Vitreous change or diminution in the number of nerve cells is of doubtful value, and capillary hemorrhages are not uncommon in cases of interstitial nephritis, such as existed in Oeller's case.

The case that Goldflam reports was extraordinary on account of the pathological changes in the nerve cells of the anterior horns, and on account of degeneration of nerve fibers of both gray and white matter and of anterior spinal roots. Many of the intraspinal vessels had thickened walls. The alteration was more intense in the cervical than in the lumbar region, and yet the paralysis in the upper and lower limbs was equal. Although these changes in the spinal cord were so pronounced, Goldflam favors the peripheral theory.

Carlo Ceni found the nerve cells of the anterior horns of the spinal cord very much degenerated, the pigment was

much increased in amount, nuclei of nerve cells were displaced or absent, and the cellular processes were imperfect.

Laslett and Warrington have observed pathological alteration of the nerve cells of the anterior horns in the cervical region, and atrophy of nerve fibers in the anterior roots of the same region in a case of lead palsy in man.

F. Quensel has found much alteration of the nerve cells in the anterior horns of the lumbar and cervical regions of the spinal cord in a case of lead poisoning in man.

In a case of lead palsy observed by Philippe and Gothard the nerve cells of the anterior horns were less numerous than normal and some were atrophied, the vessels were sclerotic and the neuroglia slightly proliferated. The anterior roots were degenerated. Peripheral nerves examined were degenerated secondarily to the lesions of the cells in the anterior horns. Muscles were atrophied. The authors believe this case offers support for the central theory.

I know of no other cases of lead palsy in man with degenerative changes in the nerve cells of the spinal cord. To the cases already mentioned may be added the one reported by me in this paper.

In a case of lead palsy with unconsciousness, examined by Carlo Ceni, the brain was edematous, as it was especially in a case reported by Chvostek.

The edema of the brain described by Ceni, Chvostek, and others, in lead palsy, possibly may explain the rapid development of cerebral symptoms, even focal in character, as in the case of hemiplegia developing in acute lead poisoning reported by J. M. DaCosta. DaCosta refers to the examinations of Maier, which show that in the brain lead has a special affinity for the cortex. Heubel has found by experimentation that next to the liver and spleen the relatively greatest amount of lead is found in the brain and spinal cord. (Cited by Quensel.)

I have asked Dr. D. L. Edsall to make an examination of the brain for lead in my case, and the following is his report:

"A portion of the cortex about an inch square was first taken, and was completely oxidized by Neumann's method (heating in a mixture of

sulphuric acid and nitric acid). The fluid was then partly neutralized with ammonia and filtered. To the filtrate ammonia was added until the reaction was only slightly acid. The residue on the filter was boiled with concentrated hydrochloric acid, and this was filtered while hot. No precipitate occurred on cooling. To this ammonia was added until the reaction was only slightly acid. H_2S was then run through both the fluids for a long time. Not the slightest precipitate was produced.

"I then carried out the same procedure with about one-third of the cerebral hemisphere that was furnished me. The result in this instance, also, was entirely negative. A large portion (about one-third) of the hemisphere was then partly oxidized with nitric acid and subsequently incinerated. The ash was boiled with concentrated hydrochloric acid, and repeatedly extracted in this way. The extract was tested for lead, with entirely negative results. As far, then, as I was able to determine, there was no lead present in the cerebral hemisphere furnished me."

Dr. Edsall's failure to obtain lead from the brain does not throw any doubt upon the diagnosis of the case, as in a number of cases of lead poisoning, as shown by Quensel, lead could not be obtained from the brain, and it has been supposed that in these cases the lead affected the brain indirectly by some alteration of the blood or some form of autointoxication.

The reports of microscopical investigations of the brain in man in lead palsy, even with encephalopathy, are not numerous.

The alteration of the nerve cells of the cerebral cortex in Ceni's case was most intense in the frontal lobe.

In a case of lead poisoning in man, F. Quensel has found very pronounced changes in the brain. The pia arachnoid was thickened, its vessels were very numerous and their walls were thickened, and recent small hemorrhages were found between the pia and cortex. In the cortex the nuclei in the walls of the vessels were poliferated, and the vessels were surrounded by accumulations of gliar cells. Deiters' cells were numerous. The nerve cells were much altered in the cerebral cortex. Quensel gives numerous references to the literature on lead palsy, and refers to cases of lead encephalopathy with necropsy. Most of these are of questionable value, and many of the examinations were only

macroscopic, and the lesions were such as edema, or anemia. The cases of lead poisoning with symptoms of paretic dementia cannot be studied to determine the lesions of lead, because similiar lesions are found in paretic dementia without lead, and the changes caused by the lead alone are uncertain. Quensel refers, however, to two cases of lead poisoning with cerebral changes, although encephalopathy did not exist in either one, in which microscopical examination was made. One was reported by Kussmaul and Maier, the other by Ceni, already referred to. The former was reported in 1872, and according to Quensel there was increase of connective tissue about the vessels, and the smaller vessels were not as large as normal. In Ceni's case the brain was atrophied, edematous, and anemic, the processes of the nerve cells appeared varicose by the Golgi stain, and the nerve cells showed fatty degeneration by the Marchi method. The walls of the vessels were not thickened, and there was not much alteration of the vessels. Quensel's case seems to be the only thoroughly satisfactory one of lead encephalopathy with microscopical examination.

The case that I report, therefore, is a contribution to this subject, little studied from a pathological aspect.

I make mention especially of the proliferation of the endothelial cells upon the surface of the cerebral pia. I have not found mention of such an occurrence in man or in the lower animals.

Stieglitz found cerebral changes in some of his animals poisoned by lead, and there were numerous smaller or larger hemorrhages about the vessels and cellular infiltration about some of the vessels.

In the brains of dogs poisoned by the acetate of lead, McCarthy has found changes more marked in the cortex around the gyrus cruciatus which corresponds to the motor area in man. The nerve cells were degenerated, the capillaries of the cortex were increased in number, and their walls were thickened and were surrounded by accumulations of cells. Small hemorrhages were found in the cortex. McCarthy's examination was confined to the brain.

Stieglitz in his experimental poisoning of animals with lead frequently found the posterior roots more or less degenerated. He remarks that even in man sensory fibers of the nerves must be affected, or else it would be difficult to explain the arthralgia which is so frequent that Tanquerel found it in 755 cases out of 2,151 (35 per cent). The degeneration in the posterior roots he found confined almost to the medullary sheaths. He remarks also that the posterior roots in man have seldom been examined in cases of lead palsy, but that Schultze found in one case a small atrophic focus in a posterior cervical root.

I have found the posterior roots of the cervical region normal, as well as those of the lumbar and sacral regions, except that the latter contained a few swollen axis cylinders.

Stieglitz found in the spinal ganglia proliferation of the connective tissue and shrinkage and vacuolation of the nerve cells from lead poisoning.

In one of his animals made to inhale lead during a period of six days, and in another during a period of eight days, the posterior and anterior spinal roots contained degenerated medullary sheaths. Numerous hemorrhages were found in the spinal cord, especially in the anterior horns and central gray matter, and the nerve cells of the spinal cord were vacuolated. These findings are especially interesting because of the rapidity of the poisoning. He refers to three cases in man reported by Tanquerel des Planches, in which palsy developed eight days after the first exposure to lead. In that reported by Da Costa, the development of the palsy occurred very soon after the exposure to lead.

Philippe and Eide have found very distinct changes in the nerve cells of the spinal ganglia in one instance of lead poisoning. The nerve cells were small and shrunken and much pigmented. They do not speak of round-cell infiltration in the ganglia in this case.

In the case that I report in this paper, changes were found in the spinal ganglia very much like those of rabies. There was distinct proliferation of the endothelial cells lining the capsules of the nerve cells, and this was evident where

there was little round-cell infiltration. In a paper read before the Pathological Society of Philadelphia, Dec. 27, 1900, I reported the finding in two cases of lesions resembling those of rabies. Neither case was one of rabies. I had no desire to diminish by this report the importance of microscopic examination in suspected cases of rabies, but I merely wished to show that one must be cautious in making a diagnosis of rabies from the lesions alone. In my case of lead poisoning, the proliferation of the enthothelial cells lining the capsules in the spinal ganglia is like the proliferation of the endothelial cells on the surface of the cerebral pia, and may show that lead has an affinity for endothelial cells. I do not know whether endothelial cells elsewhere in the body were proliferated.

Changes in the muscles have been observed in lead palsy. In Ceni's case, muscle fibers were degenerated and the nuclei in the interstitial tissue were increased in number. Madame Dejerine-Klumpke also has described such alteration of the muscles, and it is present in this case I report, in which there is an increase of the interstitial cells.

I conclude, therefore, from my study of this case and of the literature that lead affects the brain and its pia, the nerve cells of the anterior horns of the spinal cord, the ganglia on the posterior roots, the peripheral nerve fibers, and the muscles. It seems to be impossible to determine whether its effects are first manifested in alteration of the peripheral motor fibers or of the motor cell-bodies of the spinal cord, but inasmuch as both peripheral motor fibers and motor nerve cell-bodies are sooner or later affected, this question is not a very important one. The significance of the proliferatien of the endothelial cells of the capsules in the spinal ganglia and on the cerebral pia is difficult to determine.

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PLATE I.

Fig. 1. Proliferation of endothelial cells upon the surface of the cerebral pia.

Fig. 2. Degeneration of nerve cells of the anterior horns of the spinal cord.

Fig. 3. Degeneration of the median nerve, one per cent osmic acid.

Fig. 4. Cellular infiltration between muscle fibers.

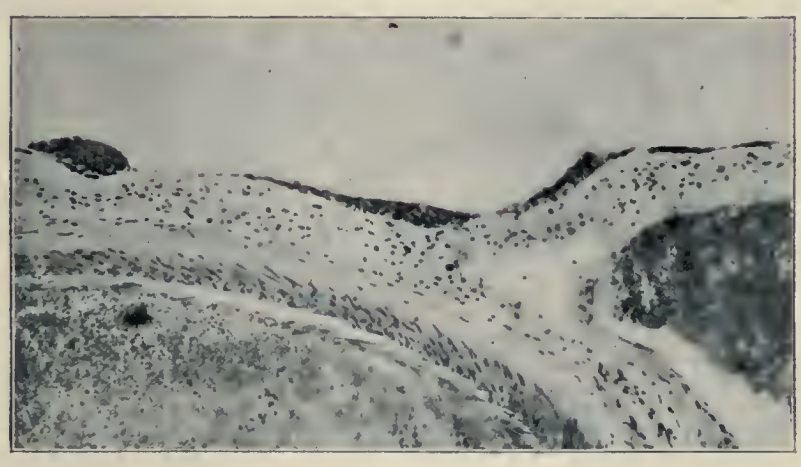

FIG. 1.

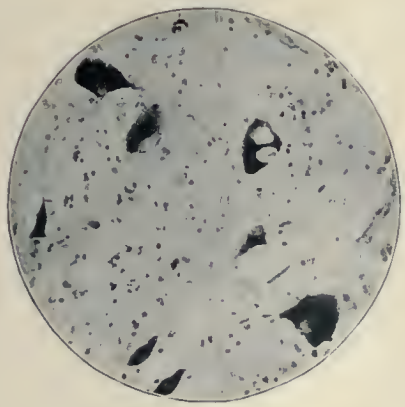

FIG. 2.

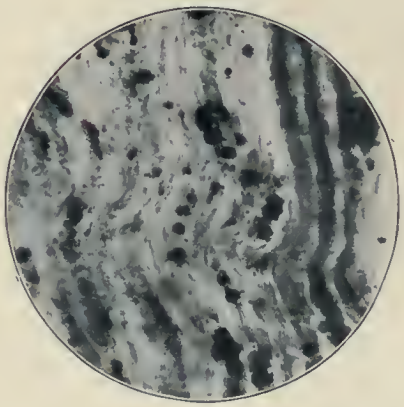

FIG. 3.

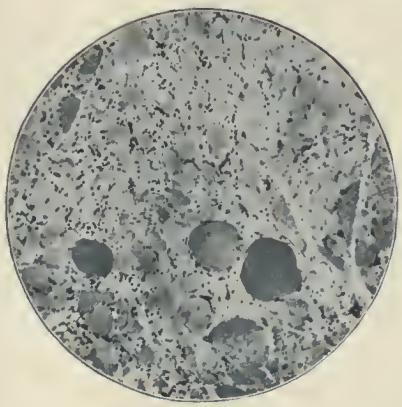

FIG. 4.

Extracted from The American Journal of the Medical Sciences, January, 1903.

A REPORT OF TWO CASES OF MULTIPLE SCLEROSIS, WITH NECROPSY:

WITH REMARKS ON MUSCULAR ATROPHY, SECONDARY DEGENERATION, AND LOSS OF TENDON REFLEXES, WITH INCREASED MUSCULAR TONICITY, OCCURRING IN THIS DISEASE.[1]

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(From the William Pepper Clinical Laboratory, Phoebe A. Hearst Foundation.)

Multiple sclerosis seems to be a rare disease in America, and scarcely any cases with necropsy are to be found in the literature of this country. I am inclined to think that some cases are overlooked, and that the disease, while uncommon, does occur more frequently than the paucity of records gives us reasons to believe. B. Sachs remarked at the time he wrote his critical digest on multiple sclerosis, in 1898, that he had been able to find only one necropsy record of a case of this disease published in America, and that was by Seguin, and was incomplete.

Since the publication of Sachs'[2] paper a case with necropsy has been reported by Burr and McCarthy[3] (1900), and another that probably should be classed under multiple sclerosis, although published only in abstract, May, 1902, by J. R. Hunt.[4] The paper by E. W. Taylor[5] is one of the best on the subject by American writers, but the cases he reports occurred in Germany, and are a contribution to German literature.

I report two cases, with microscopic examination of the nervous tissues. The first case was in the service of Dr. F. X. Dercum, at the Philadelphia Hospital, and is a typical example of the disease. I am indebted to Dr. Dercum for the clinical history and the pathological material. The second case was in my service at the Philadelphia Hospital, and forms a striking contrast in its clinical aspects to Dr. Dercum's case.

[1] Read in abstract at the annual meeting of the American Neurological Association, June, 1902.

[2] Sachs. Journal of Nervous and Mental Disease, 1898.

[3] Burr and McCarthy. Ibid., 1900.

[4] J. R. Hunt. Ibid., May 12, 1902, p. 288.

[5] E. W. Taylor. Deutsche Zeitschrift für Nervenheilkunde, vol. v.

Case I.—C. O., laborer, white, aged twenty-five years, was admitted to the Philadelphia Hospital, March 26, 1900. A brief history was taken at this time.

November 6, 1900. Chief complaint: stiffness and weakness of right upper and lower limbs, vertigo, and tremor.

Father died, at the age of fifty years, from gastric disease; mother died after labor; one brother died in infancy. Three sisters and four brothers are living and well.

The patient had measles when a child and typhoid fever seven years ago. He has used alcohol and tobacco to excess, but denies venereal disease.

Two years ago last winter he worked four or five hours one night in the hold of a vessel with nothing on but trousers, drawers, shoes, and stockings. Thus clad he came up on the deck, when it was bitterly cold and raining sleet and hail, and took a drink of ice-water. He remained on deck about twenty minutes, not noticing the cold, and then returned to the hold, where he worked for six hours more. In the morning he went home and to bed, still experiencing no ill effects from the exposure. That afternoon he felt stiff all over, and the stiffness remained for several days. Four days after this exposure he had to work seven hours in the hold of a ship shovelling wet coal. While shovelling he stood in the wet coal, and afterward had to sit in the wet, shivering, while waiting for more coal. The next morning he went directly from the hold to the deck, to sweep. As soon as he reached the deck he began to feel stiff, and staggered and was hardly able to walk. That night he experienced sharp pains in the thighs, more in the right thigh, and the stiffness was most marked on the right side.

This condition remained stationary for one month, when he awakened one morning with sharp pains in the right leg, with marked rigidity of that member. Soon after this he suffered from similar pains in the left leg, although not so severely.

His condition improved slightly for several months following, but there has been little change during the past year. He has occasionally had loss of sphincter control during the past year.

Present Condition (*November* 6, 1900). The patient is a well-developed young man. His intelligence is not impaired, but his speech is slow and scanning. Pupils are equal and the irides respond promptly to light and in accommodation. The ocular muscles are apparently normal. There is a slight tremor of the tongue. The tendon reflexes of the upper limbs are normal (later those of the right upper limb were exaggerated). The epigastric reflex is normal, but the abdominal and cremasteric reflexes are absent. The patellar reflex is exaggerated on each side, more so on the right side. Ankle clonus is present on each side. Babinski's reflex is present. Grip of the right hand by dynamometer is 41; of left, 45. He has apparently very little loss of power in the upper or lower limbs. Temperature sense is normal, except in the feet, where there is delayed sensation, and in the toes and heel of the right foot, where there is reversal of temperature sense. Tactile and pain senses are unimpaired. Station is poor. He sways with his eyes open and falls when they are closed. Gait is staggering and the right foot is dragged. Some ataxia is observed in the upper limbs, especially on the right side. Intention tremor is present in the right upper limb.

The report of the examination of the eyes by Dr. G. E. de Schweinitz, November 18, 1900, is as follows: "Light reflex normal. Each disk atrophic; atrophy more marked on temporal side. No change in vessels except a slight perivasculitis. Well-marked nystagmus."

December 8, 1901. He has wasted very rapidly during the past two months, and during the past month has had almost absolute loss of power in his lower limbs, especially on the right side. The wasting is general. Breath smells sweetish, and examination of urine shows sugar in large amount.

The patient died December 9, 1901.

The microscopic examination of the brain and spinal cord, made by me, revealed numerous areas of sclerosis, especially in the cord. It is not necessary to dwell on the pathological condition, as it was like that commonly seen in multiple sclerosis. The case was clinically and pathologically a typical one of this disease. I had the opportunity to examine this patient frequently during his residence in the hospital.

The causative relation of cold and dampness to multiple sclerosis seems to be clearly shown in this case. Krafft-Ebing has insisted on this etiology of the disease, but it is seldom that the symptoms follow so closely the exposure, as in this case. The man C. O. developed the symptoms of multiple sclerosis after repeated and long exposure to cold and dampness in shovelling coal in the hold of a vessel. Residence in a damp house was believed to be the cause of the disease in the second case. It is probable that this was not the only cause in either case.

Case II.—The patient, a woman aged fifty-one years, was in my service at the Philadelphia Hospital during the summer of 1901. She said the first symptoms of her disease began in 1891 or 1892 after a residence in a damp house. She denied venereal disease and abuse of alcohol, although she acknowledged that she had used much tobacco. Impaired gait was noticed early, but the gait soon improved, and later became worse again. She was able to walk until 1899, but staggered so that she had to be supported. In 1891, while doing housework, she suddenly became numb in the feet, and the numbness extended gradually up the limbs, with progressive loss of power. In two days the numbness had extended to the waist, and she had a girdle sensation of pressure and incontinence of urine and feces. Her speech was slow, and she had some difficulty in saying words. My notes, made June 24, 1901, are as follows:

The lower limbs appear to be completely paralyzed, and although they are drawn up at times, the movement is probably entirely involuntary. When told to move her toes she is unable to do so. The lower limbs are wasted. The right thigh in its middle portion measures thirteen inches; the left thigh in the corresponding portion measures fourteen inches. The thighs are proportionately more atrophied than the legs below the knees, but the atrophy in the latter is partly masked by œdema. The feet are very œdematous and pit on pressure. Pressure over either leg causes the leg to be drawn up; this is especially true of the left lower limb. The movement is the result entirely of reflex action, and is involuntary. The knees and feet are inverted,

and there is much spasticity of the lower limbs, which is greatly increased by passive movement. *There is no knee-jerk on either side, even with reinforcement.* This is especially noteworthy because of the spasticity in the lower limbs. The knee-jerk is not prevented by the spasticity, as the spasticity is comparatively slight when the limbs have not been irritated, and even without irritation of the limbs there is no knee-jerk. When the attempt is made to obtain the knee-jerk there is no contraction visible in the quadriceps muscle of either side. Ankle clonus is not obtained on either side. The Babinski reflex is very pronounced on each side, the great toe as well as the other toes being drawn forcibly upward. The Achilles jerk is absent on each side. Sensation for touch, pain, and temperature is normal in the lower limbs. No tenderness is produced by pressure of the nerves or muscles.

The movements in the upper limbs are free, and the resistance to passive movements in these limbs is proportional to the muscular development. The upper limbs above the elbow are fairly well developed. The interossei muscles, the thenar and hypothenar eminences are much wasted, and the grasp of each hand is almost *nil*. The forearms are wasted, but not intensely so. Sensation for touch, pain, and temperature is normal in the upper extremities and over the chest. The tendon reflexes of the upper limbs, biceps tendon, triceps tendon, and wrist-jerks on either side are not strikingly abnormal. No tenderness is felt on pressure of nerves or muscles.

The cranial nerves are not distinctly implicated. The tongue is protruded straight. The masseters contract firmly. The corner of the mouth is drawn up well on each side, and the eyes are firmly closed. At the present examination there is considerable swelling of the left eyelid.

The spinal column is normal.

The mentality is feeble. The patient replies correctly to questions, but her statements concerning her past condition are not fully reliable. She complains of numbness in her hands. She has incontinence of urine and feces.

The report of the examination of her eyes, made by Dr. H. F. Hansell, June 24, 1901, is as follows:

"Paralysis of the third nerve of the right side and also of the left, amounting to almost complete ophthalmoplegia. Pupillary response is good. Pupils are equal. Partial atrophic cupping of both optic nerves, with reduction in size of the bloodvessels, without signs of previous inflammation."

The patient grew gradually worse, and died July 5, 1901.

The microscopic examination, made by me, gives the following results:

Numerous sclerotic areas are found throughout the brain and spinal cord. One such area is found implicating the nuclei of the oculomotor, trochlear, and abducent nerves, but is not confined to these nuclei. The nerve cell-bodies of the oculomotor nuclei are not very distinctly diseased, as shown by the thionin stain, and yet some may be slightly altered. The posterior longitudinal bundle on each side is in the sclerotic area, and contains at this part a few medullated nerve

fibres. Half of the medulla oblongata at one level has undergone a sclerotic change. A sclerotic area is found in the left optic nerve, but the right optic nerve appears to be normal.

Some degeneration, as shown by the Marchi method, is detected in the sclerotic areas of the spinal cord. Secondary degeneration of moderate intensity is found in each crossed pyramidal tract, below the mid-thoracic region, but is greater on one side. No sclerotic areas are found in the posterior columns at the upper lumbar region, but in the mid-lumbar region a sclerotic area is present on each side of the posterior septum, and implicates the posterior root fibres after their entrance into the posterior columns. These areas do not extend into the lower lumbar region, but here a sclerotic area is found implicating one anterior horn and the antero-lateral column. A sclerotic area implicates

FIG. 1.

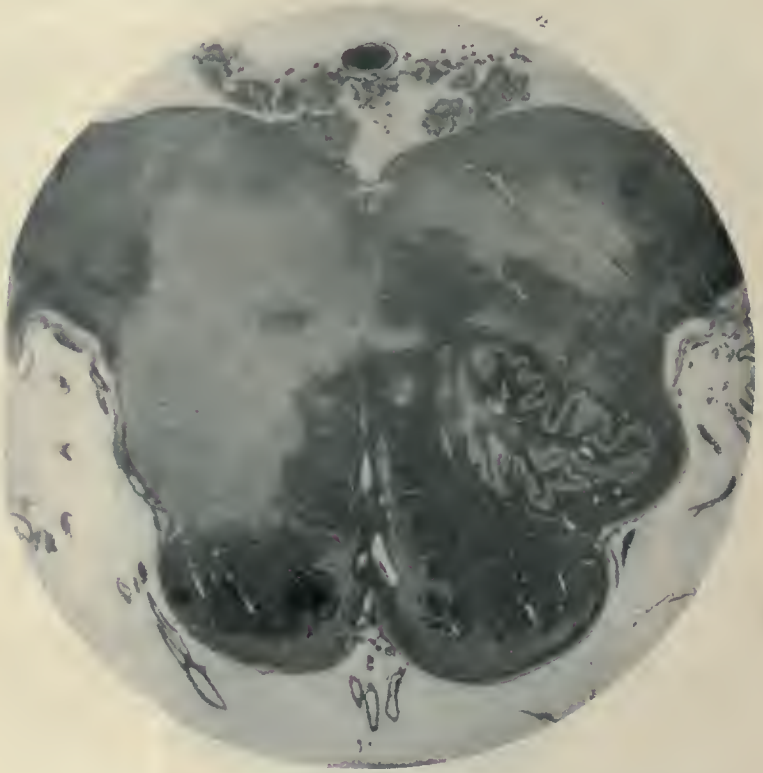
CASE II.—Section through the nuclei of the oculomotor nerves, showing a sclerotic patch implicating these nuclei.

the greater part of the left anterior and lateral columns and the gray matter of the left side and a part of the left posterior columns in the sacral region. A sclerotic area is found also in the right lateral column, and gray matter of the right side in the sacral region. Many of the nerve cell-bodies of the anterior horns of the cervical and lumbar region appear shrunken and have imperfect dendritic processes, and some are much pigmented. The thionin stain was employed. The nerve cell-bodies in a sclerotic area implicating one anterior horn in the lower lumbar region resemble very closely those of the other horn in the same section where there is no sclerotic area, and in neither horn are they normal. A branch of one of the plantar nerves is partially degenerated. Many other sclerotic areas not described are found in the brain and spinal cord.

A summary of the case is as follows:

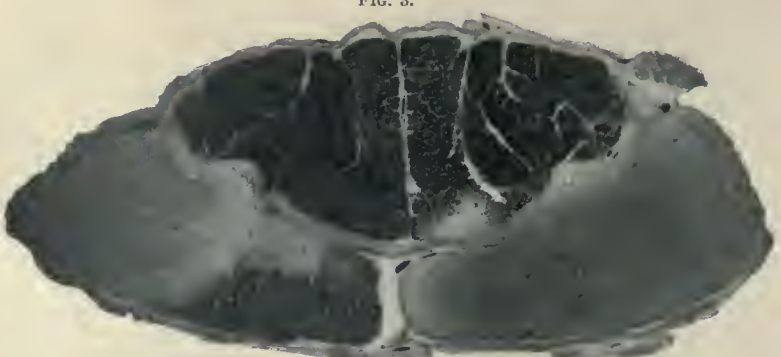
In 1891 the patient—a woman, then about forty-one years of age—complained of numbness in the feet, and soon the legs became numb.

FIG. 2.



CASE II.—A sclerotic area implicates a large portion of the medulla oblongata.

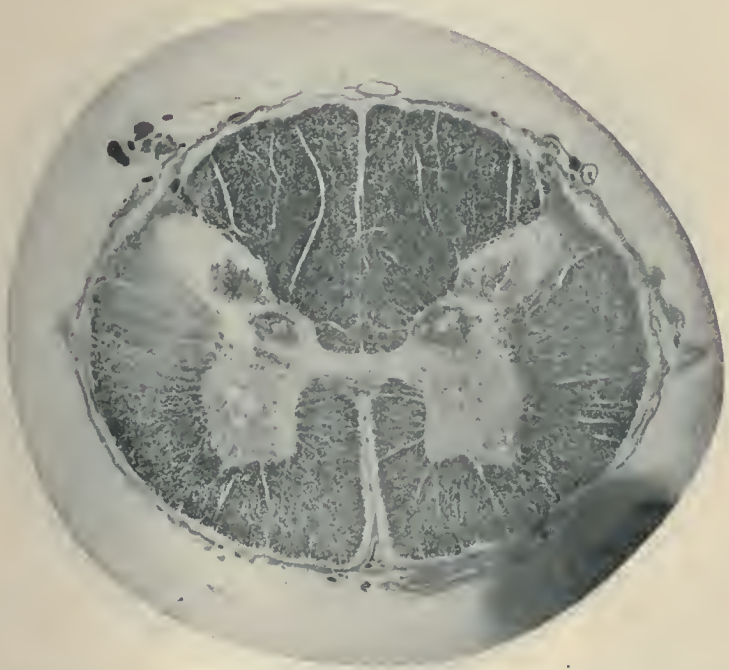
FIG. 3.



CASE II.—Section from the cervical region, showing a large sclerotic patch on each side of the spinal cord.

She had at this time progressive loss of power in the lower limbs and staggering gait. Within two days the numbness extended as high as the waist, and she complained of girdle sensation, and had complete paralysis of the lower limbs. She had also incontinence of urine and feces. She had resided in a damp house. The disturbance of gait soon disappeared for a time, and she was able to walk with difficulty until 1899, but staggered. She complained of shooting pains at times in the knees, extending to the ankles. In 1901 her speech was somewhat drawling. The lower limbs were completely paralyzed, were

FIG. 4.



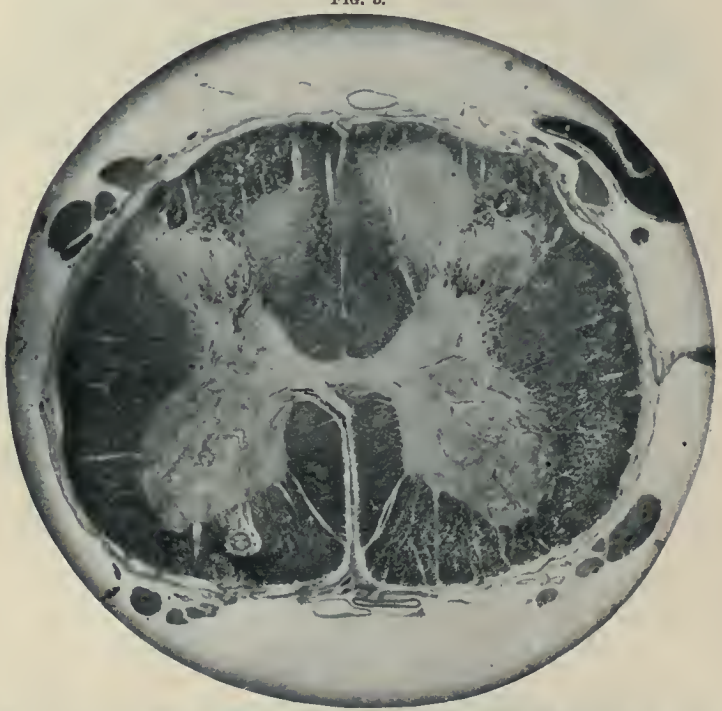
CASE II.—No sclerotic area is seen in the posterior columns in this section from the upper lumbar region. The secondary degeneration of the crossed pyramidal tracts is not well reproduced in the photographs.

much wasted, and spastic; slight irritation causing the limbs to be drawn up involuntarily, and yet the patellar and Achilles reflexes were absent. The knees and feet were inverted. The Babinski reflex was very pronounced. Sensation was normal everywhere. Voluntary movement in the upper limbs was impaired, and the grasp of the hands was very feeble. The hands were very much atrophied. The tendon reflexes of the upper limbs were normal. Mentality was feeble. She had almost complete external ophthalmoplegia and partial atrophic cupping of both optic nerves. Iritic response was good. The case

was one of disseminated sclerosis, as shown by the microscopic examination.

The interesting features of this case were: The pronounced muscular atrophy; the secondary degeneration of the crossed, pyramidal tracts, more distinct, however, on one side, in a case of disseminated sclerosis; the loss of the patellar and Achilles reflexes, with spasticity of the lower limbs, the loss of these reflexes probably being the result of sclerotic areas in the posterior columns and a part of the anterior horns of the lumbar and sacral regions; and the almost complete external

FIG. 5.



CASE II.—Section from the mid-lumbar region. A sclerotic area is seen on each side of the posterior septum only in the mid-lumbar region (compare Fig. 5 with Figs. 4 and 6). The tendency to symmetry of the areas in multiple sclerosis is well sbown in this section.

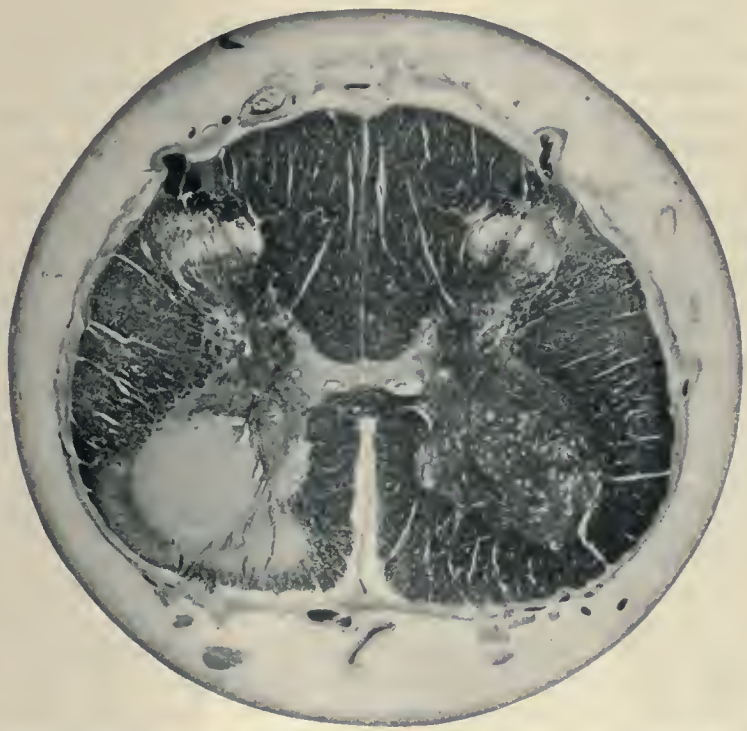
ophthalmoplegia resulting from a sclerotic area in the nuclei of the third, fourth, and sixth nerves.

The muscular atrophy was very pronounced in the lower and upper limbs, and in the latter the atrophy was more distinct in the small muscles of the hands. The atrophy in the lower limbs below the knees was partly masked by œdema. Oppenheim[1] regards muscular atrophy as a rare sign of multiple sclerosis, and states that, as a rule, the muscles preserve their normal size and electrical reactions.

[1] Oppenheim. Lehrbuch der Nervenkrankheiten, third edition, p. 314.

L. Brauer[1] believes that muscular atrophy is very uncommon in the early stages of multiple sclerosis, and he reports a case of this disease in which muscular atrophy was an early symptom and later became very pronounced. He acknowledges that muscular atrophy does occur occasionally in multiple sclerosis, and he believes it affects especially the small muscles of the hand and the peroneus distribution. He refers to cases of muscular atrophy occurring in multiple sclerosis reported

FIG. 6.



CASE II.—Section from the lower lumbar region. The sclerotic areas of the posterior columns represented in Fig. 5 have disappeared, but a sclerotic area is seen in one anterior horn extending into the white matter.

by Jolly, Ebstein, Leube, Schüle, Buchwald, Otto, Engesser, Dejerine, and Pitres. Killion also is said to have observed muscular atrophy in multiple sclerosis.

Probst[2] speaks of the infrequency of muscular atrophy in multiple sclerosis, and refers to a few cases in which it was observed. In most of these cases no very important alteration of the cell-bodies of the

[1] Brauer. Neurologisches Centralblatt, July 15, 1898, No. 14, p. 635.
[2] Probst. Deutsche Zeitschrift für Nervenheilkunde, 1898, vol. xii.

anterior horns was seen, but Probst was able to find a decrease in the number and a shrinkage of the cell-bodies in the anterior horns of the upper cervical region in one case of multiple sclerosis with muscular atrophy, although no sclerotic focus could be found in this region. This case Probst pronounces as unquestionably one of multiple sclerosis. Alteration of the nerve cell-bodies was observed by me in my case. According to Probst, alteration of nerve cell-bodies in multiple sclerosis has been observed by Bourneville, Guérard, Charcot, Fromann, Gowers, Obersteiner, Frommann, Taylor, Schuster, and Bielschowsky; but muscular atrophy does not appear to have been observed in all these cases in which cellular change existed.

Secondary degeneration is not seen in multiple sclerosis, according to some writers, and yet in my case it could be found in the crossed pyramidal tracts in the spinal cord below the mid-thoracic region. According to Probst,[1] Schultze was the first to offer as an explanation of the absence of secondary degeneration the preservation of the axons in the sclerotic foci. Secondary degeneration in multiple sclerosis is said to have been observed by Jolly in 1872, Buss in 1889, Werdnig in 1888, Babinski in 1885, Redlich in 1895, and Rossolimo—certainly a small number of cases, in consideration of the large number of cases of this disease published. In most of the cases in which secondary degeneration was found it extended only a short distance, and was only of moderate degree. In a case reported by Probst[2] secondary degeneration of the anterior and lateral pyramidal tracts existed, and extended from the proximal portion of the pons into the lumbar region. Probst mentions that possibly some might regard his case as one in which multiple sclerosis was combined with amyotrophic lateral sclerosis, inasmuch as the nerve cell-bodies of the anterior horns were not normal and sclerotic foci were not found in the spinal cord. This combination, I think, might occur, as both diseases possibly are the result of faulty development of nervous tissue in the embryo.

Since my paper was read before the American Neurological Association an interesting article in which the occurrence of secondary degeneration in multiple sclerosis is considered has been published by Schupfer.[3] He says secondary degeneration in this disease has been observed only by Jolly, Westphal, Schultze, Greiff, Babinski, Werdnig, Buss, Rossolimo, Probst, Thomas and Long, and Taylor. He subjects these cases to a critical study, and concludes that only in the cases of Buss, Probst, and Thomas and Long was the degeneration of the pyramidal tracts in connection with lesions in the spinal cord, medulla oblongata, and pons. In Thomas and Long's case the cause of the degeneration he thinks was syphilitic endarteritis. Degeneration of the pyramidal

[1] Loc. cit. [2] Loc. cit.
[3] Schupfer. Monatsschrift für Psychiatrie und Neurologie, August, 1902, p. 109.

tracts is therefore, in his opinion, extremely rare in multiple sclerosis, and may be caused by sclerotic foci or may occur independently of these. The secondary degeneration of the pyramidal tracts may be associated with diffuse sclerosis of the cerebral hemispheres with atrophy of the gyri and alteration of the cells of the central gyri, as in the cases of Schultze and Greiff. The occurrence of degeneration of the pyramidal tracts without focal lesions he finds difficult to explain. It is possible that Schupfer does not lay sufficient importance upon the short extent of some of the foci in multiple sclerosis, and important areas of sclerosis of limited extent may be overlooked. In Jolly's case and Schultze's, Schupfer says the sclerotic areas do not explain the degeneration of the pyramidal tracts, as the degeneration began at a part where sclerotic areas were not detected. It is important to bear in mind the cumulative effect of slight degeneration at different levels; this, however, Schupfer does not overlook.

The loss of the patellar reflexes, with increase in the muscular tonicity of the lower limbs, was noteworthy. There could be no mistake in regard to this, because in my notes made at the time of the clinical examination I underscored twice the statement bearing on this point. The statement reads: "The knees and feet are inverted, and there is much spasticity of the lower limbs, which is greatly increased by passive movement. *There is no knee-jerk on either side, even with reinforcement.* This is especially noteworthy because of the spasticity in the lower limbs. The knee-jerk is not prevented by the spasticity, as the spasticity is comparatively slight when the limbs have not been irritated, and even without irritation of the limbs there is no knee-jerk. When the attempt is made to obtain the knee-jerk there is no contraction visible in the quadriceps muscle of either side. Ankle clonus is not obtained on either side. . . . Achilles jerk is absent on each side."

Marie[1] has said that the tendon reflexes are never absent in multiple sclerosis.

The difference in the condition of muscular tonus and of the tendon reflexes in my case is most extraordinary. Van Gehuchten[2] has paid much attention to the relation of the muscular tonus to the tendon reflex. He believes there is a certain parallelism between the two; but the parallelism does not always exist, and the tendon reflexes may be exaggerated when the muscular tonus is not exaggerated, or the tendon reflexes may be preserved when muscular atony is found, or they may be absent when muscular hypertonia or contracture exists. I shall not discuss the theories he advances to explain these conditions, as they do not seem to me to be sufficiently founded on fact.

[1] Marie. Leçons sur les maladies de la moelle.
[2] Van Gehuchten. Journal de Neurologie, August 20, 1897, No. 16, p. 305.

Strümpell[1] also believes that exaggeration of the tendon reflexes is often, but not always, associated with hypertonia of the muscles.

On the other hand, Parhon and Goldstein[2] do not believe that the condition of the reflexes is independent of the condition of the muscular tonus, and they assert that hypertonicity never occurs when the reflexes are lost, unless the reflexes are lost because the rigidity is so great that no movement is possible. These views are held also by some American authors. I show by this case that the patellar reflex may be lost when hypertonicity of the lower limbs is present and when this abolition of the reflex is not the result of immobility of the limbs from excessive rigidity. I have not been able to obtain Parhon and Goldstein's original paper, and must depend upon an abstract.

It is possible that in my case the patellar and Achilles reflexes were lost because sclerotic areas existed in the regions in which these reflex arcs within the spinal cord were contained. In the upper lumbar region no sclerotic focus was found, but in the mid-lumbar region a sclerotic patch was found in each posterior column implicating the fibres of the posterior roots after they had entered the cord. These sclerotic patches disappeared in the lower lumbar region, but at this level a sclerotic patch was found on one side implicating the anterior horn and anterior roots within the cord. The sclerotic areas found in the sacral cord were probably the cause of the lost Achilles jerk, and, in addition, the degeneration of one of the popliteal nerves examined may indicate that some of the terminal portions of the peripheral nerves were diseased. This alteration of the nerve fibres of the peripheral nerve was probably secondary to the alteration of the cell-bodies of the anterior horns of the spinal cord. The loss of the tendon reflexes of the lower limbs seems easily explained.

The exaggeration of the muscular tonicity may have been caused by the implication of the pyramidal tracts in the sclerotic areas above the lumbar region. If the impulses from all parts of the lower limbs had been almost entirely cut off it seems hardly probable that the muscular tonicity would have been exaggerated. A slight interference with the sensory impulses concerned in the reflexes may, however, be sufficient to cause a loss of these reflexes, even in association with hypertonicity. Doubtless sufficient sensory impulses passed to the cord to cause exaggeration of the tonicity when the pyramidal tracts were diseased and the inhibition from the brain was removed.

In combined systemic disease the posterior and lateral columns are degenerated, and in some cases the spasticity later yields to flaccidity, apparently because after a certain time sensory impulses from the limbs

[1] Strümpell. Neurologisches Centralblatt, July 1, 1899, No. 13, p. 618.

[2] Parhon and Goldstein. Roumanie médicale, 1899. Abstract in Revue Neurologique, March 15, 1902, p. 223.

to the cord are almost cut off, and therefore the paralysis becomes flaccid, even though the lateral columns may continue to degenerate. In illustration I refer to a case reported by Rheinbaldt,[1] in which rigidity of the lower limbs was prominent in the commencement of the palsy of these limbs, but when the patient came under Rheinbaldt's observation the palsy had become flaccid. Systemic degeneration of the direct and crossed pyramidal tracts, of the direct cerebellar tracts, and of the posterior columns was found. Rheinbaldt refers to a still more satisfactory case reported by Rothmann,[2] in which rigidity of the lower limbs gave place within two months to flaccidity.

Raymond and Cestan[3] have reported a very interesting case of disseminated sclerosis with paralysis in the associated movements of the eyeballs. The eyeballs were in a median position, and there was no ptosis. The irides reacted well to light and in accommodation. In each lateral movement of the eyeballs toward the right or toward the left the cornea was arrested about 7 or 8 millimetres from the external angle. Convergence, however, was very slightly affected. A sclerotic plaque was found implicating the nuclei of the third and fourth nerves. They quote Parinaud as saying that these associated paralyses are common in multiple sclerosis, but are usually incomplete. The ocular paralysis in Raymond and Cestan's case was incomplete, as it was in mine, and the lesions in the ocular nuclei in the two cases were similar. In a note of June 24, 1901, by Dr. H. F. Hansell, regarding my case, the statement is made that there was paralysis of the third nerve of each side and almost complete ophthalmoplegia. Iritic response was good. The pupils were equal. There was partial atrophic cupping of both optic nerves, with reduction in size of the bloodvessels without signs of previous inflammation. Dr. Hansell, in answer to an inquiry made by me, says: "'Almost total ophthalmoplegia' means in this case that the sixth nerves were also involved. Had external rotation been preserved my expression would have been 'double third-nerve paralysis,' and the word 'ophthalmoplegia' would not have been mentioned. Again, the total third-nerve paralysis could not have been present, since the report states that the pupils were responsive to light."

The implication of the sixth nerves in my case, as in Raymond and Cestan's, suggested a paralysis of associated movement resulting from the destruction of the connection by means of the posterior longitudinal bundle between the nuclei of the oculomotor nerves and those of the abducent nerves. This form of paralysis is known by the Germans as blicklähmung. In my case at least the sixth nuclei as well as the third and fourth were implicated in the sclerotic area.

[1] Rheinbaldt. Archiv für Psychiatrie, vol. xxxv., No. 1, p. 57.
[2] Rothmann. Deutsche Zeitschrift für Nervenheilkunde, vol. vii.
[3] Raymond and Cestan. Revue Neurologique, January 15, 1902, p. 52.

AN EXPERIMENTAL STUDY ON THE REGENERATION OF POSTERIOR SPINAL ROOTS.

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and

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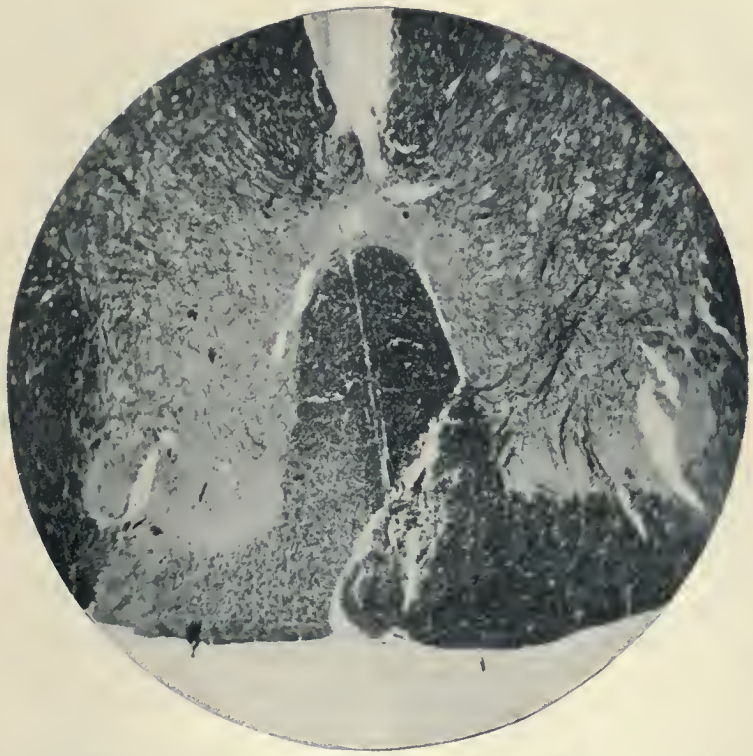
It has seemed to us desirable to determine, if possible, whether posterior roots are capable of regeneration in their intramedullary portion. The advisability of the operation recommended by us for the relief of tic douloureux—viz., the resection of the sensory root of the trigeminus—depends largely on the absence of regeneration of these posterior root fibres within the spinal cord, because, if the posterior roots are incapable of regeneration, we may assume that the sensory root of the Gasserian ganglion likewise is incapable of regeneration. With the object of finding an answer to this question, posterior roots in a number of dogs have been cut, but unfortunately the difficulties of keeping the animals operated upon alive for several months have been so great that we have had only one successful case. Animals that lived only a few weeks after the operation were not suitable for our purpose, as it might be argued that regeneration would have occurred had these animals lived longer; and delicate nerve fibres within the intramedullary portion of the posterior roots, if they had been found, might be regarded as atro-

phied fibres. Even if they appeared as newly-formed nerve fibres, there would have been no proof that they possessed sufficient vitality to exist within the sclerotic tissue.

The experiments were carried out in the following manner: A laminectomy of two or three vertebræ was performed. The preliminary operation was sufficient to expose two or three pairs of anterior and posterior roots. The posterior roots were differentiated from the anterior by the muscular contraction which followed application of an electrode to the latter, and by recognizing ganglionic enlargements on the posterior roots. This differentiation having been established, the posterior roots were in turn picked up with a blunt hook, each root was transfixed at two points, about one-sixteenth inch apart, with a curved needle armed with the finest-grade silk, and then completely divided between the two points at which the suture had been introduced. By tying the suture the divided ends of the nerve were brought into perfect apposition. The external wound was closed and the dressing applied. The manipulations upon the roots were carried out as delicately as possible, and with a view of making provision most favorable for the reunion. In some cases after division of the roots the divided ends remained in apposition, so that there was no necessity of tying the suture; the latter was then withdrawn. The operation did not require any particular technical skill, and could, if the indications arose, be practised with ease upon the human subject.

The specimen which has been most satisfactory for study was removed from a dog operated upon March 4, 1902. A laminectomy was performed, and the posterior roots of three spinal segments were exposed and divided about $1\frac{1}{2}$ cm. from the point at which they penetrated the dura. The divided ends of the lowermost root of the three were brought into apposition by a silk suture. The other two remained in apposition without any artificial means. Drainage was introduced, the wound closed, and the dressing applied. One week after the operation there was still a small sinus present at the point at which drainage had been introduced; the dog's general condition was good. The animal was killed on January 3, 1903, ten months after the operation had been performed. The spinal cord was removed and studied microscopically.

The intramedullary portions of the roots operated upon were en-



Photograph of a section of the spinal cord of a dog stained by the Weigert hæmatoxylin method. The degeneration of the intramedullary root fibres on one side of the posterior columns and in the corresponding posterior horn is shown.

tirely degenerated, and no young nerve fibres could be seen anywhere in the usual distribution of the posterior roots within the cord. The portion of the posterior column on the side of the operation where the posterior roots enter stained much lighter by the Weigert hæmatoxylin method than did the remainder of the cord, and no fibres belonging positively to the posterior roots were seen entering the posterior horn on this side. Degeneration could not be seen by the Marchi method, because all signs of recent degeneration, as shown by this method, had disappeared on account of the long time the animal was allowed to live after the operation, viz., ten months. Even by the Marchi method the degenerated intramedullary portions of the roots operated upon were readily recognized by the lighter staining of the area in which the roots enter.

A few very fine medullated nerve fibres were seen entering the posterior horn on the operated side, but it is reasonable to suppose that these came from the posterior columns, and not from the injured roots, as no medullated nerve fibres were seen passing longitudinally, in transverse sections, through the posterior columns close to the posterior horn on the operated side, although such fibres were numerous on the other side of the cord.

We regret that we have succeeded in keeping only one dog alive for several months after the operation, and yet we believe that this one case is most satisfactory in its results. The conditions for regeneration of the posterior roots into the spinal cord after the division of these roots were made as favorable as possible. The two ends of one root were joined to one another by sutures, and as regards the other two roots such means to produce apposition were unnecessary. Regeneration, nevertheless, has not occurred within a period of ten months, and we may assume that it would not have occurred had this dog lived much longer.

G. Bikeles[1] has attempted to show that regeneration of spinal roots in the dog may occur. He refers to the well-known experiments of Kahler. The latter, after compressing the posterior roots, came to the conclusion, in 1884, that regeneration does not occur in the intramedullary portion of these roots. Although all the nerve fibres were medullated within the compressed roots, and ap-

[1] Neurologisches Centralblatt, March 16, 1903, p. 248.

peared normal, except that they were small, half a year after the operation, and the roots in their extramedullary portion equalled in size those that had not been operated upon, one year after the operation; Kahler saw that the regenerated posterior root fibres disappeared at the entrance of the compressed roots into the spinal cord.

Bikeles refers also to Stroebe's experiments. This investigator, after injuring the spinal cord, saw regenerated fibres of those posterior roots that had been injured at the same time that the cord had been cut, penetrate a short distance into the scar tissue of the spinal cord. Bikeles says that he also has made a similar observation in man in a case of traumatic lesion of the spinal cord, but it should be observed that this penetration by the roots was very imperfect. Bikeles has repeated the experiments of Kahler, but his animals were allowed to live after the operation only from seven weeks to two and a half months. He found what he believed to be regenerated nerve fibres in the intramedullary portion of the compressed posterior roots. He mentions, however, that the neurogliar proliferation and sclerosis prevented an anatomical *restitutio ad integrum*, although neither the spinal cord nor its vessels had been injured. The spinal cord from an animal that had been allowed to live ten months after division of the posterior roots, as in our case, must give more valuable results as regards regeneration of posterior root fibres within the spinal cord than one from an animal that had lived only two and a half months, and even Bikeles seems to imply that the regeneration in his cases was very incomplete. Pinching of the roots is a less satisfactory method than division of the roots, because it is possible that in the pinching some axis cylinders may escape, even though their medullary sheaths are temporarily destroyed. We have no desire to lessen the importance of the work of another experimenter, and especially of one so capable as Bikeles, but we may state positively that in our case no evidence of regeneration of the divided posterior roots can be found.

The method by which regeneration of nerve fibres occurs is now exciting much interest. Recently E. Münzer[1] has questioned the correctness of Bethe's[2] statements that the peripheral portion of a divided nerve regenerates when union of the central and peripheral

[1] Neurologisches Centralblatt, December 1, 1903.
[2] Ibid., January 16, 1903, p. 60.

ends of the nerve is prevented. He says it is correct that new-formed nerve fibres may be found in the peripheral stump, but they do not originate there. A swelling forms at the central end of the peripheral stump, and this swollen end is intimately united with surrounding nerve fibres, and in this way young nerve fibres penetrate the peripheral stump.

These views of Münzer Bethe indignantly rejects, and maintains the correctness of his former statements. These radically opposed views of two well-known investigators make us await further developments before we can regard the manner of regeneration of nerve fibres as determined.

PARTIAL PARALYSIS OF ONE UPPER LIMB, RESULTING FROM A VASCULAR LESION OF THE LATERAL COLUMN AND ANTERIOR HORN ON THE CORRESPONDING SIDE OF THE SPINAL CORD.

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

Paralysis of one limb in an adult from a vascular lesion of the spinal cord is of such unusual occurrence that the case we report, in which this condition was present, seems worthy of publication, even though the clinical history leaves much to be desired. Spinal monoplegia, unless resulting from poliomyelitis, is almost unknown. As in our case the lesions were chiefly in one lateral column, and the implication of the anterior horn of the same side was probably in large measure secondary to these, it is questionable whether the case could be regarded as one of poliomyelitis.

One other case in literature has a resemblance to ours, and that was a case of congenital spastic rigidity of the limbs, the so-called Little's disease, reported by Dejerine.[1] The lesions of the spinal

[1] Bul. de la Soc. de Biol., 1897, p. 261.

cord were primarily in the bloodvessels, and were very similar to those in our case, but were on both sides of the spinal cord, whereas in our case they were unilateral.

The patient was a man, aged sixty-six years, and was admitted to the Philadelphia Hospital, January 15, 1902. He came later into the service of one of us (Dr. Spiller), but died before a thorough examination of his condition could be made. The ward notes recorded by the historian and resident physician state that he had had typhoid fever, rheumatism, and erysipelas, and had used alcohol freely, but had not had syphilis.

About three years before admission he is said to have had an attack in which speech was lost two weeks. Inasmuch as the loss of speech was temporary, and no signs of a lesion either recent or old were found in the brain, and the man was aged, it is possible that the attack was uræmic in character.

Notes made January 11, 1902, state that during the three days previous the man had been unable to use his right upper limb. He had been employed addressing envelopes. Two weeks before this time he had had a fall, striking his right shoulder on the ice. Some discoloration followed, but no loss of function.

The tongue on January 11th was protruded straight, and station and gait were good. The knee-jerks were slightly exaggerated. Ankle clonus was not present. The notes also state that the weakness of the right hand was first noticed by the patient one morning on awakening. He was unable to lift anything, and the hand felt cold. Two months after the paralysis of the upper limb occurred some return of power was observed in this limb.

The history unfortunately is very incomplete, and it is uncertain whether the paralysis of the right upper limb developed gradually or not, although it seems to have been of sudden development. The man had had a fall, but it is important that about eleven days are said to have elapsed after the fall before weakness of the upper limb was noticed, and that when the upper limb was paralyzed station and gait were good.

The case while in the hospital was supposed to be one of paralysis of the right upper limb, possibly from a lesion of the brachial plexus. The limb was almost in a natural position at the side of the body; the movement at the shoulder-joint was very limited, that

at the elbow-joint was fairly good, and the man was able to place his right forearm over the abdomen and to move the fingers fairly well. The forearm was slightly flexed. He was able to touch his face with his fingers. The condition of the spinal cord would indicate that the paralysis of the upper limb had existed probably more than a few months, as no degeneration by the Marchi method was found, and the degenerative changes in the spinal cord were unquestionably of long duration. The most important statement in this history is that the man had weakness of his right upper limb, and it is uncertain in what way it developed.

The primary area of alteration was in the eighth cervical and first thoracic segments. The bloodvessels were sclerotic within the portion of the right lateral column adjoining the anterior horn and as far as the periphery of the cord. The walls of the vessels here were much thickened, and when stained with acid fuchsin had a glassy appearance. (Fig. 1.) The neuroglia surrounding many of these vessels near the right anterior horn was much proliferated, and many of the neurogliar fibres were cut longitudinally in transverse sections of the cord. One bloodvessel in the right lateral column had a greatly thickened wall. The lateral and median portions of the right anterior horn were rarefied and stained more faintly than the rest of the horn. (Fig. 2.) The Weigert hæmatoxylin stain showed a great reduction in the number of medullated nerve fibres within these portions of the right anterior horn, and the antero-posterior diameter of this horn was much less than that of the left anterior horn. The lateral portion of the right horn contained scarcely any medullated nerve fibres, and the right posterior horn also contained fewer fibres than did the left posterior horn. The nerve cells had entirely disappeared in the portion of the right anterior horn where the alteration was most intense—*i. e.*, in the lateral portion, and were very abnormal in appearance where the alteration was less severe.

A small area of slight proliferation of the neuroglia was seen in the columns of Goll along the posterior septum, but did not extend very far upward or downward.

No signs of meningitis were seen, and the bloodvessels of the pia were only moderately thickened.

At a little higher level of the cord, about the seventh cervical seg-

ment, the right anterior horn still contained distinctly fewer medullated nerve fibres than did the left anterior horn, and the extreme external portion of the right horn was almost free of nerve fibres, those present having a longitudinal course in transverse sections of the cord. A distinct narrow area of sclerosis was seen extending from the lateral portion of the right horn about half-way across the lateral column, and most of the nerve fibres coming from the right lateral column and passing to the right anterior horn through this area had been destroyed. The nerve cells in the lateral portion of the right anterior horn were few in number; some were enlarged and had eccentric nuclei. The right anterior roots obtained in these sections did not appear to be degenerated, but very few roots were obtained.

Sections from the lower cervical region stained by the Marchi method showed no recent degeneration.

Above the lower part of the cervical swelling and below the first and second thoracic segments the sclerotic area became less intense and gradually disappeared.

Sections from the upper part of the cervical region and from the midthoracic region appeared normal. It was, therefore, impossible that this sclerosis could have been caused by a lesion higher than the cervical region.

The destruction of the lateral portion of the right anterior horn was sufficient to explain the brachial palsy, because the cells in this portion of the horn are probably the most concerned in voluntary motion and in the preservation of the muscle substance.

Among recent writers who have mentioned degeneration especially marked in the antero-lateral group of cells of the anterior horns occurring in cases of pronounced muscular atrophy in man, Stanley Barnes,[1] Mott and Tredgold,[2] may be mentioned. The former, in a case resembling one of multiple neuritis with intense atrophy of the hands, found that at the level of the seventh cervical segment the antero-lateral group of cells was the one most markedly affected, only a few dark-staining, shrunken cells remaining; in the other groups of cells little acute change was present, and in the main they were normal.

[1] Brain, Winter, 1902, vol. xxv. p. 499.
[2] Ibid., pp. 405, 411.

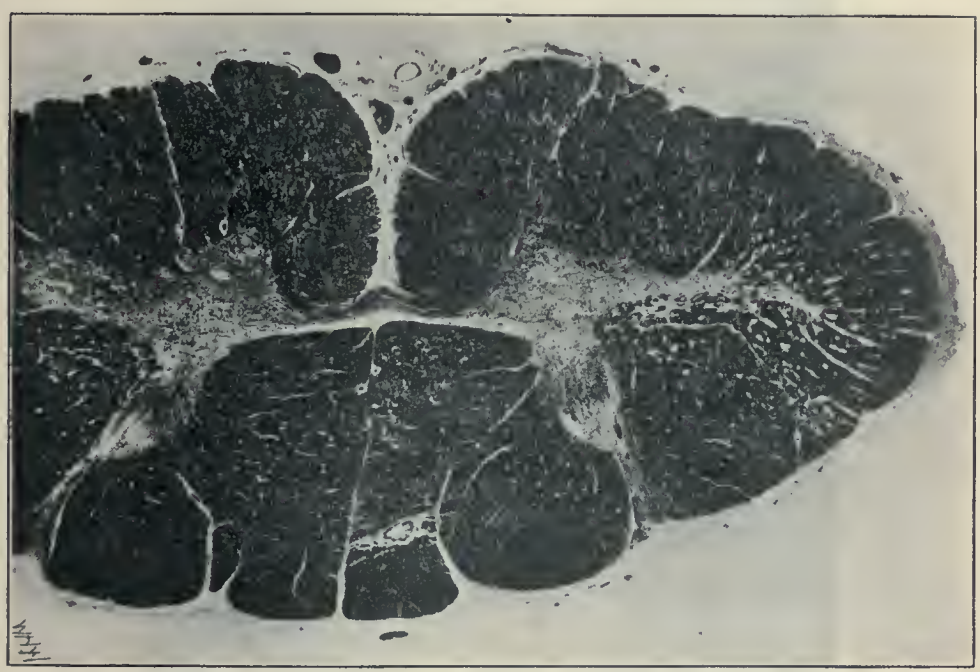

FIG. 1.—Photograph of a section from about the first thoracic segment. The right anterior horn is much smaller and contains fewer nerve fibres than the left. The sclerotic bloodvessels in the right lateral column are shown.

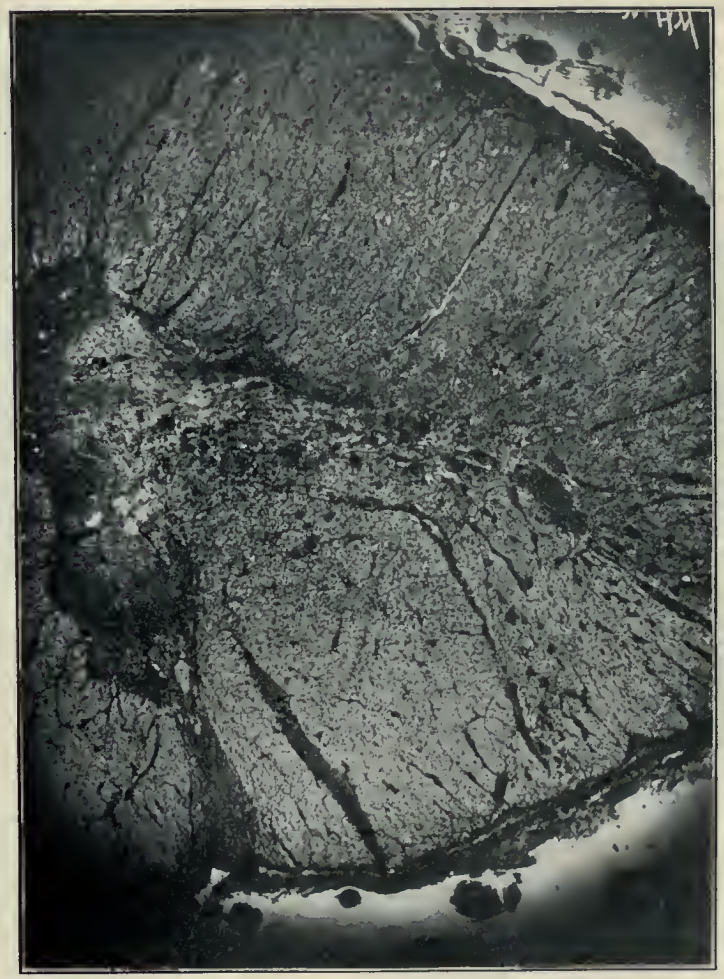

FIG. 2.—Photograph showing the right anterior horn and the right lateral column under higher magnification. The rarefaction of the lateral portion of the anterior horn and the sclerotic bloodvessels in the right lateral column are shown.

Mott and Tredgold found a similar condition in two cases of amyotrophic lateral sclerosis. The changes of the anterior horn cells of the cervical region in one case, they say, did not affect all the cell groups; the mesial-anterior group was practically normal, and the change was most marked in the lateral and postero-external groups; within these groups there were scarcely any large ganglion cells having a healthy appearance. In regard to the other case, they say that the diminution in the number of the anterior horn cells was practically confined to the lateral and postero-external cell groups, the mesial-anterior group showing scarcely any change.

Bikeles and Franke,[1] after cutting certain nerves of the brachial plexus in animals, found by the Marchi method degeneration of nerve fibres within the anterior horn of the cervical region on the operated side. These degenerated nerve fibres could easily be traced toward the lateral group of nerve cells, and none were found passing toward the medial group. They studied also the nerve cells by the Nissl method, in order to determine what groups of cells were degenerated after resection of the peripheral nerves. The most important groups of cells in the anterior horn of the cervical region are the ventro-medial, the ventro-lateral, the dorso-lateral, and the central. The names indicate the situations of these groups. In all their experiments on the dog, the ventro-medial, the central, and the ventral part of the lateral group were free from degenerated nerve cells, as shown by the Nissl method. The alteration in all cases was confined to the dorso-lateral group.

These experiments are very valuable, and in connection with the observations on man seem to indicate that the nerve cells situated laterally and dorsally in the anterior horn are the most important in regard to motor function, and it was these cells in our case which were directly implicated in the sclerotic area of the lower portion of the cervical region, so that we have in the microscopic examination of this case satisfactory evidence that the brachial monoplegia was of spinal origin.

[1] Deutsche Zeitschrift für Nervenheilkunde, vol. xxiii., Nos. 3 and 4, p. 205.

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A CASE OF PROGRESSIVELY DEVELOPING HEMIPLEGIA, LATER BECOMING TRIPLEGIA, RESULTING FROM PRIMARY DEGENERATION OF THE PYRAMIDAL TRACTS.[1]

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In this contribution the clinical and pathological details of a case of progressively developing hemiplegia, which later became triplegia, due to primary degeneration of the pyramidal tracts, will be presented, with a review of the literature of similar clinical cases. A summary of the literature of primary bilateral sclerosis will also be given.

J. S., white, was admitted to the Philadelphia Hospital August 9, 1897, where he died January 14, 1903. He was fifty-four years old when admitted. With the exception of a short time during which he was treated in the Men's Medical Ward for diarrhea or dysentery, he was during this period of six years a patient in the Men's Nervous Ward.

Omitting some unessential points, his history as traced in the hospital records is as follows: The family history obtained has

[1]Read at the meeting of the American Neurological Association, May 12, 13 and 14, 1903.

From the William Pepper Clinical Laboratory, Phœbe A. Hearst Foundation.

no etiological value. He denied venereal disease. He was a heavy drinker and also used tobacco. He had had rheumatism six years before admission to the hospital. The earliest note referring to any nervous symptoms was made August 9, 1897, when a statement was recorded that two years before admission he had been paralyzed on the right side. It is probable that at this time (during 1890-1895) his loss of power first began to show itself.

On September 28, 1897, the record stated that right hemiplegia (more correctly hemiparesis) was present, that the biceps-jerk and knee-jerk were increased, and that the plantar reflex was absent. Ankle clonus also was absent.

On September 24, 1899, it was noted that he could use his right leg for various willed movements, but that it showed loss of power as compared with the left; also that there was some loss of power in the right arm as compared with the left. His grip measured by the dynamometer indicated fifty-five for the right and seventy-five for the left. Speech was a little thick. The knee-jerk on the right was much exaggerated, and the quadriceps-jerk and gastrocnemius-jerk were also increased. Both ankle-clonus and patellar clonus of moderate degree were present on the right. No note was made at this time as to the Babinski phenomenon. Biceps-jerk, triceps-jerk and all muscle jerks in the right upper extremity were increased. The tendon and muscle responses on the left were all present but not exaggerated as on the right, and patellar clonus and ankle clonus were absent on the left. Sensation for touch and pain was retained all over the body, and the stereognostic perception was undisturbed. The irides reacted to light and in accommodation, and other examinations for nervous phenomena gave negative results.

On May 17, 1901, the patient complained that the right leg was weaker than it had been one year previous. The reflexes and other symptoms were much as before recorded.

Although the case was seen from time to time no further notes as to his nervous symptoms were made until December 29, 1902, at which time it was recorded that the movements of the face and tongue were normal; the upper limbs could be moved voluntarily and fully in all parts; the grasp of the right hand was feeble, of the left normal; voluntary power in the right lower limb was very slight; in the left lower limb it was a little better than in the right but much impaired. The right upper limb and both lower limbs were spastic, but contractures and wasting were not present. The biceps, triceps and wrist reflexes were much exaggerated in the right upper extremity, and in the left they were a little more prompt than normal. Patellar and Achilles reflexes were exaggerated on both sides, but more so on the right; patellar clonus was present on the right but not on the left; ankle clonus was elicited on each side. The Babinski reflex was present but not

very prominent on the right; it was absent on the left. Sensation to touch and pain was everywhere normal.

This man suffered at times from severe intestinal and cardiovascular symptoms. On August 6, 1897, he began to have severe pain in the abdomen with diarrhea, with numerous stools accompanied by straining and pain. He was treated for these symptoms in the medical wards. The heart sounds at this time were feeble and accompanied by a low systolic murmur at the right base. The sounds were feeble on the left also, and were best at the ensiform cartilage. On December 11, 1898, the records show that he had a soft blowing systolic murmur at the second aortic interspace. May 31, 1899, the patient complained of pain in the chest most marked over the precordia. A soft double systolic murmur was heard above the second cartilage. The heart's action was weak and irregular. A few unimportant notes, chiefly negative, were made in September, 1899. The presence of the cardiac murmurs above described was reiterated. On January 17, 1902, the patient complained of constant and severe pain over the precordial region; the heart sounds were very feeble. The pulse on the left side was imperceptible, owing to the atheromatous condition of the arteries and to the cardiac weakness. The pulse on the right side was perceptible but weak, and the radial arteries on both sides were hard and rigid. The patient suffered at this time and later from cardiac weakness and anginal pains for which he was treated with various remedies.

About January 1, 1903, he began to show signs of great weakness and rapid failure. He had at times attacks of vomiting. He lost flesh, his pulse became weak and intermittent, and the right lung became edematous. He died January 14, 1903, his death being preceded by a slight convulsion.

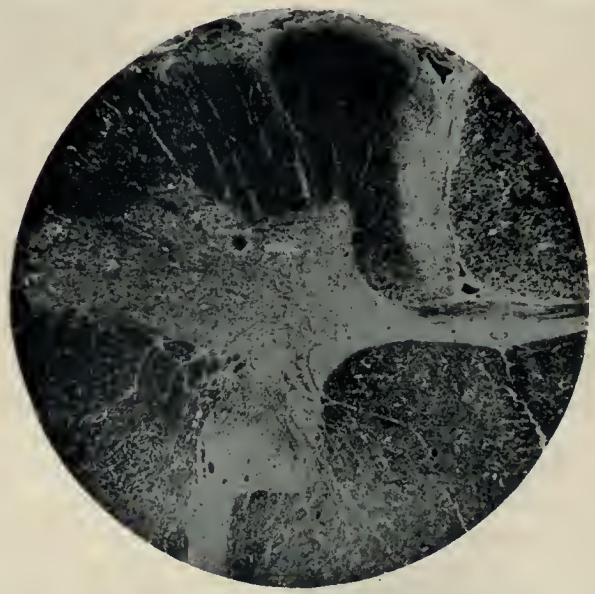
The necropsy showed a serious pathological condition of the vessels and many of the viscera: chronic pleurisy and tuberculosis with cavity formation; endocarditis, contracted kidneys and chronic marked atheroma. The heart muscles were soft and pale, the valves distorted, thickened and calcareous, the aortic extensively atheromatous. Both kidneys were very firm, dark in color, with granular surface and irregular cortex. The stomach was decidedly contracted and the seat of chronic catarrh. Beginning at the junction of the transverse and descending aorta was a unilateral dilatation of this vessel, which increased in diameter to about 4 cm. This structure was atheromatous and contained a flattened clot. The brain and cord were removed for microscopical examination, of which the following is a record.

The degeneration in the lumbar region was very distinct by the Weigert hematoxylin stain in the crossed pyramidal tracts, and more intense in the right than in the left. The direct pyramidal tracts by this stain did not appear degenerated at this level of

the cord. The nerve cells of the anterior horns were not distinctly altered, they were numerous and some were much pigmented, which, considering the man's age, was not remarkable. The chromophilic elements were well formed and the nuclei central. It may be said that the nerve cells of the anterior horns of the lumbar region had the usual appearance in persons of the same age. The anterior roots on each side in the lumbar region were normal.

At the eighth cervical segment the degeneration of the right crossed and left direct pyramidal tracts was very distinct by the Weigert hematoxylin stain. The left crossed and right direct pyramidal tracts were much less degenerated. The nerve cells of the anterior horns of this region may be said to have been normal, although in examining a number of sections a few cells were found that were not normal; the nerve cells in general were remarkable for their excellent state of preservation.

Sections from the lower cervical region stained by the Marchi method showed no recent degeneration in the right crossed and left



Long-standing degeneration of the left direct pyramidal tract, recent degeneration of the right direct and of the left crossed pyramidal tracts. The dots in the crossed tract are not so large as those in the direct tract (Method of Marchi).

direct pyramidal tracts. The left crossed and the right direct pyramidal tracts contained numerous small black dots, and those of the crossed tract were much smaller and less numerous than those of the direct tract. At the outer border of the right direct

pyramidal tract the dots were smaller than in the median and inner portions of this tract.

The anterior roots in the lower cervical region were normal. There was no distinct meningitis; here and there a slight accumulation of round cells was found in the pia.

Both pyramidal tracts were much degenerated in the oblongata and pons, but the left tract was much more degenerated than the right. The right pyramidal tract was much degenerated in the oblongata and pons by the Marchi method, while the left showed no recent degeneration by this method. About the middle of the pons, the left pyramidal tract contained a large proportion of normal nerve fibers, but a part of it was much degenerated. No degeneration could be detected in the foot of the right or of the left cerebral peduncle by the Weigert hematoxylin method, but degeneration by the Marchi method could be found in the middle portion of the foot of the right cerebral peduncle and also where the foot of the right cerebral peduncle becomes the lower part of the posterior limb of the internal capsule; the degeneration however was slight. No degeneration could be seen by the Marchi method in the foot of the left cerebral peduncle.

Sections of the left paracentral lobule contained Betz cells that appeared normal. They were not numerous, but this does not mean that there had been a loss of the cells, as the number of these cells seems to vary greatly in different cases.

Cellular infiltration of moderate intensity was found in the pia about the cerebral peduncles and pons, but it seems hardly probable that this could explain the long-standing degeneration of the pyramidal tract from the left cerebral hemisphere, and for this reason we have spoken of the degeneration of the pyramidal tracts as primary. No focal lesion could be detected anywhere.

Summarized, this case was one in which hemiplegia gradually developed on the right side, the lower extremity being more markedly and probably earlier affected than the upper, the case therefore at first belonging to the clinical type of unilateral progressive ascending paralysis. After several years the left lower extremity also became paralyzed, but not to the same extent as the right. The reflexes were all markedly exaggerated, the Babinski response being present. Sensory symptoms were absent. Microscopical examination showed intense and long-standing degeneration of the right crossed and the left direct pyramidal tracts, the degeneration extending into the pons but not into the left cerebral peduncle; also comparatively recent degeneration of the left crossed and the right direct pyramidal tracts, traced by the

method of Marchi into the lower part of the right internal capsule. No lesions, degenerative or focal, were found elsewhere in the brain or spinal cord; the case, therefore, was one of primary degeneration of the motor tracts, much greater and older in the right crossed and left direct pyramidal tracts. The case may be regarded as a corroboration of the clinical type described by Mills in the JOURNAL OF NERVOUS AND MENTAL DISEASE for April, 1900.

In the JOURNAL OF NERVOUS AND MENTAL DISEASE for April, 1900, in a paper entitled "A Case of Unilateral Progressive Ascending Paralysis, Probably Representing a New Form of Degenerative Disease," which was presented to the Philadelphia Neurological Society on December 18, 1899, an interesting case is detailed, reference being made to another somewhat similar case previously observed. The patient, a man fifty-two years old, about two years before coming under observation began to show signs of weakness in the right lower extremity, as indicated by his method of walking. The paresis came on slowly and insidiously. Weakness in the arm appeared for the first time eighteen months after the weakness was noticed in the lower extremity. This weakness soon became more and more evident, and was accompanied by the tendency to carry the arm raised against the body and flexed at the elbow. When first examined the paresis in the upper extremity, although easily determined, had not nearly reached the degree of impairment observed in the leg. The right side of the face was also slightly but undoubtedly paretic. The patient had had at one period some hyperesthesia in the right lumbar region and in the lower extremity, and later in the right upper extremity. Herpes appeared in the lumbar and lumbosacral regions, lasting for a short time. Wasting was distinct in the right lower extremity, the measurements showing a difference of one and a half inches for the thigh, and five eighths of an inch for the calves. The various movements of the right leg were distinctly weaker than those of the left, but were nowhere absolutely abolished. Similarly all the movements of the right arm were distinctly impaired, but were nowhere absolutely lost. The dynamometer showed 180 for the right and 160 for the left. Faradic contractility was retained. The affected limbs were not spastic nor contractured. Careful examination

showed retention of all forms of sensation. The tendon and muscle phenomena on the right side were all somewhat exaggerated. Knee-jerk was plus on the left side, but was considerably more exaggerated on the right. Patellar clonus was present on the right but not on the left, and the right side showed a slight ankle clonus, which was absent on the left. The plantar reflex was normal on the left; but on the right, while the Babinski reflex was not present, the normal response was distinctly less marked than on the left. It might be described as between normal plantar flexion of the toes and the dorsal flexion of the Babinski reflex.

This case has recently been made the subject of reinvestigation by Dr. Hugh T. Patrick, who inclines to the opinion that the case is one of paralysis agitans without tremor, the disease up to the present time having attacked only one side of the body. His report of the case was presented at the meeting of the American Neurological Association, and will be found in its Proceedings, with the discussion of the case by Dr. Mills. At the time when the patient was examined by Dr. Mills, among the reasons for believing that the case was not paralysis agitans were the absence of spontaneous tremor; the presence of markedly exaggerated reflexes on the affected side, even including ankle clonus and patellar clonus; the existence of decided wasting on one side, especially of the lower extremity, and the absence of the facies of paralysis agitans and of a fixed position of the body and head.

According to Sir William Gowers, both primary lateral sclerosis and paralysis agitans are probably abiotrophies (*Lancet,* April 12, 1902), and it may be that in the case under consideration the two abiotic diseases are conjoined.

In the same paper in which this case is detailed a second case is reported. This patient was under the care of Dr. Mills seventeen or eighteen years ago, and had previously been a patient of the late Dr. E. C. Seguin of New York, who believed that there was a cerebral lesion causing changes in the crossed pyramidal fasciculus analogous to lateral sclerosis. The view taken by Mills was that the changes in the crossed pyramidal tract were of the nature of a lateral sclerosis, but were primary and not secondary to any cerebral lesion. The patient was a woman forty-

three years old, who first noticed weakness in her leg while pregnant with her last child, three years before coming under observation. The left arm became paretic a few months after the left leg. The reflexes were much increased on the affected side. The patient remained under observation for many months, the paresis of the leg and arm slowly increasing. Neither arm nor leg was contractured, and sensibility was preserved. The patient complained at times of pains like neuralgias in the limbs, and of nervous twitching in the leg and arm. This patient was alive three or four years ago, and had become entirely unable to walk, but just how she was affected was not learned.

In the paper reporting these cases the differential diagnosis from an unusual form of unilateral disseminated sclerosis, from unilateral amyotrophic sclerosis, from a progressive hemiplegia due to slowly increasing focal cerebral lesion involving the motor subcortex or the internal capsule, from a degenerative motor neuritis, and from a functional hemiparesis was discussed. Reasons were given why the cases did not seem to fit in exactly with any one of these diagnoses.

In addition, as has been indicated above, the diagnosis must be made from unilateral paralysis agitans. Syphilitic hemiplegia later becoming a triplegia might also have some points in common, but could usually be separated by the presence of such concomitant syphilitic affections as paralyses of the cranial nerves.

In the *Philadelphia Medical Journal,* Feb. 9, 1901, Spiller has recorded the case of a man, forty-one years old, who began, four years before coming under observation, to feel weak in the left lower limb while walking. The weakness increased, and in about a year the left upper extremity also showed signs of feebleness. He was never unconscious and never had headache or vertigo or other signs of focal intracranial disease. When the case was recorded the movements of the left lower limb were spastic, but not ataxic; the toes of the left foot were scraped along the ground and the foot turned inward. Both knee-jerks were prominent, but the left much more so than the right. Ankle clonus was obtained on the left but not on the right, and the Babinski reflex was distinct on the left, but uncertain on the right. Sensation was normal. The resistance to passive movement and the grasp of the hand were decidedly weak. The left upper limb

was weaker than the right; it was also spastic, but the weakness and spasticity were less than in the lower extremity. The left upper limb was held slightly flexed at the elbow and against the body, but no contractures were present anywhere. Speech was normal, but the mouth could not be drawn up as well on the left side as on the right. The tongue went slightly to the left on protrusion. Ophthalmoscopic examination by Dr. H. F. Hansell showed white atrophy of the left optic nerve. After giving the details of his case, Spiller discusses its probable diagnosis, and concludes that the cases reported by Mills and by him have the symptoms which one should expect from unilateral lateral sclerosis, but he also called attention to the fact that other lesions might cause the same symptoms. The wasting is like that occurring in hemiplegia.

Potts (Journal of Nervous and Mental Disease, Oct. 1901), under the title, "A Case of Progressive Unilateral Ascending Paralysis Probably Due to Multiple Sclerosis," has reported a case somewhat similar to the case described by the authors of this paper. The patient, a youth of nineteen, when about fifteen years old began to drag his right foot, this foot in walking showing a tendency to cross over the other. Two years after the impairment of power, diplopia appeared and remained for five months. It was discovered at about this time that the right leg was smaller than the left. Weakness in the right arm was first noticed about three and a half years after its appearance in the right leg. Examination showed that when the patient walked the right leg was rigid and the toe dragged. All movements of the leg were preserved but impaired. The right arm was distinctly weaker than the left, but was not spastic. Both the arm and leg were decidedly atrophied, as shown by careful measurements. The adductor pollicis was not so large or firm as the left. The reflexes were prompt everywhere but exaggerated on the right, the Babinski response being present. The right side of the face showed slight paresis with some tremor on voluntary effort. Paresis of the muscles of the right side of the throat was present. Nystagmus was present especially when the eyes were turned to the right. There was paresis of the left inferior rectus, and paleness of the temporal halves of the discs. All forms of sensation, including stereognosis, were normal. A slight Romberg symp-

tom and tendency to incoördination were sometimes shown. The right hand and foot were colder to the touch than the left. Potts, while recognizing the resemblance between his case and the cases reported by the writers, holds that his case is probably one of disseminated sclerosis, and suggests that our cases might also be classed in this category, a view which we cannot accept. This diagnosis in Pott's case may be correct, although it is also probable in this and similar cases of disseminated sclerosis that the degeneration first and for a long time is chiefly confined to the pyramidal tract on one side.

Gowers, in his paper on "Abiotrophy" (*Lancet,* April 12, 1902), says truly "that the symptoms of systematic degeneration are not alone ground for the diagnosis of insular sclerosis, nor is the additional presence of nystagmus. Nystagmus on movement of the eyes is met with in many spinal degenerations of pure systemic type."

In his paper on "Chronic Progressive Hemiplegia," read at the present meeting of the American Neurological Association, Patrick describes a case which he regards as clearly indicating the progressively developing hemiplegia due to degeneration of the pyramidal tract of one side. During a recent visit to Chicago one of us (Dr. Mills) had the opportunity, through the courtesy of Dr. Patrick, of seeing this case, that of a young woman, eighteen years old, whose motor disability appeared about four years previously. The essential features of this case are the unilateral and progressive character of the paralysis which probably began first in the lower extremity, the exaggeration of the reflexes on the affected side, the absence of all forms of sensory disorder and of visceral symptoms, and the moderate wasting of the limbs and face. The reader is referred to Dr. Patrick's paper for fuller particulars of this case.

Another case of unilateral progressive ascending paralysis has been in our care at the University Hospital.

From a study of the cases presented in this paper, and in the light of the pathological findings in the case with autopsy, it may be concluded that there is a form of progressively developing hemiplegia, usually of ascending type, sometimes becoming triplegia or even quadriplegia, due to a progressive primary degeneration of the pyramidal tracts, which begins on one side and

may extend to the other. This clinical picture may be produced by other lesions, but we believe that we have established the fact that primary progressive degeneration of one pyramidal tract occasionally occurs. This is a unilateral lateral sclerosis, and in this connection it is interesting to devote some space to the subject of bilateral lateral sclerosis.

In a recent address in London, Erb[2] spoke of the spastic spinal paralysis first described by him in 1875. He believes that sufficient cases have been published to show that primary bilateral sclerosis exists. The following cases he gives as indisputable, and capable of standing any criticism.

Case 1. Minkowski.[3] Clinically the picture was one of spastic spinal paralysis. Anatomically there was a nearly pure sclerosis of the crossed pyramidal tracts, with slight changes in the direct cerebellar tracts.

Case 2. Von Strümpell.[4] The patient was a man, aged sixty-three years, who had a brother suffering from the same disease. Clinically the case presented the typical picture of spastic spinal paralysis for at least twenty years. Anatomically there was a typical degeneration of the pyramidal tracts from the lumbar to the cervical region, and in addition a slight degeneration of the direct cerebellar tracts and a still more trifling degeneration of the tracts of Goll in the upper part of the spinal cord. Strümpell would, on this account, reckon the affection among the combined system diseases, but the degeneration of the pyramidal tracts was certainly the most essential lesion, and is to be regarded as primary.

Case 3. Dejerine and Sottas.[5] Clinically this was a pure case of spastic spinal paralysis of twenty-five years' duration, death occurring from pneumonia in the sixty-sixth year. Anatomically there was marked sclerosis of the pyramidal tracts from the lumbar to the cervical cord, with slight partial sclerosis of Goll's tracts in the cervical region.

Case 4. Donaggio.[6] The patient was a man aged sixty-one years. Clinically there was for two and a quarter years the typical picture of pure spastic spinal paralysis; death resulted from pneumonia. Anatomically there was pure, exclusively primary degeneration of the pyramidal tracts from the lumbar to the cervical region (a quite typical case).

Case 5. Friedmann.[7] The patient was a male, aged fifty-two years. Clinically for two years the picture was one of a spastic spinal paralysis (trace of disturbed sensation being present?). The patient suffered from apoplexy, death resulting from pneumonia. Anatomically there was classical primary degeneration of the pyramidal tracts only, there being a trace of degeneration in the direct cerebellar tracts as well as endarteritis obliterans of the basilar artery.

Case 6. Von Strümpel.[8] Clinically a picture of spastic spinal paralysis was present, death occurring after the disease had lasted for thirty-five years. Anatomically there was quite typical moderate degeneration of the pyramidal tracts from the lumbar cord to the region of the pyramids. The direct cerebellar tracts were scarcely affected and the tracts of Goll very slightly in the upper cervical region. The anterior columns and brain were entirely free (belongs to the hereditary form).

Cases 7 and 8. Bischoff.[9] The patients were two brothers who, from their eighth and tenth years respectively, suffered from spastic rigidity of the limbs, ascending slowly from the legs to the head. Intellectually development was poor, but otherwise clinically the typical picture was one of spastic spinal paralysis. Death took place from phthisis after about twenty years' duration. Anatomically there was a typical degeneration of the pyramidal tracts, extending upwards beyond the oblongata, but not farther. The direct cerebellar tracts and Gowers' bundles were all but free. Goll's tracts were extremely affected. In the gray matter of the anterior columns there was atrophy of the ganglion cells (evidently occurring towards the end of life). The author calls the change in the spinal cord primary tract degeneration (quite analogous to the condition found by Strümpell), and holds that thereby the existence of an infantile form of hereditary spastic spinal paralysis has been proved.

Case 9. Ida Democh.[10] The case is clinically and anatomically somewhat complicated; clinically there was a typical picture of spastic spinal paralysis, combined with signs of chronic alcoholism, pains, tremors, etc. Anatomically there were primary degeneration of the tracts of Goll and congenital hydromyelia in the lumbar and dorsal cord; the direct cerebellar tracts were free; nevertheless, as proved by the author, this can be termed a case

of primary degeneration of the pyramidal tracts in spastic spinal paralysis.

Case 10. A case clinically typical of spastic spinal paralysis described by Kühn, in which von Strümpell made the microscopical examination of the spinal cord. He found an essentially characteristic primary degeneration of the lateral columns.

Erb regarded the sclerosis of the direct cerebellar tracts and the slight degeneration of the columns of Goll in some of these cases as of secondary importance.

He thinks that the case described by Strümpell[11] in 1894 as a primary isolated system degeneration of both pyramidal tracts, showing only slight transitions to amyotrophic lateral sclerosis, might come under this head.

To this record we would add the case reported by us in this paper, and also the case reported by one of us (Spiller[12]) in which there was primary degeneration of the pyramidal tracts with comparatively slight alteration of the nerve cells of the anterior horns of the spinal cord.

Note—Since this paper was read, another communication by Erb on spastic spinal paralysis has been published in the *Deutsche Zeitschrift für Nervenheilkunde,* Vol. 23, Nos. 5 and 6. He refers to the ten cases mentioned in his previous paper, and includes the well known case of Morgan and Dreschfeld.

[2]Erb. Lancet, 1902, p. 970.
[3]Minkowski, Deutsches Archiv f. klin. Med., Vol. 34, 1884.
[4]Von Strümpell, Archiv f. Psych., 17, 1886.
[5]Dejerine and Sottas, Archives de Physiologie Normale et Pathologique, 1896, p. 630.
[6]Donaggio, Rivista sperimentale di freniatria, Vol. 23, 1897.
[7]Friedmann, Deutsche Zeitschr. f. Nervenheilk., Vol. 16, 1899.
[8]Von Strümpell, Neur. Centralbl., 1901, p. 530.
[9]Bischoff, Jahrbücher f. Psych. und Neur., Vol. 22, 1902.
[10]Ida Democh, Archiv. f. Psych., Vol. 33, 1900.
[11]Von Strümpell, Deut. Zeitschr. f. Nerv., Vol. 5, p. 225.
[12]Spiller, JOURNAL OF NERVOUS AND MENTAL DISEASE, May, 1902.

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PARALYSIS OF ALL FOUR LIMBS AND OF ONE SIDE OF THE FACE, WITH DISSOCIATION OF SENSATION, DEVELOPING IN A FEW HOURS AND RESULTING FROM MENINGO-MYELOENCEPHALITIS[1].

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We are familiar with acute syphilitic meningo-myelitis chiefly as disease of the thoracic cord. Out of twelve cases tabulated by Williamson[2], in ten the lesion was wholly or almost wholly thoracic. In one it was thoracic and lumbar, in the other it was thoracic and cervical. The cases which have fallen under our observation have been thoracico-lumbar chiefly. It may be said that the localization to one portion of the cord is seldom absolute, in other words, although the lesion may be situated chiefly in one region of the cord, as the thoracic, some infiltration of round cells, and other evidences of meningo-myelitis are usually found in other regions. Cervical or cervico-bulbar forms of acute syphilitic meningo-myelitis, which might be designated clinically as high myelitis, are almost as rare as high tabes compared with the tabes which attacks the cord at lower levels, but in this cervical form the lesions are not confined to the cervical region, and are merely most intense in this portion of the spinal cord. Syphilitic meningo-myelitis is often associated with meningo-encephalitis. The following case is therefore in the first place of interest because of the unusual

[1]Read at the annual meeting of the American Neurological Association, June 5, 6 and 7, 1902.

location of the myelitis. It also has other points of interest, as the manner in which the facial nerve and its nucleus on one side were attacked, its simulation of hemorrhage into the cervical portion of the spinal cord, and the interesting sensory and reflex phenomena.

The patient, a colored man, forty-five years old, a laborer, was admitted to the Men's Nervous Wards of the Philadelphia Hospital, January 28, 1902. He had had gonorrhea twice, and a sore on the penis two years before. He had been a hard drinker. His family history was unimportant.

On September 26, 1901, the patient stated that he fell from a wagon, striking on his shoulder. He immediately rose, climbed to his wagon and continued working. Two weeks later he was obliged to quit work on account of pain in his left arm. He went to the Philadelphia Hospital for treatment, where he remained for about three weeks, at the end of which time he was again able to work. He worked until December 25, 1901, when pain in his left arm and between his shoulders compelled him to discontinue. The pain lasted for about one month.

At about 3 P.M., January 22, 1902, he suddenly lost the use of his left arm, this paralysis being followed in a short time by loss of control of the left leg; later by paralysis of the right side of the face, of the right arm and then of the right leg. Five or six hours elapsed between the time when he first noticed paralysis of the left arm and the time when the right leg became paralyzed.

He complained of swelling and of dull pain in the parts after they were paralyzed, but more especially in the left arm. He felt no pain immediately preceding the paralysis, and he was not unconscious at the time. He was not aphasic. After the paralysis he had a severe headache which ceased only the day before his admission to the hospital.

On admission (January 28, 1902), his general appearance was that of a well developed and well nourished colored man. He had had no movement of his bowels for five days before admission, and had voided no urine for at least twelve hours. Examination showed right facial paralysis, including the frontalis and orbicularis palpebrarum muscles. When the eyebrows were elevated no wrinkles were produced on the right side of the face. He was unable to fully close the right eye, and lachrymation was present. Speech was muffled, the mouth being drawn to the left side when attempts were made to talk, and whistling was impossible. Paralysis of the sixth nerve was not apparent. Hearing on the left side had been affected since the patient was eight or nine years old, and he could not hear

the tick of a watch close to his ear; on the right he could hear the tick at about ten or twelve inches. Tinnitus aurium was not present. He had no difficulty in swallowing, but complained of difficulty in keeping food in his mouth when eating. The uvula was not deflected to either side. His sense of taste was preserved, a solution of quinine and spirits of camphor and sweetened water being recognized on the tip and right half of the tongue. The tongue deviated slightly to the left. The pupils were contracted, the left irregular in outline; irides reacted sluggishly to light and on accommodation. Hemianopsia was not apparent. Knee-jerks and Babinski reflex were absent; the grip on both the right and left side was zero.

His chest appeared normal, the clavicles were large and prominent, and the supraclavicular fossæ depressed. The lungs were resonant anteriorly. Examination of the heart revealed a systolic murmur; his pulse was rapid, full and easily compressed. His abdomen was normal in appearance and was not distended.

The patient was again examined on January twenty-ninth. His breathing was labored, and his voice weaker than on the day previous. He complained of pain in his shoulder. On the thirtieth of January his breathing was less labored. He did not talk much, and answered by nodding his head. It was reported that he passed blood with his stools. His appetite was good and he had slept well the night previous.

Between January twenty-ninth and February first he was visited several times by both of us. The results of our examinations are summarized below, his general condition not changing much during this period.

The patient was fully conscious, and had no aphasia. His voice was a mere whisper, but he understood all that was said to him. He said positively that he had not been unconscious even during the development of the paralysis, and he was equally positive that he had not had convulsions. Wrinkles had disappeared on the right side of his forehead. Bilateral ptosis, equal on both sides, was present, and could not be overcome by voluntary efforts to open his eyes. When the eyelids were closed distinct paresis of the right orbicularis palpebrarum was present, the right palpebral fissure being about 5 cm. in width. In showing his teeth his mouth was drawn to the left side, the right side of his face remaining immobile. The tongue protruded very slightly toward the left, even when the right corner of the mouth was drawn up by the hand of the examiner; the masseter contracted firmly; the uvula was in the median line, and no distinct paralysis of the soft palate was present. The pupils were equal; both irides responded to light

and promptly in convergence. The eyeballs exhibited nothing abnormal. Movements of the head from side to side and from before backward could be freely made.

The patient could shrug his shoulders well, but with the exception of this movement paralysis of both upper extremities was complete. The limbs were flaccid, no contracture being present. Both lower limbs were paralyzed in all parts. The ophthalmic (supraorbital) reflex was present on the left, absent on the right. The conjunctival reflex was normal on the left, and greatly diminished on the right. Jaw-jerk was slightly exaggerated. The coraco-brachial or inner shoulder reflex was present. Biceps-jerk was almost lost on each side; the triceps-jerk was preserved on each side. The wrist-reflex was lost on each side. Knee-jerk was present on each side, but diminished, a little prompter on the right. The ankle-jerk was present on each side, and slightly exaggerated on the right. Ankle-clonus and the Babinski reflex were absent on each side.

The sensory conditions of this patient were of unusual interest. Tactile sense was preserved on both sides of the face, in the upper extremities and on both sides of the thorax and abdomen. Temperature sense (tested for heat and cold), and pain sense, were preserved on both sides of the face and neck, but were lost on the right side of the chest and abdomen, and diminished on the left side of the same. Temperature and pain senses were also lost in the distal portions of the right upper extremity. At a point about three inches above the elbow, hot, cold, and painful impressions began to be recognized. The pain and temperature senses were diminished in the left upper extremity. Sensation for touch was fully preserved in the left lower extremity, and somewhat diminished in the distal portion of the right lower extremity. Sensation for heat, cold and pain was almost completely lost in the left lower extremity, and completely lost in the right.

Respiration was entirely costal in type. The heart-beat was very rapid; a loud systolic murmur was present, loudest at the second intercostal space on the left side; the second sound of the heart was accentuated. The murmur was fully as distinct in the second intercostal space on the right side as in the corresponding space on the left. He had had no disturbance of bowels or bladder previous to his paralytic attack. When examined on January twenty-ninth and thirtieth he had incontinence of urine and feces; catheterization was necessary. He had had no dizziness nor vomiting at any time preceding the paralysis. He stated that his sight had been poor for three months. No ophthalmoscopic examination was made.

On February first he was somewhat duller, and early in the day did not seem to know where he was. On the next day his

condition was much the same, but his pulse and respiration were more rapid, and he complained of pain between the shoulders. On the third of February the patient frequently protruded his tongue to moisten his lips, and complained of his mouth being dry. He was duller and weaker than on the previous day, and did not pay so much attention to questions. His respirations were shallow. He had not slept well the night before. He refused milk, but asked occasionally for water; his appetite was fairly good. On February 4, 1902, at 2.30 A.M., he died.

A summary of the most important coarse pathological appearances found on necropsy is as follows: Edema of the spinal cord in the upper cervical region, adhesion of the dura: chronic splenitis and perisplenitis, old fibrous splenic adhesions; calcified tuberculous nodules of the right lung. A detailed account of the examination of the brain is subjoined.

The calvarium was thick, measuring at the occipital end 1.25 cm. and at the frontal end 1 cm. The dura was tightly adherent to the calvarium and a small new growth was present directly in front of the pituitary fossa, not extending above the surface of the dura. This growth had two distinct parts. A small nodule was present in the middle cerebral fossa (left), and was soft to the touch.

The brain was somewhat edematous in the parietal and occipital lobes. There was no indication of hemorrhage in the brain or pons, and no hemorrhage in either lateral ventricle was apparent. The fluid in the lateral ventricles was not increased in amount.

No distinct abnormalities of the choroid plexus were observed. Horizontal section of the upper portion of the basal nuclei revealed no pathological condition. No gross lesions were found in the brain. The masses noted in the base of the skull did not extend into the bone itself, but lay within the dura.

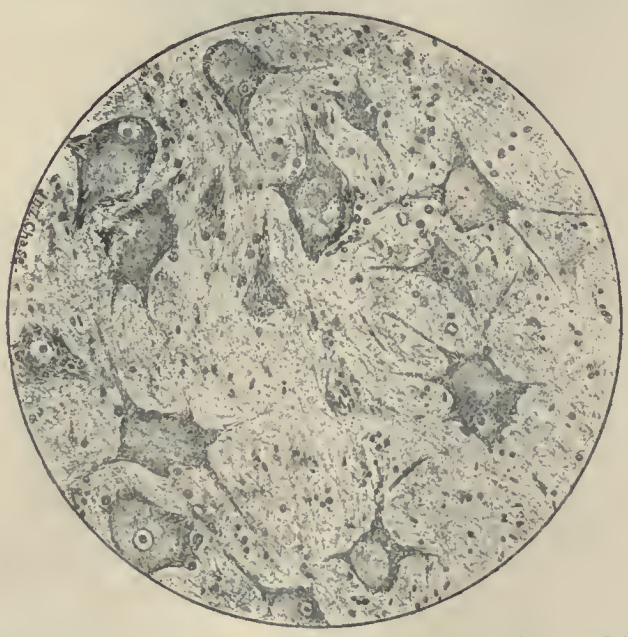
An increased amount of cerebrospinal fluid was found between the meninges and cord.

The brain and spinal cord were removed and examined microscopically.

Sections of the brain and spinal cord were stained by the Weigert hematoxylin and Marchi methods, by thionin, hemalum and acid fuchsin. Intense round-cell infiltration was found in the pia over the optic commissure, both in the walls of the vessels of the pia, and about some of the blood vessels within the commissure. The optic nerves and commissure as shown by Weigert's hematoxylin stain, were not degenerated.

Intense round-cell infiltration was found in the pia covering the medulla oblongata and the walls of some of the pial vessels were thickened. Here and there within the medulla oblongata a small vessel was found with round-cell infiltration about it.

Some of the cell-bodies of the left facial nucleus were degenerated, *i.e.,* the nucleus was displaced to the periphery of the cell-body and the chromophilic elements were broken up, but most of the cell-bodies of the left facial nucleus were normal or nearly normal. The right facial nucleus was exceedingly degenerated, and in most of the cell-bodies the chromophilic elements at the center of the cell-body had become granular or had disappeared, and only a few of these elements remained at the periphery of the cell-bodies; in others, no chromophilic elements



Nerve cell-bodies of the right facial nucleus seen in one field of the microscope. The cell-bodies are drawn in their relative positions as shown by the microscope, and almost all are intensely degenerated.

at all were found. The nuclei were displaced to the periphery of the cell-body. The contrast afforded by the two facial nuclei was very striking. The intramedullary portion of the right facial root was deeply stained by the Weigert hematoxylin and did not appear to be degenerated by this method. The degeneration of the facial nerve was evidently of very recent origin, and it was impossible to say whether the disease of this nerve began in its nucleus or in its peripheral portion. The alteration of the cell-bodies was such as could be produced by disease of the peripheral portion of the nerve. The round-cell infiltration in the pia over the medulla oblongata was not greater on

the right side than on the left, so that the degeneration of the right facial nerve could hardly be explained by the meningitis. The nerve may have been injured in its peripheral portion by a small growth like those described within the dura of the base of the skull; and the paralysis may have existed longer than the patient was aware of.

The fourth, fifth and sixth cervical segments were so softened by inflammatory changes that the normal relations of white to gray matter were entirely altered, and a large portion of a transverse section at this level was not colored at all by the Weigert hematoxylin stain, because of degeneration of the medullary substance. The round-cell infiltration within the spinal cord and pia at this level was intense. Here and there were swollen axones or spaces from which the axones had disappeared. Some of the small blood vessels within the spinal cord and pia at this level had much thickened walls, and numerous very small hemorrhages were found within the spinal cord. Some of the vessels of the pia were almost entirely closed by the intense proliferation of the intima.

The round-cell infiltration within the pia was very intense at the eighth cervical segment, but considerably less so than at the area of softening. The veins of the pia were thickened, and in some of them round-cell infiltration was intense, especially within the inner coat. The small arteries of the pia at this level were not intensely thickened. No degeneration at the eighth cervical segment could be found by Weigert's hematoxylin method. The direct pyramidal tracts were found degenerated when the Marchi method was employed, but elsewhere at the eighth cervical segment the degeneration as shown by the Marchi method was very slight. Slight degeneration was found by this method in the left column of Burdach near the posterior horn, and may have been caused by degeneration of the posterior roots of this segment. The destruction of nerve fibers at the area of softening had not existed sufficiently long to cause much secondary degeneration detectable even by the Marchi method. Most of the cell-bodies of the lower cervical region, as shown by the thionin stain, were normal or nearly normal. Collections of small bacilli were found within the spinal cord at the eighth cervical segment. It seems hardly probable that these bacilli were the cause of the alteration of the central nervous system, and they may have invaded the spinal cord shortly before or shortly after death. The intense thickening of the blood vessels at the area of softening indicated that the process had been of long standing, and that the softening was probably the final result of a long-existing impaired circulation. The changes were such as are seen in syphilis, and the case probably was one of syphilis.

Round-cell infiltration was found in the pia of the mid-thoracic region, but was not quite so intense as in the eighth cervical segment. No degeneration by Weigert's hematoxylin stain was found at the mid-thoracic region.

The round-cell infiltration of the pia in the lumbar region was about as intense as in the mid-thoracic region. Some of the cell-bodies of the anterior horns of the lumbar region were tumefied and much pigmented.

In this case the rapidity with which the paralysis of the four extremities and of the face, with sensory, pulmonary and other symptoms of a serious character, developed made the diagnosis of spinal hemorrhage into the cervical region or into the oblongata-spinal transition seem probable, and this diagnosis was at first made. The pathological examination showed acute myelitis of high grade, the foundations of which were laid in previous disease of the vessels and membranes. Numerous small hemorrhages were present in the more or less inflamed and disintegrated cervical cord, but these were secondary, or at the most concomitant with the attack of myelitis. In severe acute myelitis hemorrhages almost invariably occur, these in some instances being punctiform, in others of considerable extent, even sufficient to cause some bulging of the cord; not infrequently both punctiform hemorrhages and those of larger size are present in the same case. The fundamental disease in these cases is, however, the myelitis, although this usually occurs on the basis of previous disease of the spinal vessels.

When the question of diagnosis is between myelitis and hemorrhage, this is understood to mean between primary hemorrhage into the spinal cord (hematomyelia) and myelitis, or between primary hemorrhage into the spinal membranes (hematorrhachis) and myelitis. The manner of onset may give the clue to the diagnosis between hemorrhage into the cord and acute myelitis. In hemorrhage the attack is usually sudden and without premonitory symptoms, although this rule is not without rare exceptions, as when a paralysis preceded by some paresthesia comes on slowly. The development of paralysis in the case here recorded was relatively rapid; nevertheless five hours were occupied in its completion. Prodromal symptoms were not entirely absent, even presuming that the pain in the arm which followed the fall of

four months previous had no connection with the attack of myelitis, it will be remembered that for one month previous to the development of paralysis in the four extremities the man had had pain between his shoulders and in his left arm. Other prodromal symptoms were absent, but this was sufficient to cast some doubt upon the diagnosis of primary hemorrhage into the cord. The usual causes of hemorrhage were absent, unless the fall of four months previous may have been thought to bear some causal relation to the attack, but the traumatism was too remote to have induced a gross spinal hemorrhage. It was more likely to play a rôle in the determination of an inflammatory process in the spinal cord of a syphilitic subject. The patient had suffered from syphilis, the common cause of acute myelitis.

The diagnosis from spinal meningeal hemorrhage, extradural or subdural, was less difficult than that from primary hematomyelia. In spinal meningeal hemorrhage the symptoms of irritation come on suddenly and are usually of a very severe type, although even this rule is not without exceptions, probably in cases in which the hemorrhage into the spinal spaces occurs gradually. A meningeal hemorrhage sufficient to have produced the profound paralytic, sensory, reflex and other symptoms which were present in our case, would in all probability have been ushered in by severe pain in the back and in the distribution of the nerves whose roots were irritated by hemorrhage, and in addition by rigidity of the back, possibly local spasm in nerve distributions, contractures and even more or less generalized convulsions. With the exception of a steady pain in the back and one arm these irritative phenomena were not exhibited by the patient prior to the paralysis. In spinal meningeal hemorrhage paralysis usually occurs after the phenomena of irritation have been well marked, while in both acute myelitis and hematomyelia, whether primary or secondary, the paralysis is one of the earliest symptoms. The usual causes of spinal meningeal hemorrhage were absent in our case, while as already stated, syphilis, the common cause of myelitis, acute or chronic, was present. The course taken by the disease was not that of spinal meningeal hemorrhage, which usually results in death because of the extent of the inundation, or in partial recovery

through absorption after the lapse of considerable time. The rapid development of the paralysis of all the limbs resulting from myelitis makes the case one of unusual interest.

Another disease from which a case like the one here recorded might need to be differentiated is spinal or cerebrospinal tuberculous meningomyelitis. A pure spinal tuberculous meningitis is rare, but the cerebrospinal affection is not uncommon, and when the lesions are basal and spinal, the latter predominating, the case may show some features similar to those presented by a syphilitic cervical or cervicothoracic myelitis of the acute or at least of the subacute type. A case has been reported by Hensen[3] in which the diagnosis of cerebrospinal syphilis was made, but in which the autopsy showed the case to be one primarily of tuberculous meningitis, inflammation and degeneration of the spinal cord taking place secondarily. This case is in itself one of unusual interest, and is worthy of being recorded in detail in this connection.

A woman forty years old became sick eight days before she was received into the hospital with chill and severe headache. These symptoms were soon followed by severe pain in the back and the region of the kidneys, especially on the right side. A few days later disturbances in micturition occurred, requiring catheterization. On the eighth day of her disease she was taken into the hospital with a diagnosis of kidney and bladder disease. On admission she was mentally disturbed, confused and excited. She had pains in her head and back, in the region of the kidneys and in the legs. The atlanto-occipital articulation was tender to pressure, but no rigidity of the neck was present. There was, however, extraordinary rigidity of the whole vertebral column. No vertebra, however, was especially tender. Slight abducens paresis on the right side; bladder distended, detrusor paralysis; some hyperesthesia in the legs; patellar reflex exaggerated; other reflexes normal. The patient with support and even alone was able to take a few steps, although with rigid back and legs. No choked disc, not even later. The statement that out of 12 children she had borne most of them had died in early life aroused the suspicion of syphilis, although no other symptoms of syphilis were obtained. Some improvement occurred in the patient's condition, the mental excitement diminished, and voluntary urination became possible. Temperature was diminished. On the other hand, however, rigidity of the neck and of the vertebral column became constant. The hyperesthesia also diminished. On the eighteenth

day of the disease indisputable symptoms of spinal cord disease in the thoracic region developed. She complained of paresthesia in the right leg and then in the left. She was unable to raise the lower limbs. The muscles became flaccid, and marked reflex contractions developed in testing for the patellar reflex and in irritation of the skin. A few days later girdle pain in the abdomen developed on each side as high as the eighth rib; the abdominal reflex was lost. On the twentieth day of the disease the legs became completely paralyzed, and sensation in the lower parts of the body was almost lost. The patellar reflex was lost, the muscle excitability in the peroneal muscles on both right and left side was increased. In the left anterior tibial muscle there was beginning reaction of degeneration. Incontinence of feces and tendency to decubitus. Now cerebral symptoms again became conspicuous. The sensorium became clouded. The patient became somewhat delirious at night, and there was some evidence of facial paralysis which sometimes seemed stronger on the right side, sometimes stronger on the left. The abducens paralysis which at first had come on had disappeared. The muscles of the eye were not implicated. On the twenty-first and twenty-second days the mental disturbance developed into profound stupor, and slow forced movements appeared in the upper limbs, and only occasionally seemed to be somewhat coördinated. The diagnosis was made of cerebrospinal syphilis.

At the necropsy the diagnosis of syphilis was not confirmed, but a basal tuberculous meningitis with more extensive tuberculous meningitis of the spinal membranes, especially in the thoracic region, and secondary softening of the cord were found. Also miliary tuberculosis in the lungs, liver, kidneys and ulcers in the vermiform appendix.

The microscopical examination showed that the pia-arachnoid was in a state of inflammation throughout the entire length of the spinal cord, but more especially in the thoracic region. The inflammatory condition was more pronounced on the posterior aspect than on the anterior. The walls of the vessels, arteries as well as veins, were thickly infiltrated by round cells, almost difficult to recognize, and their layers could not be distinguished. Some vessels were thrombosed. The small-cell infiltration extended from the vessels into the surrounding pia. Distinct tubercles were not found, possibly on account of the short duration of the disease, but the absence of tubercles is not uncommon in tuberculosis of the cerebral membranes. However a few typical giant cells were present. In the middle thoracic region only scattered portions of the gray matter could be recognized, in which a few ganglion cells could be discovered after considerable searching. By the Pal stain a few normal nerve fibers were found, most of them, however, had disappear-

ed. No tubercles were found in any part of the spinal cord substance.

From the pathologico-anatomical point of view the degeneration of the spinal cord was secondary to the meningeal disease, especially of the vessels of the meninges—everywhere where there was meningeal disease of high grade there was degeneration in the border zone of the spinal cord also, whereas in the thoracic region there was complete destruction and dissolution of the spinal cord substance. The primary lesion, however, was the vascular lesion of the meninges.

A comparative study of Hensen's case and of the case here recorded shows that in the case of tuberculous meningo-myelitis the paralytic, sensory and reflex symptoms of grave type developed gradually and after a period in which the symptoms of meningeal irritation were prominent. It was eighteen days before indisputable symptoms of involvement of the cord were exhibited, and twenty days before paralysis was complete. The extensive meningeal inflammation was shown by the rigidity of the back, and also probably by the hyperesthesia of the extremities. In our case paralysis of all four limbs was complete in five hours, and the grave sensory, reflex and visceral phenomena came on with almost equal rapidity. With the exception of pain between the shoulders and in the left arm, symptoms of meningeal inflammation were absent. Basal symptoms were present in both cases, but most of these developed in the tuberculous case late in the disease, while the facial paralysis in our case was a prominent feature in the paralytic syndrome which came to the surface in the short period of five hours if the patient's statement may be relied upon.

It is well to add that the diagnosis of tuberculous meningomyelitis in Hensen's case was made from the condition of the lungs and intestines, and not from the presence of tubercle bacilli within the spinal cord.[4]

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[2]"Syphilitic Diseases of the Spinal Cord," Manchester, 1899.

[3]Hensen, H., Deutsche Zeitschr. f. Nervenheilk., v. 21, No. 3-4, p. 240.

[4]A case of tuberculous meningomyelitis with paralysis has been published by Joseph Collins in the December, 1902, number of this JOURNAL.

A CASE OF MULTIPLE FIBROMATA CONFINED TO THE INTERNAL PLANTAR NERVE.[1]

By Wm. J. Taylor, M.D., and Wm. G. Spiller, M.D.

[1] The clinical portion of this paper has been published in the Journal of Nervous and Mental Disease, April, 1903.

REMARKS BY DR. WM. G. SPILLER.

The report of a case of multiple fibromata confined to the ulnar nerve was published by Dr. W. W. Keen and myself in May, 1900. In that paper reference was made to the case of Dr. W. J. Taylor, now described at length. In view of the fact that Garrè, in speaking of his case, remarked that the presence of multiple fibromata in the skin of the sole of the foot was very extraordinary, and that v. Recklinghausen emphasized the immunity of this part and of the palm of the hand, it seems strange that in the two cases in which I have been concerned the hand was affected in one and the sole of the foot in the other. In one case the tumors were confined to the ulnar nerve, and in the other to the internal plantar. In Dr. Taylor's case a sprain of the left foot preceded the development of the symptoms of fibromata about four years, and the ankle after the injury remained weak. This accident may have been the immediate cause of the proliferation of the fibrous tissue in the left internal plantar nerve in a person predisposed to such proliferation. Dr. Keen's patient was a laborer, and trauma possibly aided in the formation of nerve tumors in the palm of the left hand. Trauma alone does not explain this singular process, or else multiple fibromata confined to a single nerve would be common, instead of being a very rare finding. Indeed, they seem to be more uncommon than the generalized neurofibromatosis. In the paper with Dr. Keen I referred also to a case of tumors confined to one nerve, reported by J. K. Mitchell and one by Bowlby.

In some cases heredity plays an important rôle, and members of different generations in the same family have exhibited neurofibromatosis. (Menke, Herczel, Bruns, Czerny.) It is impossible to believe that the process is purely an acquired one, and even in the cases in which the tumors have been confined to one nerve

it is probable that the tendency to proliferation exists in other nerves, and that the proliferation may be called forth by trauma, or possibly by disease of the blood vessels. In the specimens sent to me by Dr. Taylor for examination the blood vessels removed with the nerve and tumors are greatly diseased, and the walls of the arteries are much thickened; some vessels indeed are thrombotic and without any lumen. This interference with the nutrition of the nerve may have aided in the production of fibrous

A tumor dependent from the nerve trunk by several bands of fibers.

tissue within the nerve bundles. The tumors are fibromata and contain only such nerve fibers as have not become degenerated by pressure; they therefore are not true neuromata in the sense that proliferation of true nerve tissue has occurred. In amputation neuromata there is a formation of young nerve fibers with the proliferation of fibrous tissue, so that these are truly neurofibromata, but in the specimens I have examined from Dr. Keen's patient and in those from Dr. Taylor's patient the fibrous tissue alone is proliferated.

In one of the small tumors removed by Dr. Taylor which I

have cut lengthwise and examined microscopically, medullated nerve fibers may be seen entering the tumor at one end, and then after entering separating and passing to the periphery of the tumor, and gradually disappearing from view, so that where they become widely separated from one another they can not be traced at all. As in Dr. Keen's case the proliferation has probably begun in the endoneurium of the nerve, and therefore the tumors are somewhat elongated, with their long axes parallel to the nerve. As the perineurium becomes thickened it offers some resistance to further growth of the tumor, and the proliferation of the fibrous tissue occurs more rapidly where resistance is less, viz., at the two ends of the tumor.

The tumors removed by Dr. Taylor, with one exception, are small, as were those removed by Dr. Keen from his patient.

It is easy to discover the cause of the intense pain in these cases. The nerve fibers are pressed upon and irritated by the proliferating connective tissue, and although many nerve fibers degenerate and thus lose the power of conducting painful stimuli, the process is progressive, and new nerve fibers are attacked as those previously diseased disappear.

One tumor, the size of a small walnut, removed by Dr. Taylor, is of peculiar interest, because it is dependent from the large nerve trunk by several thin bands of fibers. These seem on inspection to be bands of connective tissue, but one of these bands cut in microscopical sections consists of nerve fibers embedded in and surrounded by much fibrous tissue. This tumor has evidently grown from several small nerves, or else it has grown from one nerve and surrounded and embedded others within it.

The long duration of the process in Dr. Taylor's case and the repeated operations deserve mention, because removal of these fibrous proliferations of nerves has been regarded by some writers as liable to cause a change from fibrous into sarcomatous tissue. This has not occurred in Dr. Taylor's case.

I have discussed the subject of neurofibromatosis at length in the paper published in collaboration with Dr. Keen in May, 1900, and shortly after the appearance of this paper the excellent monograph on the same subject by Alexis Thomson was published. It is unnecessary therefore to say anything further concerning the specimens from Dr. Taylor's case.

Extracted from The American Journal of the Medical Sciences, July, 1903.

A REPORT OF TWO CASES OF MULTIPLE SARCOMATOSIS OF THE CENTRAL NERVOUS SYSTEM AND OF ONE CASE OF INTRAMEDULLARY PRIMARY SARCOMA OF THE SPINAL CORD.[1]

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AND

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Sarcomatosis of the central nervous system apparently has not received much attention from American physicians,[2] although a few cases have been reported by English writers and quite a number may be found in the German literature. Cases of this character must have occurred in this country, and it is to be hoped that they will be put on record. One such has recently been seen in the service of Dr. F. X. Dercum, although the sarcomatosis in this case was not confined to the nervous system. Two cases of sarcomatosis of the brain and spinal cord, or of their membranes, in one of which the sarcomatosis was certainly confined to the central nervous system, and in the other was probably so confined, have been observed by one of us (Spiller), and are reported here in connection with a case of primary sarcoma of the substance of the spinal cord. The first case was to have been reported by the late Dr. W. F. Hendrickson, and the material had been partially studied by him at the time of his death. His notes are in quotation marks.

The patient[3] was in the service of Dr. Van Gasken, at the Woman's Hospital of Philadelphia, and I am much indebted to her for permission to use the clinical notes and to report the case.

Case I.—L. K., aged twenty-one years, married, was admitted to the Woman's Hospital of Philadelphia, January 4, 1902, when the following notes were made:

[1] Read at the meeting of the American Neurological Association, May 12, 1903.

[2] Dr. H. T. Patrick has called my attention to a case of diffuse sarcoma of the cerebral and spinal pia mater, reported by George K. Weaver in the Journal of Experimental Medicine, 1898, vol. iii., No. 6.

[3] A brief reference to this case was made in a paper published in the University of Pennsylvania Medical Bulletin, April, 1903.

The family history was unimportant.

The patient had been strong as a child. She had had scarlatina, diphtheria, and other diseases. She menstruated when fourteen years of age, but her periods were not always regular. They were painless, and lasted from four days to a week. She was well until after she was married, at the age of twenty years. She gave birth to a child five months ago; the labor was normal. She has not had much sore-throat, but last fall her hair came out.

Three days after her child was born she had a severe headache in the occipital region. The pain was shooting, and began at the base of the brain and extended upward; it was very severe but transient. Occasionally she had a sensation of pressure on the head. After the headache passed off she felt giddy and saw everything double, and shortly afterward she was told that she was cross-eyed. She had not had any paralysis of the ocular muscles previously. She had no fever. She had profuse sweating followed by cold, creepy feeling, after which she became very giddy. She had a shooting pain under the sternum. She has been confined to bed thirteen weeks. The toes first began to get stiff, and the stiffness gradually extended upward until now she has no power below the waist. At the first appearance of stiffness of the limbs she suddenly lost power to urinate voluntarily, and since then urination and defecation have been involuntary.

About a week ago a red spot appeared on the hip, and ulceration has occurred at this place.

The tongue is dry and coated.

Pulse, 108; temperature, 98.4° F.; respiration, 28. Two large bed-sores are found on the left thigh.

January 5th. Patient has complained of pain in the back and over the epigastrium.

The result of the examination of the eyes by Dr. Mayo, January 6th, is as follows: Pupils react normally to light and in convergence. Complete paralysis of the external rectus of each eye with paralysis of one of the oblique muscles, but the condition of the patient renders it impossible to determine which one. Ophthalmoscopic examination: Media clear; marked swelling of optic disks with hazy outlines; vessels tortuous; no hemorrhages; macular region normal.

I saw the patient in consultation January 7, and the result of my examination is as follows:

Pupils are equal and react promptly to light. The inward movement of the left eye in convergence is greater than that of the right. Head is slightly retracted, and neck is somewhat stiff. She has apparently no deafness. A papulopustular eruption is seen on the face and upper parts of the limbs. Tongue is protruded partially; no fibrillary tremor and no atrophy of tongue. No paralysis of facial muscles. Masseter contracts firmly on each side. Headache is general, but more severe in the frontal region; sometimes it is occipital. It is not worse at night. Patient moans continually as if in pain. Sensation to touch, heat, and pain is normal in the face. The head is rotated from side to side slowly and with much pain in the neck.

The grasp of the hands is nearly normal, but the effort to use the hand causes intense pain in the lumbar region. The upper limbs are moved freely in all directions. During the examination the patient yawns frequently. Sensation for touch, heat, and pain in the upper

limbs is normal. Biceps tendon, triceps tendon, and wrist reflexes are normal. The muscles of the upper limbs and the ulnar nerves are not tender to pressure. Pressure along the spine is not distinctly painful except between the shoulders.

The lower limbs are completely paralyzed. The patellar reflex on the right side is present but diminished, and on the left side it is almost lost, and on each side the reflex is very little increased by reinforcement. Slight ankle clonus is obtained on the right side, but not on the left. Achilles tendon jerk is exaggerated on the right side, normal on the left. Babinski's reflex is present on the right side, but soon exhausted. It is present also on the left side, and the big toe moves distinctly upward. The plantar reflex is decreased on each side. Sensation for touch, pain, and temperature is apparently abolished in the lower limbs. Muscles and nerves of the lower limbs are without sensation from pressure. Any passive or reflex movements of the lower limbs causes intense pain extending from the front of the abdomen to the back. Sensation to pin-pricks, temperature, and touch is first perceived on the trunk at a level with the seventh rib in the sternal line. The area where anæsthesia passes into normal sensation is not sharply defined. No distinct deformity of the vertebral column is seen.

Cerebro-spinal fluid was obtained by Dr. Everitt in lumbar puncture. It was clear, and without reddish tinge. Fibrin was present in small amount. No cells or bacteria were found. Cultures on agar-agar showed a few colonies. Examination after twenty-four hours' growth showed the presence of a micrococcus. This report was given by Dr. A. W. Peckham.

The patient slept very badly, was restless, and suffered much pain. She died January 22, 1902.

The necropsy was made by Dr. Hendrickson and the following notes are by him:

"*Anatomical Diagnosis.* Multiple tumors of the spinal cord, tumor of cerebellum, congestion of cord and brain; slight congestion of lungs, spleen, liver, and kidneys.

"*Histological Diagnosis.* Small spindle-cell sarcoma of the cerebellum with multiple new-growths of like character of the spinal cord; congestion of heart, spleen, liver, and kidneys.

"*External Appearance.* Body that of a fairly well-developed, but poorly nourished white female. Rigor mortis present in both upper and lower extremities, to a slight degree, although body is still warm. No œdema. Slight post-mortem lividity of dependent portions. On right thigh over head of femur is found a large, deep bed-sore, fully 8 cm. in diameter. There is also a smaller, more superficial one over the left side in corresponding position.

"*Abdominal cavity* normal.

"*Pleural cavity* normal.

"*Pericardial cavity* normal.

"*Heart.* Not removed or opened.

"*Lungs.* Incision *in situ* shows considerable congestion and œdema, but otherwise negative.

"*Spleen.* Normal except for slight congestion.

"*Gastro-intestinal Tract.* Not opened.

"*Liver.* Surface everywhere smooth and glistening. In size the organ is normal. On section there is found to be slight congestion of bloodvessels, but surface markings are everywhere distinct. Consistency normal. There is absolutely nothing indicating a syphilitic lesion. Gall-bladder negative.

"*Kidneys* of normal size, capsule strips easily, surface markings fairly distinct. There is slight congestion.

"The above examination of organs was done very hurriedly and necessarily somewhat incompletely because of lack of time; the examination of the brain and cord having received the most careful attention.

"*Spinal Canal.* On removal of vertebral arches from the upper cervical region down to the cauda, the external surface of the dura mater covering the cord is found to show moderate congestion of the bloodvessels. There is also a slight deposition of fibrin over this surface in the dorsal region which is found blood-stained, probably from hemorrhage in removal of the cord.

"After the removal of the cord from the spinal canal and removal of dura mater, the following condition is found: There is no evidence of inflammation of the pia-arachnoid coat, although there is moderate congestion of the bloodvessels. In the dorsal region, however, beginning about 14 cm. (5½ inches) from the lower extremity of the cord and extending upward for a distance of 5 cm. (2 inches), a distinct fusiform swelling of the cord is seen. This swelling at the point of greatest thickness measures 15 mm. (⅝ inch), as compared with the adjacent cord, which measures 12 mm. (½ inch).

"The consistency of the swelling is firm, being slightly more so than that of the adjacent uninvolved cord. Meninges over this area show nothing remarkable. One centimetre (⅜ inch) above the upper border of this swelling there is another small nodule not more than 1 cm. (⅜ inch) in length. In this case as in the lower swelling the enlargement is symmetrical, but not quite so distinct; the diameter being not more than 14 mm. (½ inch). Section through these enlarged portions of the cord reveals an apparent new-growth. All the surface markings normally found have been obliterated, and instead is seen a uniformly gray, more or less translucent tissue of rather firm consistency. There is no dilatation of the central canal. There is no evidence of hemorrhage in the involved area.

"*Brain.* There is marked uniform congestion of the bloodvessels of the pia-arachnoid coat. No evidence of inflammatory exudate. No thickening of meninges. No œdema. After removal of brain from skull there is found lying over the superior surface of the left cerebellar lobe a diffuse, irregularly lobulated tumor of fairly firm consistency. It extends practically from the median line separating the right from the left cerebellar lobe, over the superior surface of the left cerebellar lobe to the extreme left border, and from a point corresponding to the anterior border of the pons to within 1 cm. (⅜ inch) of the posterior border of the cerebellum. The tumor is roughly divided into three large lobes of irregular shape, with smaller lobes subdividing them. The borders are for the most part abrupt and in places give the impression of pedunculation, but elsewhere they seem to become lost gradually into the surrounding pia and brain tissue. There are no congested bloodvessels over the surface. Tumor mass is 2 cm. (¾ inch) above the general cerebellar surface. Section into tumor at one point

shows the growth to extend fully 3 cm. (1⅛ inches) deep. In color it is gray and corresponds in general appearance to the masses found in the cord. There is no evidence of softening at the point incised. No hemorrhage. The inferior surface of the left occipital lobe shows slight flattening of convolutions corresponding to the situation of the underlying cerebellar tumor, and it is probable that the entire inferior surface of the left occipital lobe was subjected to direct pressure. As far as can be ascertained without considerable dissection, there is no connection of the cerebellar new-growth with any portion of the brain aside from the cerebellum.

"*Cerebellar Growth.* Sections from different portions show practically the same condition. The growth is found to consist of small, spindle-shaped cells of the embryonic, connective tissue type. These cells compose the bulk of the tumor; they are closely packed together and are found to follow no order in distribution and arrangement. In places there is a very delicate connective tissue stroma lying between the cells. This stroma when present in sufficient amount tends to form small alveoli in which the tumor cells lie. The bloodvessels are fairly numerous throughout the sections examined, and are seen to have very thin walls. In many places nothing but endothelium exists between the lumen and tumor cells. The underlying brain tissue is found to be infiltrated with tumor cells in varying degree. No evidence of degeneration can be discovered in any part of the tumor.

"*New-growths of the Spinal Cord.* They resemble in all respects the new-growth in the cerebellum. Sections from the larger growth referred to in the gross description reveal complete obliteration of the entire cord. The small, spindle-shaped tumor cells form one diffuse mass occupying the entire transverse section of the spinal cord. The pia-arachnoid coat is also involved. It is considerably thickened and shows everywhere in varying degree infiltration with tumor cells. This is especially well marked about the congested bloodvessels.

"In the centre of the growth occupying the cord are discovered several irregularly shaped areas of small size which take up the eosin stain more markedly. Examination with high power shows few nuclei to be present and those which are do not stain well with hæmatoxylin. There is considerable finely granular detritus which stains light pink and a few compound granular corpuscles. No nerve fibres can be made out. Sections from the smaller of the two nodules referred to in gross description show practically the same condition as seen in the large one, but the process has not advanced so far. Although there has been complete replacement of the spinal cord by the new-growth, the pia-arachnoid coat is not invaded to such a marked degree. Throughout the pia there is considerable œdema, but very slight cellular exudate from the vessels. That which exists is confined entirely to the zone immediately about the vessels, which is also the seat of most marked growth of tumor cells. No areas of degeneration are to be found."

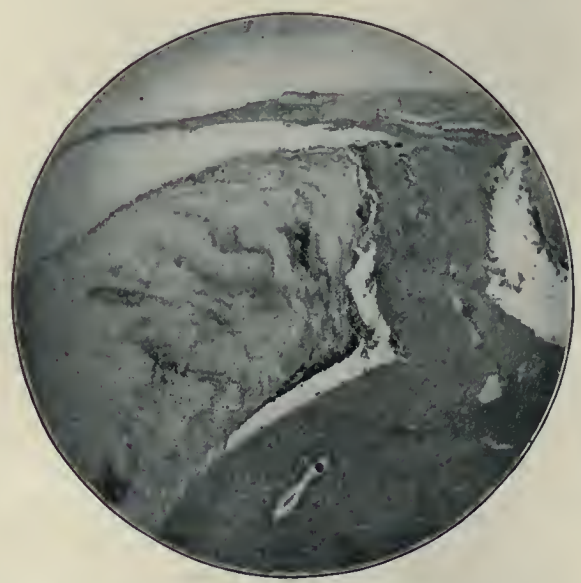
The examination of the sections from this case was not completed by Dr. Hendrickson, but further study has been made by me.

Numerous small tumors are scattered throughout the pia of the spinal cord, especially in the posterior portion. The origin of one of the large intramedullary tumors of the cord can be traced distinctly to

the pia. Cells are seen in great numbers extending through the pia of the anterior fissure into the substance of the cord, where they have proliferated to form the tumor, which is surrounded by a narrow band of partly degenerated cord substance. (Fig. 1.) In the greater part of the spinal cord the tumors of the pia do not infiltrate from the pia into the cord substance, but here and there a beginning infiltration may be seen. (Fig. 2.)

The pia of the anterior fissure is infiltrated with tumor cells at portions where no tumor is found within the cord. The nerve cells of the anterior horns in the lower cervical and lumbar regions stain well by thionin, and appear to be in a very good state of preservation. The anterior and posterior nerve roots, though surrounded by tumor masses, appear to be in an excellent condition.

FIG. 1.



Photograph of a section from the thoracic region of the spinal cord in Case I., showing an intramedullary tumor surrounded by the partially degenerated spinal cord. The connection of the tumor with the pia is shown by the sarcoma cells within the pia of the anterior fissure, extending from the intramedullary tumor to the pia surrounding the cord.

Sections from about the eighth cervical segment, and, therefore, above the intramedullary tumors, stained by the Weigert hæmatoxylin method show that the spinal cord was little degenerated. Scattered through these sections are small, faintly stained areas in which the nerve fibres have disappeared. The absence of pronounced ascending degeneration can be explained by the softness of the intramedullary tumors and the absence of compression and destruction of many axis cylinders passing through the tumor, and by the absence of degeneration in the posterior roots. The bloodvessels of the pia and of the spinal cord are not diseased.

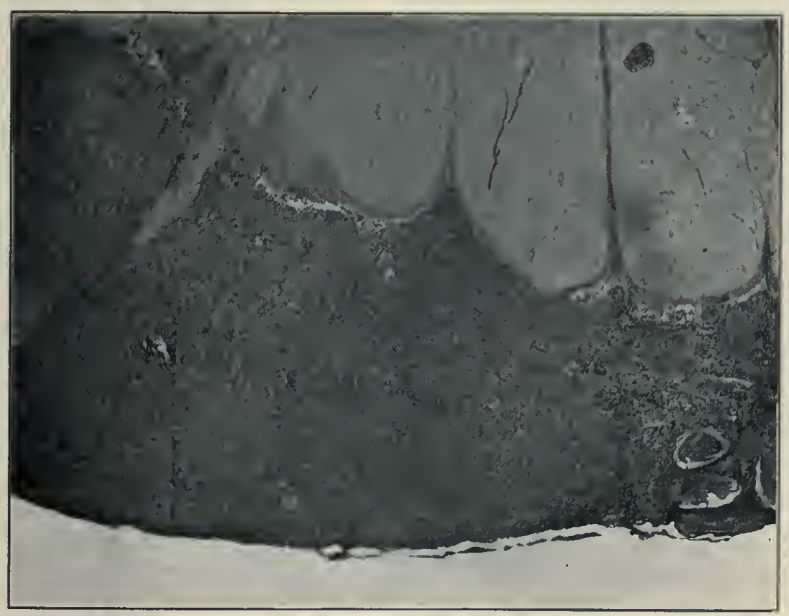
Sections from the lumbar region stain well by the Weigert hæmatoxylin method, and do not show distinct degeneration.

The Marchi method could not be employed.

CASE II.—The patient, a man aged forty-two years, was admitted to the University Hospital, into the service of Dr. C. K. Mills, December, 1902, and later came under my care when Dr. Mills went off duty.

He was married and had five children. He had been a glass-worker and glass-blower all his life. His father had died at the age of sixty years; his mother at the age of sixty-two years, of Bright's disease. Two sisters are living and well.

FIG. 2.



Photograph of a section from the spinal cord in Case I., showing the infiltration of the pia with sarcoma cells. In most places the sarcomatous tissue is sharply defined by the spinal cord, but at one side of the photograph the invasion of the spinal cord by the tumor cells is shown.

He had never had earache or any discharge from the ears. About one year ago he began to complain of failure of eyesight. At that time he was able to work. A short time after his eyesight began to fail he began to have pain in the left occipital region extending to the left temporal region. The pain is now constant but much worse at night, especially late in the night or toward morning. He cannot lie on the left side because the pain in the head is increased by this position.

He sleeps better in a chair than in bed. For about six months he has had difficulty in walking; he becomes dizzy and falls. He has had two attacks of unconsciousness, one during the past summer, and one two weeks ago, lasting several hours. He did not have convul-

sions in either attack. At times he has attacks of vomiting without any apparent cause. He has a voracious appetite, and eructation of gas occurs after eating. He has also shortness of breath, some failure of memory, and at times homicidal impulses, especially when suffering intense pain.

The report on his aural condition given by Dr. B. A. Randall, December 29, 1902, is as follows: "He has a labyrinthine involvement; on right side apparently total, with marked deafness on the left side."

The report of the ocular examination made by Dr. E. A. Shumway, December 30, 1902, is as follows: "Optic neuritis (choked disk), O. D. Optic atrophy, O. S. Paralysis of external rectus in each eye. Convergent strabismus (paralytic). V.—R. E., 6/12 V.; L. E., fingers

FIG. 3.

Photograph of the man described in Case II., showing paralysis of each external rectus, greater on the right side.

six inches. *Pupils:* O. S. larger than O. D., rather dilated. Both pupils respond to light. Diplopia impossible to elicit on account of poor vision in O. S. External rectus paralyzed on each side; eyes will not move beyond median line. Eye-grounds—Right: choked disk; difference of level of 4 D. ($1\frac{1}{3}$ mm.) between nerve head and retina; surrounding retina swollen, opaque; veins tortuous, dipping in and out of swollen retina. Left: atrophy of nerve, veins slightly tortuous, edges of nerve clean cut, no heaping up of connective tissue, arteries reduced in calibre."

An examination made by me December 31, 1902, gave the following results: The man is very deaf, but his intelligence is good and he replies promptly to signs. The facialis is not involved on either side. The sensory and motor portions of the trigeminus are not involved on

either side. He contracts both masseters equally and well, and moves the lower jaw freely from side to side. He has no disturbance of sensation on either side of his face, either for pain or touch.

The tongue is protruded in the median line, but has a slight tendency to deviate to the left.

When the eyeballs are at rest they are in convergent strabismus, the right eye being turned more inward than the left. (Fig. 3.) When he attempts to move his eyeballs from side to side, neither eyeball passes beyond the median line outward. He has no nystagmus, even in attempting to look to one side or the other.

He complains of soreness over the left supra-orbital and infra-orbital foramina, but has no tenderness over the left mental foramen, and no tenderness on pressure over the exit points on the face of the right trigeminus. The oculomotor nerve is not affected on either side.

The grasp of the hands is good on each side, and there is no impairment of the voluntary movements of the upper limbs. A slight tremor is noticed in each hand as he touches the first finger to the nose; this seems to be a form of ataxia. Biceps tendon, triceps tendon, and wrist reflexes are prompt on each side, and very little if at all exaggerated. The voluntary power in the lower limbs is normal. Gait is slightly ataxic with the eyes open, and the ataxia is a little increased when the eyes are closed. The erect station is good with the eyes open or closed. The patellar reflex is a little exaggerated on each side. He has a slight tendency to ankle clonus on the right side, but not on the left. The Babinski reflex is not present on either side. The Achilles tendon reflex is a little prompter than normal on each side. Hemiasynergy cannot be obtained.

An examination made by Dr. Mills and myself January 1, 1903, gave the following results: The man says he can hear a bell when it is struck, he hears it in the left ear but not in the right, and he hears the voice but does not understand words, and has not been able to hear words during the past two weeks.

Sugar was not tasted at first on the left side of the tongue after thorough rubbing, but was tasted when it was rubbed over the entire tongue. Salt was tasted promptly on the left side of the tongue. The sense of smell was preserved.

Percussion of the head just behind the left ear causes pain, but there is no tenderness on percussion of the left side. The man says that he has no pain in the right side of his head, but on the left side the pain begins in the back of the head and extends to the frontal region. The chief area of tenderness is just behind the left mastoid, and he flinches when pressure is made at this spot. He has less tenderness over the mastoid process.

The diagnosis of cerebellar tumor, probably on the left side, was made.

My examination on March 4, 1903, gave the following results: In walking he staggers slightly and his tendency is to go toward the left. Vertigo comes in attacks, and at these times he has great difficulty in walking because of his staggering gait. He has been seen in these attacks by the head nurse. The attacks of vertigo are of short duration, not over a few minutes. He was seen in an attack also by the resident physician, Dr. Hunter. The patient was sitting on the edge of the bed; his head fell forward on his chest, the trunk bent forward,

the upper limbs shook, and the body lunged toward the left and slightly forward; this was followed by partial recovery and then another lunge. The attack lasted about one minute and a half.

The man's condition has not changed much since last December. The patellar reflex on each side is prompt and not much exaggerated. Ankle clonus and Babinski's reflex are not obtained, the movement of the toes being flexion from irritation of the sole of the foot. The Achilles jerk is prompter than normal on each side. The resistance to passive movements in the upper and lower limbs is normal on each side. The grasp of the hands is good. Tendon reflexes of the upper limbs (triceps tendon, biceps tendon, and wrist reflexes) are about normal. There is no involvement of the sensory or motor portions of the trigeminus or of the facialis on either side. Pain is promptly perceived in the face on each side. The corner of the mouth is well drawn up and the forehead well wrinkled on each side. The tongue is protruded straight. Nystagmus is not distinct, but when the patient moves his left eyeball far to the right a little inco-ordination is observed in this eyeball. Nystagmus probably is prevented by the paralysis of each external rectus.

FIG. 4.

Photograph of the cerebellum, pons, and medulla oblongata from Case II. A tumor is shown in the left cerebello-pontile angle, and the medulla oblongata is very much enlarged on account of a tumor on the floor of the fourth ventricle.

The operation for removal of a cerebellar tumor was done by Dr. C. H. Frazier, March 6, 1903. The man was restless, delirious, and violent after the operation, and he never regained consciousness fully. The pulse rate was high, 140 at times. He died March 9, 1903.

The necropsy was made by Dr. Richard M. Pearce, who very kindly placed the material in my hands. Permission was obtained only for the removal of the brain and spinal cord.

A deep incision, extending about half-way into the left cerebellar hemisphere, with softened brain tissue about it, is the result of the operation.

A tumor 2 cm. (¾ inch) in anteroposterior diameter and 2.5 cm. (1 inch) in lateral diameter was found in the angle made by the pons at its junction with the left cerebellar hemisphere. (Fig. 4.) The facialis and acusticus on this side were compressed by the tumor, and

a smaller tumor was found enveloping these nerves and lying posterior to the larger tumor. A tumor about 1 cm. (⅜ inch) in each diameter was found in the angle made by the union of the pons with the right lobe of the cerebellum, but it did not implicate the right facialis and acusticus. The left trigeminus at its entrance into the pons was enveloped in a small tumor mass.

The medulla oblongata was much enlarged, and the posterior portion of it fluctuated as though a cyst were contained within it, but this fluctuation was caused by a soft tumor filling the posterior half of the fourth ventricle and infiltrating slightly the dorsal part of the medulla oblongata. Although the circulation of cerebrospinal fluid within the fourth ventricle must have been disturbed by this growth, the fourth ventricle was not enlarged.

FIG. 5.

Photograph of the conus medullaris and cauda equina from Case II. Numerous small tumors are found growing about the nerve roots.

The right facialis and acusticus were embedded in a small, soft tumor at their entrance into the internal auditory meatus, and the right glossopharyngeus, vagus, and accessorius were embedded in a similar mass at their entrance into the jugular foramen.

The pituitary body, optic chiasm, and each Gasserian ganglion were embedded in soft tumor masses. Each Gasserian ganglion was about twice the usual size on account of tumor formation about and within it.

A small papillomatous mass was found protruding from the dura over the front part of the second left frontal convolution, and when the dura was removed this mass was found to be adherent to the pia and to have penetrated the dura.

The left olfactory bulb was embedded in a small tumor.

Small tumors, some the size of a pin's head and some larger, were

found scattered throughout the spinal pia and enclosing many of the spinal roots, especially in the cauda equina. (Fig. 5.) They were more numerous on the posterior aspect of the spinal cord. Some of these tumors in the cauda equina had a papillomatous appearance.

Several of the cranial nerves implicated by the tumors were cut in microscopic sections and examined.

Transverse sections of the left opticus showed that the sheath of the nerve was infiltrated by tumor cells, but nowhere within the nerve were distinct tumor masses found, although there were many cells resembling those of the tumors scattered between the nerve fibres. Weigert hæmatoxylin sections of the nerve showed that much degeneration of nerve fibres had occurred.

Sections of the left Gasserian ganglion showed that the tumor had infiltrated between the nerve bundles and nerve cells of the ganglion. Some of the nerve cells were partially degenerated, having a shrivelled appearance, and the nuclei were eccentric. Some of the nerve cells stained very faintly and contained few chromophilic elements.

Sections of the right Gasserian ganglion stained by the Marchi method showed that the nerve fibres of the ganglion were in a moderate degree of recent degeneration.

The right abducens contained numerous areas free of nerve fibres, and yet by the Weigert hæmatoxylin stain the nerve appeared to be in a fair state of preservation. Degeneration was not found within the nerve by the Marchi method.

The left facialis was partly degenerated, as shown by the Weigert hæmatoxylin stain, and very intensely degenerated, as shown by the Marchi method. It is, therefore, remarkable that facial paresis did not exist.

The left acusticus was also much degenerated, as shown by the Weigert hæmatoxylin stain.

The right accessorius appeared to be normal by the acid-fuchsin and Weigert hæmatoxylin stains, but was shown to be distinctly degenerated by the Marchi method.

The tumor on the floor of the fourth ventricle infiltrated the dorsal part of the medulla oblongata, but did not invade the nuclei of the hypoglossal nerves.

Although numerous small tumors were present in the pia of the spinal cord, at no place were they found infiltrating the cord. They surrounded many of the nerve roots, and yet caused very little degeneration of these roots. Secondary degeneration, either ascending or descending, was not found in the spinal cord by the Weigert hæmatoxylin or acid-fuchsin stains, but very slight degeneration of the posterior columns, both in the cervical and lumbar regions, was detected by the Marchi method. Posterior root fibres could be seen passing through the small tumors of the pia, and yet staining well by the Weigert hæmatoxylin or acid-fuchsin methods. A spinal nerve root embedded in a small tumor was found to be normal with the exception of a few slightly swollen axis cylinders. The bloodvessels of the pia and of the spinal cord were normal.

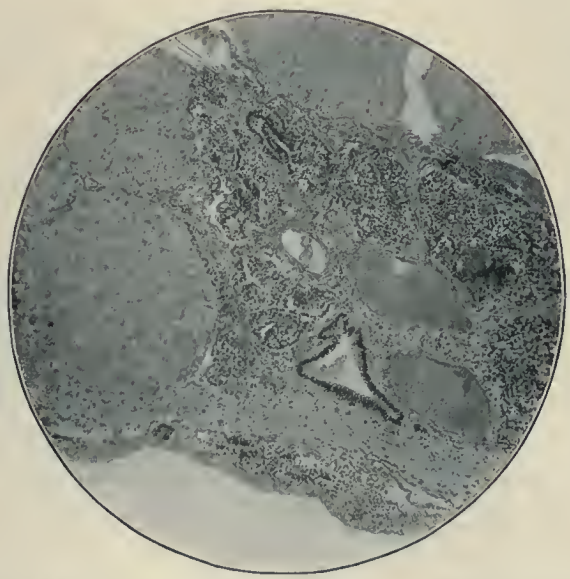
Many of the nerve cells in the anterior horns of the lumbar region stained by the thionin were much vacuolated, otherwise they were normal.

The resistance of the nervous tissue proper to tumor infiltration

throughout the brain and cord is remarkable, and little degeneration has been caused by the numerous tumors, because they were soft and produced little pressure.

The tumors everywhere have much the same structure. They consist of round or somewhat elongated cells, and even by Mallory's neuroglia stain contain very little intercellular tissue. In some places the cells are distinctly columnar and resemble those of the ependyma. (Fig. 6.) The columnar cells are arranged in long rows and have a large nucleus situated at one end of the cell. These rows of cells are found especially about the bloodvessels, but also where there are no bloodvessels. There is unquestionably a close resemblance between these cells and those of the ependyma, and the temptation,

FIG. 6.



Photograph of a section from the spinal cord in Case II., showing the infiltration of the pia with tumor cells. These cells have not invaded the spinal cord, and the nerve roots surrounded by the tumor mass appear normal. The columnar cells are seen in places.

therefore, is to call the tumor an ependymoma, but it seems remarkable that an ependymoma, being a form of glioma, should give extensive metastasis to the pia of the spinal cord, which is of mesodermic origin. This, and the absence of glia fibres between the cells, and the distinct tendency to the formation of rows of cells about the bloodvessels, seem to justify the classification of the tumors under the sarcomata, possibly endotheliomata or peritheliomata, and yet the close resemblance of some of the cells to those of the ependyma may permit us to regard the growth as a mixed one, and as being partly a sarcoma and partly an ependymoma. The ependyma is known to proliferate in cases of syringomyelia when the cavity extends to the central canal, and to cover in part the wall of the cavity. It is not unreasonable to suppose that a sarcoma growing from the pia may extend to the fourth

ventricle, and by irritation of the ependyma lead to its proliferation, and cause in this way a mixed tumor. This view is supported by another case in which a very similar tumor was found growing over the pons and implicating the posterior part of the fourth ventricle. A smaller tumor, probably metastatic, was found in the pia of the spinal cord, and the rows of ependyma-like cells were not so evident in this, although they were very striking in the large tumor. The tumors in Case II. have a resemblance to those described by Rosenthal,[1] Fraenkel, and Benda[2] as neuro-epitheliomota, and yet in some respects they are very different.

Case III.—J. C., aged thirty-nine years, a laborer, Italian, was admitted to the Philadelphia Hospital, in my service, June 28, 1902. He had paralysis of both lower limbs. His history so far as it could be obtained was as follows:

About three weeks before admission to the hospital he had had pain in the lower thoracic region and sensation of pressure about the waist, probably a girdle sensation. The pain had persisted in the abdomen and back. The left lower limb became weak, and soon the right lower limb was affected.

Notes made July 20th recorded that for three weeks he had had incontinence of urine and feces. He had not had pain in the lower limbs. The lower limbs were almost completely paralyzed. He was able on great effort to make slight movement of the right lower limb, chiefly with the thigh muscles. The limbs, except the soles of the feet, were not atrophied. The feet were œdematous and pitted slightly on pressure. The legs and thighs were not œdematous. The lower limbs were not contractured and were flaccid, especially the right. The patellar reflex was present on each side, but was diminished; the leg and foot on each side were very slightly moved voluntarily, but contractions were seen in the quadriceps muscles. The patellar reflex on the left side was a little prompter than on the right. Ankle clonus and Achilles reflex were not obtained on either side, and the loss of these reflexes was not caused by rigidity of the muscles. Talipes equinovarus was present on each side, although the varus position was not pronounced. Babinski's reflex was not obtained on either side, and the toes did not move distinctly in either direction. The soles of the feet were scaly. Sensation for touch and pain was lost in the lower limbs and over the lower part of the trunk, both back and front, to a line passing about two inches below the nipples. A bed-sore was over the left buttock. The upper limbs and head were not affected. The right pupil, however, was much larger than the left. The spinal column was not deformed.

A diagnosis was made of transverse lesion of the upper part of the thoracic cord, causing complete or nearly complete destruction of the cord at this part.

On August 9th the man's condition was as follows: He had still incontinence of urine and feces, and had had this since his admission to the hospital. He was in semi-stupor. The face appeared emaciated. The upper limbs were well developed, but not muscular. The only voluntary movements possible in the lower limbs were in the flexor muscles of the thighs. Babinski's reflex was distinct on each

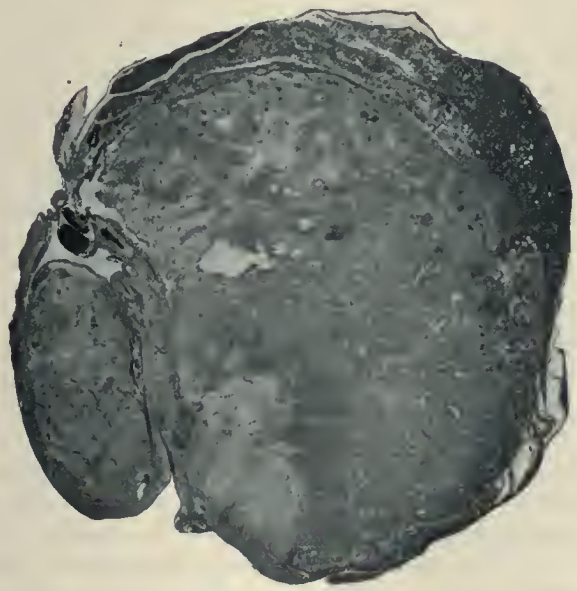
[1] Ziegler's Beiträge, xxiii. [2] Deutsche med. Wochenschrift, 1898, xxiv. p. 457.

side at this examination, but ankle clonus, Achilles tendon reflex, and patellar reflex were not obtained on either side. The plantar muscles of the feet were much wasted. The man died September 9, 1902.

After the spinal dura was opened an elongated swelling was found in the spinal cord just above the midthoracic region. This enlargement was about one inch in length. When a transverse cut was made through the middle of the swelling a tumor embedded within the substance of the spinal cord was found. No tumor could be detected elsewhere in the spinal cord, brain, or their membranes. Only the brain and cord were examined. The material was hardened in Orth's fluid.

A transverse microscopic section through the middle of the tumor shows that it is composed of spindle cells; it is, therefore, a large

FIG. 7.



Photograph of a section from the thoracic region of the spinal cord in Case III., showing the intramedullary sarcoma partially surrounded by the degenerated spinal cord.

spindle-cell sarcoma, the cells being considerably larger than those within the tumor of the first case reported in this paper. The tumor fills the centre of the spinal cord and has a narrow band of cord substance about it, although on one side it extends to and invades the pia. (Fig. 7.) The cord substance at the periphery of the tumor is very much degenerated and stains poorly with the Weigert hæmatoxylin. The bloodvessels everywhere in the section are much congested. Round-cell infiltration is present about some of the bloodvessels of the pia, and infiltration of tumor cells is found in some of the nerve roots. Some of the nerve roots are degenerated.

Sections taken just below the tumor show the changes commonly seen in compression myelitis, viz., loss of nerve fibres, proliferation of

neuroglia, some swelling of axis cylinders, and small, recent hemorrhages. The spindle cells of the tumor are not present at this level, either within the cord or pia. Sections stain well by the Weigert hæmatoxylin method, but contain numerous areas of necrosis. It is impossible to trace anywhere an origin of the tumor from the pia.

The nerve cells of the anterior horns in the lumbar region appear to be normal. Much degeneration is revealed by the Marchi method in the direct and crossed pyramidal tracts of the lumbar region. Flechsig's oval field in the posterior columns is partly degenerated. Sections stained by the Weigert hæmatoxylin method are a little pale; otherwise they appear to be normal.

Sections taken above and near the tumor stain well by the Weigert hæmatoxylin method, but the posterior columns, especially those of Goll, are partially degenerated. The anterior and lateral columns appear by this stain to be normal. Sections taken a little lower and at the upper border of the tumor reveal great degeneration, numerous necrotic areas, and much recent hemorrhage. Except at the level of the tumor sarcoma cells are not found in the pia.

Sections from the eighth cervical segment stained by the Weigert hæmatoxylin appear to be normal, except that the columns of Goll are much degenerated. By the Marchi method great degeneration is seen in the columns of Goll at this level, slight degeneration in the columns of Burdach, and very considerable degeneration in the direct cerebellar and Gowers' tracts and along the periphery of the antero-lateral columns. The nerve cells of the anterior horns at this level are deeply pigmented, but otherwise they appear to be very little altered.

A brief summary of the cases is as follows:

Case I.—The patient, a woman, had been well until one year after marriage. Three days after the birth of her child she had severe headache in the occipital region. After the headache ceased she was dizzy and had diplopia from external ocular muscle palsy. The lower limbs gradually became stiff and weak, until finally they became completely paralyzed, and control over bladder and rectum was lost. Examination of the eyes showed paralysis of both external recti muscles, with paralysis of one of the oblique muscles, but the patient's condition made it impossible to determine which one. There was marked swelling of the optic disks, with hazy outlines, and the vessels were tortuous. Five months after the birth of her child her head was slightly retracted and the neck was a little stiff, and she moved the head from side to side with difficulty. The headache was still severe. The upper limbs were moved voluntarily and freely, and sensation in the upper limbs was normal. The lower limbs were completely paralyzed, and the patellar reflex was much diminished on each side. A slight ankle clonus was present on the right side, and Babinski's reflex was present on each side. All forms of sensation were lost in the lower limbs.

Two intramedullary sarcomata were found in the thoracic region of the spinal cord, and there were numerous small sarcomata in the spinal pia; a large sarcoma also was found in the left cerebellar lobe.

Case II.—The patient was a man, aged forty-two years. About a year before admission he began to have failure of eyesight and constant pain in the left occipital region. Six months later he began to have difficulty in walking and would get dizzy and fall. He had two attacks of unconsciousness, but without convulsions. He had also attacks of vomiting Dr. B. A. Randall found labyrinthine involvement, apparently total on the right side, and on the left side the deafness was intense. Dr. E. A. Shumway reported that the man had choked disk in the right eye and optic atrophy in the left. Both external recti muscles were paralyzed. The man had a little tenderness over the left supra-orbital and infra-orbital foramina. He had occasionally attacks of vertigo.

An attempt was made by Dr. C. H. Frazier to remove a cerebellar tumor which was believed to be present, and probably on the left side, but was unsuccessful. The operation in this case will be described by Dr. Frazier. A tumor was found in each cerebello-pontile angle, but the larger one was on the left side. Tumors were found about the Gasserian ganglia, pituitary body, floor of the fourth ventricle, right internal auditory meatus, and right jugular foramen, and numerous small tumors were found in the pia of the spinal cord.

Case III.—The patient was a man who had had pain in the lower thoracic region and girdle sensation about three weeks before admission to the hospital. The pain persisted. The left lower limb became weak, and this was followed by weakness of the right lower limb. He had incontinence of urine and feces. He did not have pain in the lower limbs, but the lower limbs became almost completely paralyzed and flaccid, and sensation was lost in these parts and in the trunk as high as a line passing about two inches below the nipples. The tendon reflexes of the lower limbs were absent, but Babinski's reflex was obtained on each side. A primary sarcoma was found within the spinal cord just above the midthoracic region.

Sarcomatosis of brain and cord and of the pia covering them may cause great difficulty in diagnosis, and in some cases a correct diagnosis may be impossible, as in the second of the cases here reported. Extensive alteration may cause few symptoms, and this has been remarked upon by a number of authors. Schlesinger[1] speaks of it in his monograph on spinal tumors, and it was true of Hippel's[2] case, in which the sarcoma cells pushed apart the elements of the nervous tissue. In A. Westphal's[3] case, also, the extensive sarcomatosis was remarkable in that it caused comparatively few symptoms. The importance of this knowledge, when a question of operation is under consideration, is

[1] Beiträge zur Klinik der Rückenmarks- und Wirbeltumoren.
[2] Deutsche Zeitschrift f. Nervenheilkunde, vol. ii. p. 388.
[3] Archiv f. Psychiatrie, 1894, vol. xxvi. p. 770.

great, because, if evidence of sarcomatosis is found, the case is an inoperable one. The soft tumor masses grow in the pia about the spinal cord and about the nerve roots, especially those of the cauda equina, and about the cranial nerves, and cause few clinical signs of their presence, because they produce little or no compression or destruction of nervous tissue. In a case like Case II. of this paper, the pia of the spinal cord and brain and the dura at the base of the brain may be extensively infiltrated with sarcoma cells, the Gasserian ganglia and cranial nerves may be embedded in tumor masses, and yet few signs of disturbed function be manifest.

Westphal especially emphasized that sarcomatosis of the membranes has little tendency to invade the spinal cord, whereas in tuberculosis and syphilis the invasion of the nervous tissues is common. He also mentions that in all the recorded cases the posterior part of the pia was the part most affected. This part was also most affected in Case I. and Case II. Sarcomatosis of the membranes of the cord and brain is, according to him, a rapidly fatal disease.

C. Busch[1] remarks that his case of sarcomatosis of the pia, as well as the cases of Schataloff and Nikiforoff afford proof that sarcoma of the pia has very little tendency to invade the spinal cord and extramedullary roots, even when it surrounds these structures. Case II. of this paper is further evidence of the correctness of this opinion, but Nonne[2] says that sarcomatosis may invade the nervous tissues, and he gives as examples the cases of Lilienfeld and Benda. He quotes Bruns as saying that the process has very little tendency to implicate the nervous tissues, whereas Schlesinger remarks that a direct invasion of the spinal cord by the sarcoma cells is frequent. The resistance of the extraspinal roots to the process has been observed by A. Westphal, Schlesinger, Nonne, Benda, and others.

Case I. of this paper shows that occasionally sarcomatosis may extend into the substance of the spinal cord and brain, and both Case I. and Case II. afford evidence of the resistance of the nerve roots to infiltration by tumor cells.

It is partly because of this escape of the nervous tissue in many cases that a correct diagnosis of the extent of the process may be impossible.

The infiltration of the pia resembles that caused by syphilis or tuberculosis, for the process is, if we care to so call it, largely a sarcomatous meningitis. An incorrect diagnosis of syphilis is not unlikely. Nonne called attention to the resemblance of a case of his to one of acute cerebro-spinal syphilis, but no history of syphilis and no clinical signs of this disease could be discovered, mercury and iodide were without

[1] Deutsche Zeitschrift f. Nervenheilkunde, vol. ix. p. 114.
[2] Ibid., vol. xxi., Nos. 5 and 6, p. 369; Archiv f. Psychiatrie, vol. xxxiii. p. 393.

effect, and such severity of symptoms and rapidity of development he thought were very uncommon in syphilis. To the naked eye the brain and spinal cord in Nonne's case appeared to be normal, and yet the pia everywhere was infiltrated with cells which were believed to have had their origin from the endothelium lining the lymph spaces about the vessels—*i. e.*, the so-called perithelium. The infiltration was especially marked about the optic chiasm and over the pons, and was greater over the posterior portion of the cord than over the anterior. This method of selection is like that occurring in syphilis. The cells invaded the nervous tissue at different places, and this invasion was especially by means of the pial septa. In the cervical region infiltration into the cord was by way of the anterior fissure, as in the case of Mrs. K. (Case I.). A difference from syphilis was found in the absence of circumscribed tumors, so common in syphilis; in the absence of disease of the vessels, and in the uniformity of the infiltration of the pia. The latter without the formation of small tumors here and there was very remarkable, and it seems to be the only case of the kind. The symptoms at first indicated hysteria and later a diffuse process of brain and cord.

The possibility of syphilis in the case of Mrs. K. (Case I.) and also in Case II. was carefully considered. The symptoms in Case I. were strongly suggestive of syphilis, and they had developed a year after the patient's marriage; it was therefore possible that she had contracted syphilis from her husband. The process was evidently a diffuse one involving the brain and spinal cord. Syphilis could cause just such a symptom-complex, but the cerebral symptoms and complete paralysis of the lower limbs without impairment of function in the upper limbs was unlike a syphilitic symptom-complex. It is true that the thoracic region is often the most diseased part when syphilis attacks the spinal cord, but it is not common even in such cases to find an entire absence of symptoms indicative of implication of the cervical region of the cord. If weakness does not develop, at least pain in the upper limbs is common when the syphilitic process invades the brain and spinal cord. This apparent escape of an intervening part of the central nervous system is suggestive of sarcomatosis, because the sarcoma cells may invade the spinal cord only at one place and cause disturbance of function in the portion of the body innervated from the cord below the diseased area, while the soft tumor masses of the pia above produce no symptoms.

In Case II. syphilis was regarded as possible and antisyphilitic treatment was employed without very brilliant results. The bilateral deafness, the paralysis of each external rectus, the choked disks, the headache and attacks of vertigo could be easily explained by syphilis, and yet the case was one in which tumor cells infiltrated between and

about many nerve fibres, and even between the nerve cells of the Gasserian ganglia, and caused very few symptoms.

In F. Schlagenhaufer's[1] case both trigeminal nerves and the optic chiasm were embedded in tumor masses, but microscopically the tumor cells were found to implicate the pia alone about these nerves. A small-cell sarcoma in the cervical region was believed to be the primary growth, but sarcoma cells were found in the pia of the brain and of the spinal cord. Schlagenhaufer thought that the sarcoma of the cervical region had its starting point within the cord, and was not the result of extension of a growth into the cord from the pia. He believed that to Schlesinger's classification he could add another division, viz., primary sarcoma of the spinal cord with secondary sarcomatous infiltration of the pia.

Schlagenhaufer's case resembles Case I. of this paper in the involvement of the cord by a tumor, and yet the origin of one of the tumors in Case I. could be traced from the pia surrounding the cord through the pia of the anterior fissure. Schlagenhaufer's case resembles Case II. in the implication of cranial nerves by the tumor masses.

Inasmuch as the symptoms in Case I. began three days after the birth of a child, it seemed possible that septic infection had occurred, and that the patient was suffering from purulent meningitis. The duration of the symptoms for five months without any signs of disease of the cervical cord was rather against the diagnosis of purulent meningitis.

That sarcomatosis may give the signs of tuberculous meningitis is shown by a case in a child, aged four years, reported by Lereboullet.[2]

In Cases I. and II. reported in this paper both abducent nerves were paralyzed, and yet in neither case was there any direct implication of these nerves or their nuclei by the tumor masses; paralysis of both external recti, therefore, does not prove that a tumor is situated on or in the pons.

Tenderness of the vertebral column was one of the first and most striking signs in A. Westphal's[3] case, and it has been observed in other cases, and is suggestive of meningitis, but it is not always present in sarcomatosis of the spinal pia. It was not present in Case II., but was present over a portion of the spinal column in Case I.

Syphilis has sometimes caused the clinical picture of disseminated sclerosis, and therefore it is not surprising that sarcomatosis should simulate the same disease, as in a case reported by Hippel.[4] The symptoms in this case were optic neuritis passing into atrophy, nystagmus, headache, vertigo, scanning speech, progressive dementia,

[1] Obersteiner's Arbeiten, vol. vii. p. 208.
[2] Abstract in Revue Neurologique, January 30, 1902, No. 2, p. 98.
[3] Loc. cit.
[4] Loc. cit.

vomiting, intention tremor, exaggerated tendon reflexes, ataxic gait, and pain in the extremities. The findings were: sarcoma of the right half of the cerebellum; multiple sarcomata of the cerebral and spinal dura, of the pia, choroid plexus, brain, and spinal cord; diffuse sclerosis of the central nervous system, and metastatic sarcomata of the skin.

In this case, as in Case II., a tumor was found at the internal auditory meatus, and in two cases reported by Soyka (cited by Hippel), which were probably cases of sarcomatosis, a tumor was found in each at the internal auditory meatus; so that this, like the pontile cerebellar angle, seems to be a favorite location for sarcoma.

In Case II. the age was more advanced than that at which sarcomatosis is most common. A. Westphal says that most persons with sarcomatosis of the central nervous system have been very young, and that two-thirds of the cases have occurred in childhood. In Case I. the age was twenty-one years.

Schlesinger, in his excellent monograph on spinal tumors, divides primary sarcoma of the nervous system into: 1. Solitary sarcoma. 2. Multiple sarcomatosis.

Tumors of the first group may occur: 1. In the substance of the spinal cord. 2. Primarily in the meninges or nerve roots and (*a*) remain limited to these parts, or (*b*) invade the spinal cord.

Multiple sarcomatosis may occur as: (*a*) Disease of the nervous substance and meninges. (*b*) Multiple sarcomatosis of the membranes without sarcoma of the cord or brain, when it is (1) in the form of multiple small tumors, or (2) as diffuse sarcomatous infiltration of the membranes.

Schlesinger succeeded in finding in the literature (1898) 18 cases of primary sarcomatosis of the central nervous system with implication of the cord or its membranes, and to these he adds 2, making 20 cases in all. In 14 of these cases implication of the brain and cord, or of their membranes, occurred. In 9 of these 14 cases cerebellar tumor was found, and in 3 the medulla oblongata was affected. It appears, therefore, that when the brain or its membranes are implicated in sarcomatosis, usually the structures of the posterior cranial fossæ are affected, and that in about two-thirds of the cases a tumor of the cerebellum is found. The diffuse infiltration of the spinal membranes seems to be more extensive in the lower portion of the vertebral canal.

In a case of Bruns and in one of the Vienna Pathological Institute the sarcomatous process extended entirely across the cord. In other cases of sarcomatosis of the nervous system an isolated tumor has been found within the cord, separated by cord tissue from the sarcoma cells of the pia.

Disease of the walls of the bloodvessels, according to Schlesinger, has been observed in only a few cases of sarcomatosis. The vessels were normal in both Case I. and Case II.

Since the publication of Schlesinger's monograph a few more cases of sarcomatosis of the central nervous system have been reported.

The occurrence of a cerebellar tumor in so many of these cases is remarkable, and recently Henneberg and Koch[1] have mentioned that the angle made by the pons and the lobe of the cerebellum on either side is a common seat for tumors of the posterior fossæ. The symptoms seem to indicate that these tumors arise most frequently in the acusticus, but it is possible that the acusticus is the cranial nerve first compressed. These authors point out that the tumor is more frequently on the left side, in the proportion of 3 to 2. It was on the left side in both Case I. and Case II. They say that often neurofibromata cause no disturbance of function in the affected nerves; so that this absence of symptoms is as true of fibromata as of sarcomata.

One of the most recent papers on the so-called tumors of the acoustic nerve is by Fritz Hartmann.[2] He calls the location in which they commonly occur the recessus acusticocerebellaris, and he, as others have done, emphasizes that these tumors are loosely attached to the brain, and that their attachment may be easily ruptured. The tumors are usually in organic relation with the acusticus, more rarely with the facialis, and in some cases the acusticus entirely disappears within the tumor; consequently, deafness of central origin is one of the earliest symptoms, as it was in my Case II.

On account of the frequency of tumors in the cerebello-pontile angle, such as occurred in Case II., the important paper relative to operation on the posterior cranial fossa recently published by F. Krause may be referred to here.

He has shown by a successfully operated case that it is possible to divide the acusticus intracranially for the relief of severe tinnitus aurium. He entered the skull through the posterior fossa and divided the acusticus. The tinnitus was lessened, but the patient died from pneumonia five days after the operation.

In another case Krause[3] exposed at different operations both cerebellar hemispheres, and although a cerebellar tumor was not found, but internal hydrocephalus was, the condition of the patient was improved, and death did not occur until three years after the operation. The case showed that a cerebellar hemisphere might be incised to a depth of 2 or 3 cm. ($\frac{3}{4}$ to $1\frac{1}{8}$ inches) without causing serious symptoms.

Krause has also exposed both cerebellar hemispheres by one flap.

[1] Archiv f. Psychiatrie, vol. xxxvi., No. 1, p. 251.
[2] Zeitschrift f. Heilkunde (interne Medicin), 1902, vol. xxiii. p. 391.
[3] Beiträge zur klin. Chirurgie, vol. xxxvii., No. 3, p. 728.

The patient died six days after the operation, and was found to have internal hydrocephalus and deformity of the base of the skull. Although such an opening permitted a view of a large part of the cerebellum, it does not follow necessarily that it would have made possible the removal of a tumor situated in the cerebello-pontile angle without causing the death of the patient. A tumor so situated in a case of M. Allen Starr was removed, but the patient died a few days after the operation.

The primary sarcoma within the substance of the spinal cord in Case III. is a very uncommon form of tumor. It is primary, at least so far as the central nervous system is concerned.

Schlesinger[1] says that primary sarcoma of the cord without implication of the meninges, especially exclusive of the gliosarcoma and the myxogliosarcoma, is of very rare occurrence. He has been able to find only 13 cases. The tumor is usually sharply defined from the surrounding cord tissue, and sometimes encapsulated, which he thinks is important surgically, and yet I do not believe that an encapsulated tumor of the spinal cord can be removed with much benefit to the patient. In 8 cases the primary sarcoma was in the cervical region, in 1 in the midthoracic region, in 1 in the lower thoracic region, in 1 it extended throughout the entire thoracic and lumbar regions, in 1 it was in the lumbar region, and in 2 it extended throughout the length of the spinal cord. In 2 of the 13 cases cavities in the cord were found. In my case the sarcoma was in the thoracic region.

[1] Loc. cit.

A CASE OF SOLITARY TUBERCLE OF THE PONS. REMARKS ON THE PATHWAY FOR SENSATIONS OF TASTE FROM THE ANTERIOR PORTION OF THE TONGUE.[1]

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With Pathological Report and Remarks on Palsy of Associated Ocular Movements.

By William G. Spiller, M.D.,
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(From the Philadelphia Hospital and the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

Summary. A man, aged fifty-five years, with marked weakness of the right arm and leg; weakness of the muscles of the left side of the face, excepting the orbicularis palpebrarum; of the muscles of mastication on the left side, fibrillary tremors of these muscles; weakness of the left external rectus, with the loss of the power of associated movement of the eyes to the left, but with preservation of the power of convergence. Diminution of the power of appreciating touch, pain, heat, and cold on the right arm, leg, side of the trunk, neck, occipital region, and ear (Figs. 1, 3, and 4). On this side also were astereognosis and loss of the sense of position. Diminution of the power of recogniz-

[1] Read before the Philadelphia Neurological Society, October 27, 1903.

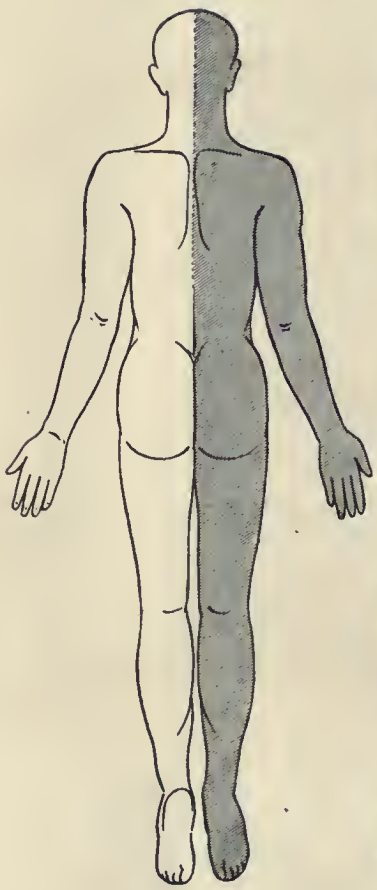

Fig. 1.

Fig. 2.

Fig. 4.

Fig. 3.

.... Nearly complete anæsthesia and analgesia and loss of temperature sense. The former more marked than the latter.

\\\\ Hypæsthesia and hypalgesia and impairment of temperature sense. These were more intense on the leg and back. There was also some difficulty in discriminting between heat and cold on the right side of the face.

ing touch, pain, and heat and cold on the left side of the face and head, as shown in Fig. 2. Slight loss of power of recognizing heat and cold on the right side of the face. Anæsthesia of the conjunctiva, mucous membrane of the nose, mouth, and tongue on the left side; also deafness in left ear and loss of sense of taste in the left anterior half of the tongue. Some ataxia of both legs, most marked in the right. A tuberculoma involving the left side of the pons found at the autopsy.

Gustav B., aged fifty-five years, by occupation a weaver; on July 11, 1902, was admitted to the nervous wards of the Philadelphia Hospital, complaining of "weakness of the right arm and leg and dizziness."

Family History. His father and mother had both died of "heart disease," and one of his sons had had tuberculous glands removed from the neck.

Previous History. He had had the diseases of childhood, malaria early in life, and typhoid fever at the age of sixteen years. Otherwise he had always been healthy. Tobacco and alcohol had been used moderately, and venereal disease was denied.

History of Present Illness. For the past two years he had suffered considerably from headache, but was not prevented from working. In December, 1901, he noticed numbness and tingling of the right arm and leg, the headache, principally on the left side, became constant and very severe. About this time also he began to see double. The right arm and leg gradually became weaker, and in January, 1902, he was obliged to cease work. He had never had any convulsive or spasmodic seizure, and never had been unconscious.

Examination. The patient was a tall, well-developed man, with a pallid complexion. Walking without support was impossible. When, with help, he did walk he at times dragged the right foot; at others he threw it forward with a jerk, resembling somewhat the gait of an ataxic. The left leg was also thrown forward in a jerky, ataxic manner, but not so markedly as the right. There was also difficulty in standing alone, which seemed partly to be due to weakness and partly to some degree of Romberg's symptom. When he smiled or made voluntary movements the angle of the mouth could not be drawn as well to the left

as to the right side, and the nasolabial fold was not so well marked upon the left side as upon the right. Weakness of the upper part of the face was not present.

Both eyes could be opened and closed normally. The pupils were unequal, the left being the smaller; both responded sluggishly to light and better in accommodation. Lateral nystagmus was present in both eyes when the patient looked either to the right or to the left. There was inability to look to the left with the left eye, also inability to make associated movement of both eyes to the left. Convergence was well performed, but not quite so well with the right eye as with the left. All other movements of both eyes could be well performed. Owing to circumstances beyond our control the fundus was not examined. His eyesight, however, was fair. On the left side contractions of either the masseter or temporal muscles could not be felt. The pterygoids on that side were also weak, as the point of the chin could be drawn better to the left than to the right. The tongue was protruded straight, could be moved well in all directions, and showed no evidences of atrophy. All movements of both arms could be performed; on the right side they were distinctly weaker than those of the left, which were of good strength, and those of the distal part were more affected than the proximal. All movements of both legs could also be performed, but were much weaker on the right than on the left side. The loss of power seemed to be greater in the leg than in the arm. There was no rigidity of the limbs; the muscles were flaccid, but not atrophied. Fibrillary tremors were noticed in the masseter and muscles about the angle of the mouth of the left side, especially when attempts were made to use them. Jaw-jerk was absent. The tendon jerks of the arms were present on both sides, but were much more active on the right. The cremaster reflex was not present on either side. The abdominal was absent on the right side and present on the left side. The knee-jerk was increased on the right, normal on the left side; a similar condition maintained for the Achilles jerk. Ankle clonus was absent. The plantar reflex was present on both sides; on the right a well-marked Babinski phenomenon was present; on the left it was absent, the toes being flexed.

His speech was thick and rather indistinct; there was no evidence of aphasia.

Sensory paralysis was present, as indicated in Figs. 1 to 4. The line of demarcation was not quite so sharp as indicated in the diagrams. In addition, the conjunctiva and mucous membrane of the mouth and nose on the left side were anæsthetic. As has been said, his vision seemed to be fair, and hemianopsia was not present. On the right side the tick of the watch was heard at four inches; on the left at contact. Tests were not made to determine if deafness was due to nerve or middle-ear trouble. On the right side there was inability to appreciate when passive movements of the fingers and toes were made and to recognize positions in which they were placed. Owing to the restricted movements of the arm and leg of this side it could not be determined if there was ataxia of these limbs. Astereognosis was present on the right side. No trophic symptoms were present, and, with the exception of cold feet, none of the vasomotor symptoms. The heart, lungs, kidneys, and other viscera were practically normal. A diagnosis of tumor involving the left side of the pons was made.

On August 18th it was noted that the patient complained of coldness of the feet, particularly on the right side. Dribbling of saliva from the left side of the mouth and some weakness of the muscles of the upper part of the face (occipitofrontalis and corrugator supercilii) on this side were noted, but the eyelids could still be tightly closed.

On August 22d he left the hospital at his own request.

After returning to his home it was ascertained that his headache increased in severity; he became more helpless, his eyesight failed, and in the latter part of September he committed suicide by hanging.

The brain was removed by Dr. W. G. Spiller.

The fact that the sense of taste was affected only on the anterior portion of the left side of the tongue would seem to bear witness to the view that taste sensations from this portion of the tongue reach the brain by way of the fifth nerve and not by the glossopharyngeal. If the latter idea is true it is hard to explain why

taste was not also lost in the posterior portion. It must also be borne in mind that none of the other functions of the ninth nerve were affected.

McConnell and Bundy[1] have reported a case of tumor of the pons in which there was loss of taste sense on one side of the tongue both anteriorly and posteriorly. As there was no paralysis of the muscles supplied by the ninth nerve they held that this nerve was not damaged and that their case was an argument in favor of the fifth nerve being a conductor of sensations of taste. Mills[2] in discussing this case explains this away by saying that "It was more likely that the gustatory pathway from the glossopharyngeal nuclei through the pons to the higher regions was implicated, the probable course of this tract being in the lateral or superior mesal fillet." While this, in the absence of autopsy, may serve as a hypothetical explanation of McConnell and Bundy's case, in which the entire one side of the tongue was involved, it does not explain why in the present case the anterior portion of the tongue was affected and not the posterior. In our case the fillet on the left side was completely destroyed, yet as there was hypæsthesia and not complete anæsthesia on the right side of the body, some sensory impressions must have reached the cortex from that side, presumably by means of the right fillet. Probably, also, in the same way sensations of taste from the posterior portion of the tongue reached the cortex in the way mentioned by Mills, and quoted above. If the nerve of taste for the anterior portion of the tongue is also the glossopharyngeal, it seems reasonable to suppose that sensations from this portion of the tongue should have reached the cortex by the same path, which, as a matter of fact, they did not. The fifth nerve, however, was found to be much degenerated; in fact, the sensory loss was more profound in the distribution of this nerve (Figs. 1 and 3) than anywhere else, and it seems reasonable to suppose that the involvement of the fibres of this nerve was responsible for the loss of taste in the anterior portion of the tongue.

The non-involvement of the occipitofrontalis and corrugator

[1] Annals of Ophthalmology and Otology, 1896, vol. v.
[2] Nervous Diseases, p. 702.

supercilii until some time after the muscles supplied by the lower facial were affected, and the escape of the orbicularis palpebrarum from any degree of paralysis, is of interest. It might be explained, as has been done recently by Jacoby,[1] that the upper facial is especially resistant to pathological influences, and in this connection it is a significant fact that the fibres of the facial were not directly involved, but were merely subjected to pressure. A better explanation, however, would seem to be a decussation of certain fibres of the facial after they have left their nucleus, these fibres being those which go to supply those muscles which habitually act together, as those supplied by the upper facial do. The fact that the left posterior longitudinal fasciculus was involved in our case certainly tends to disprove the belief, formerly much taught, that the nuclear origin of the fibres which supply the orbicularis palpebrarum is in the nucleus of the third nerve, and that by way of this tract they join the fibres of the seventh nerve after the latter have left the facial nucleus.

REMARKS BY DR. WILLIAM G. SPILLER.

We were permitted to retain only the pons for microscopic examination.

The left side of the pons was much larger than the right. In its upper part, just above the entrance of the fifth nerve, a tumor was found occupying the left half of the tegmentum and invading a little the pyramidal tract on the same side. The right half of the pons was not implicated. In the lower part of the pons the tumor implicated the left middle cerebellar peduncle and the pyramidal fibres on the left side, but did not invade the dorsal part of the tegmentum. The right side of the pons was not encroached upon by the tumor at any part. The nucleus of the sixth and probably that of the seventh nerve escaped, but the fibres of these nerves within the pons must have been compressed by the tumor. The left posterior longitudinal bundle was directly invaded in its upper part by the tumor. The tumor was

[1] Journal of Nervous and Mental Disease, October, 1903, p. 589.

much harder than the surrounding brain tissue, and microscopic examination showed it to be a tubercle.

The left third nerve, stained by the Marchi method or teased and stained by a 1 per cent. osmic acid solution, was normal.

The left fifth nerve, teased and stained by a 1 per cent. osmic acid solution, showed much degeneration of nerve fibres. The degeneration was not so evident in sections stained by acid fuchsin.

The left sixth nerve appeared to be slightly degenerated by the Marchi method, but not by acid fuchsin.

The left seventh nerve was degenerated, as shown by the Marchi stain. Some infiltration of the nerve by cells with small round nuclei was also found.

The left temporal muscle was slightly atrophied.

One symptom especially has been to me of great interest in this case. I refer to the paralysis of lateral conjugate movement of the eyeballs toward the left. The man was unable to look toward the left with either eye, but the inward movement of the right eyeball in convergence was good—*i. e.*, the contraction of the right internal rectus was preserved when it was not associated with contraction of the left external rectus. This phenomenon was observed by both Dr. Potts and me.

In the interesting case of double paralysis of the lateral conjugate movement of the eyes reported by Alexander Bruce,[1] with necropsy, a small, tuberculous tumor was found in the upper and posterior part of the pons. It occupied the position of the two abducens nuclei, the facial nerves, and the posterior longitudinal fasciculi, but did not reach the fillet.

Bruce believes that the view suggested by Foville, in 1858, that the abducens nuclei are the lower centres for the lateral conjugate deviation of the eyes, has been firmly established by a sufficient number of experimental and of combined clinical and pathological observations, but that the exact path by which each abducens nucleus controls the opposite internal rectus has not as yet been completely demonstrated. He says, further, that there is a fairly general consensus of opinion that the fibres which form the first part of this path, after leaving the abducens nucleus

[1] Review of Neurology and Psychiatry, May, 1903, p. 329.

ascend within the posterior longitudinal fasciculus, but that there is no such agreement as to whether they enter directly into the third nerve and pass by it to the internal rectus, or whether they terminate in the nucleus of the third nerve. If the latter view be correct, it is not determined whether these fibres end in the third nucleus of the same side, or whether they cross over to the nucleus of the opposite side; and if they do pass over to the other side, whether they do so at the level of the abducens, or of the oculomotor nucleus, or at some intermediate point.

Bruce cites Van Gehuchten and Held as maintaining that the posterior longitudinal fasciculus is composed entirely of descending fibres, derived, according to the former, from the "nucleus of the posterior longitudinal fasciculus," and, according to Held, from the anterior corpora quadrigemina. This opinion of Van Gehuchten and of Held, Bruce regards as erroneous, basing his statement on the study of his own case and the investigations of others, but he thinks it has not yet been demonstrated that any of the ascending fibres of the posterior longitudinal fasciculus arise in the sixth nucleus. Assuming that such fibres exist, Bruce believes that the cases of Wernicke and Long and his own demonstrate that these nerve fibres do not pass directly into the third nerve, and that the connection of the abducens nucleus with the opposite oculomotor nerve must be indirect. The point of decussation of these fibres to the oculomotor nucleus of the opposite side is uncertain, but Bruce thinks it is clear that the crossing takes place considerably above the level of the sixth nucleus. This opinion our case supports, as the sixth nuclei could not have been implicated in the tumor, judging from a study of the macroscopic sections.

Raymond and Cestan[1] have reported several cases of paralysis of conjugate movement of the eyeballs, with necropsy. In their most recently published case the paralysis was double, but more marked in the attempt to look to the right. The power of convergence was good. A large tubercle was found in the tegmentum of the pons. The nuclei of the third and sixth nerves were normal, and the trunks of the third and sixth nerves were not de-

[1] Revue Neurologique, January 30, 1901, p. 70, and June 30, 1903, p. 644.

generated. They believe that this case demonstrates that paralysis of lateral associated movement of the eyeballs may result from a lesion not implicating the nuclei of the third and sixth nerves, but from an internuclear lesion. As no degeneration was found in the third nerve, their case is further evidence that nerve fibres do not pass directly from the sixth nucleus into the third nerve. In 1901 they reported two very similar cases, with necropsy, in each of which a tubercle of the tegmentum of the pons was found.

A. v. Kornilow[1] has been able to obtain references to a number of cases of paralysis of associated ocular movement, and he concludes that paralysis of lateral conjugate movement is the result of a lesion in or near the nucleus of the third nerve. This seems to be a well-established opinion, and it is hardly necessary to refer to other reported cases.

In the case that we report the paralysis of lateral associated ocular movement was probably caused by the lesion above the nucleus of the left sixth nerve; but as the posterior longitudinal fasciculus was implicated in the tumor in the middle and upper part of the pons, the case was not a suitable one for determining where the decussation of nerve fibres in this fasciculus took place, although it is probable that the decussation did not occur near the sixth nucleus.

The symptoms in this case, as shown by Dr. Potts, indicated that a lesion of the left side of the pons existed, and the presence of the paralysis of lateral conjugate movement of the eyeballs toward the left permitted us to make an almost certain diagnosis of a growth implicating the left half of the tegmentum of the pons, and removed all doubt as to the existence of a tumor upon the surface of the pons. The diagnosis of the location was exactly correct. As tubercle has been found in a number of similar cases, the tumor was believed to be a tubercle before the necropsy was made.

I think it well to emphasize the importance of the paralysis of lateral associated movement of the eyeballs in clinical diagnosis. In such a case as the one described in this paper there might be

[1] Deutsche Zeitschrift f. Nervenheilkunde, Bd. xxiii., Nos. 5 and 6, p. 417.

doubt whether the symptoms were caused by a tumor on the pons or by a tumor within the pons. As we have been trying for some time to remove by operation a tumor upon the pons or in the cerebellopontile angle, it is evident that if we could find a clinical sign indicating that the tumor were intrapontile we should consider operation inadvisable when this sign was present. Such a sign, I believe, we have in the paralysis of lateral conjugate movement of the eyeballs, and I should be unwilling to recommend operation for removal of a pontile tumor if this form of ocular paralysis were present; its absence, however, is no proof that the pons is not invaded, but merely that the posterior longitudinal fasciculus is intact.

THE CHANGES IN PERIPHERAL NERVES PRODUCED BY TOXIC SUBSTANCES APPLIED TO THE SKIN. A MEDICO-LEGAL STUDY.

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The subject-matter of this paper is the result of a series of investigations carried out on the experimental animals to determine, if possible, whether toxic substances could penetrate the integument in sufficient quantities to produce degenerative changes in the peripheral nerves without destroying the convexity of the superficial tissues. The subject was brought to my attention by a suit for damages instituted by a man suffering from a paralyzed condition of both arms, which, he asserted, was due to the action of chemicals on the exposed tissues.

The case is as follows: S. L., married, aged fifty-eight years, Hebrew, was admitted to the clinic of Dr. Spiller, August 10, 1901, suffering from a paralytic condition of both arms. He had been in perfect health until March, 1901. At that time he was employed for two days in a patent process for etching plates. He was supposed to wash off these plates in a bath of some acid material, and was thus compelled to have his hands and forearms in this material. He used his bare hands, unaware of any danger in the procedure, although the older employés were apparently aware of the deleterious action of the bath, as they wore rubber gloves. The right hand was kept in the fluid longer than the

left, the latter being used only to wash off the surplus fluid from the surface of the plate.

A few days after being thus employed his hands and arms became swollen, very painful, and, according to the testimony of

Showing paralytic condition of both arms. The weakness of the left arm is shown by the tremor (blurring in the photograph).

Dr. Lapin, who treated him at that time, were "swollen, hard, and white; there was no sensation in any part of the hands or fingers. The condition of the hands was terrible."

His condition on examination, August 10, 1901, was as follows: He has complete musculospinal paralysis on the right

side; he is unable to extend the right hand. Flexion of the right hand is very feeble. Resistance to passive movement at the right elbow and shoulder is good. Sensation to all forms of stimuli is good in both arm and hand. He is sensitive to pressure over the forearm, and to slight pressure over the hand. The nerve trunks are not especially tender to pressure.

Left arm: Flexion is good. Extension is much better than the right, but impaired. Tenderness over forearm near wrist and on the hand. Fibrillary tremors are very marked in the left arm.

The reaction to the galvanic current in both arms is very prompt, and to a much smaller current than is required in the normal muscle. There is very slight if any "slow reaction" to closure of the current.

Two months later the response to the galvanic current by the extensor muscles of the right hand (fingers) was very imperfect, scarcely any contraction being obtained by the strongest currents. There is, however, strong contractions in the adductor of the thumb. June 7, 1901: The grip of the right hand is feeble. There is still extensor paralysis of the right hand, possibly some atrophy about the shoulder; the supinator longus contracts normally. Power of the upper arm is good.

Examination. In the left arm the extension of the hand is fair, but not up to normal; the same is true of flexion The upper arm movements are good. There is distinct and marked atrophy of the thenar eminence, and also of the left foramen on its palmar aspect. The supinator longus is distinctly palsied on this side. There is no reaction in the extensor of the right hand to the galvanic current.

The final examination, noted January 11, 1902, revealed practically the same condition as described above. The atrophy in the left hand, forearm, and shoulder is more marked ; the extension of wrist is good, but the grip very feeble.

The knee-jerks were somewhat exaggerated. Plantar flexion on the left side, and a questionable result on the right side.

To resume: A male, aged fifty-eight years, after immersion of the arms in a secret preparation (in all probability containing hydrofluoric acid), develops an acutely swollen, anæsthetic con-

dition of the hands, followed by paralysis and atrophy, progressive over a course of two years.

The testimony presented in favor of the plaintiff was in favor of a diagnosis of peripheral neuritis, with degeneration of the nerves. On the part of the defendant it was held by the experts that the case was one of obscure lead intoxication, on account of the freedom from involvement of the supinator longus, although the left was distinctly involved, and also that the condition was due to a central cause, as degeneration of the anterior horns of the spinal cord, or, possibly, the roots, and antedated the acute local condition. A verdict in favor of the plaintiff was rendered.

With a view of determining the effect of poisons applied locally to the extremities, hydrofluoric acid, carbolic acid, lead acetate, and formaldehyde in varying solutions were used in the following experiments :

Series 1. Hydrofluoric acid, 50 per cent. (Merck), was diluted to a 25 per cent., 12 per cent., 10 per cent., and 5 per cent. solution, and applied to the forelegs of the rabbits. The hair was cut to within an eighth of an inch of the skin, and the solution applied on cotton, covered with gauze, and protected by a rubber dam to prevent evaporation.

The results were not altogether satisfactory, on account of the tendency of the acid to produce skin lesions. The stronger solutions acted as would any highly corrosive poison, diluted, and three of the rabbits were excluded on account of abrasions produced by rubbing against the cage. In rabbits killed four, six, and eight days, and one after two weeks, typical degeneration of the peripheral nerves was present by the osmic acid method applied to the fresh, unhardened nerves. The integument was very soft and boggy, slipped easily on pressure, and the subcutaneous tissues were caseated and more or less necrotic. Not only the nerves in this necrotic material, but also the deeper nerves, showed this degenerative change. In the animals that were permitted to live for only one week this change, while not as marked, was still present and distinct. Necrotic changes were very slight, and only affected the subcutaneous fat.

The experiments carried out by the application of carbolic acid solutions gave the following changes: A 50 per cent. solution of

carbolic acid resulted in extensive changes, as manifested by hardening of the integument. While there was no ulcerative lesion of the skin tissues, *i. e.*, interfering with their continuity, and, although the degenerative changes in the nerves were marked, these lesions could not be said strictly to represent the penetrating action of toxic substances. And yet, according to the above clinical history, the acute changes produced in the skin of the hands of the workman must have been similar to the changes here described. With weaker solutions of the acid (10, 15, or 20 per cent.) slight changes were observed in the nerves, but not of sufficient intensity as to be regarded as conclusive.

In the third series of experiments acetate of lead was employed, but gave entirely negative results.

In the fourth series formaldehyde (the commercial 40 per cent. solution diluted with equal quantities of water, and also as a 40 per cent. solution undiluted) was employed. The same precautions to prevent evaporation and excoriation as were employed in the hydrofluoric acid experiments were carried out. The results obtained were most satisfactory. After six days, during which time the formalin was twice changed, the tissues showed the following changes: The skin was slightly reddened but otherwise perfectly normal. There was no blistering, softening, or ulceration. The limb was, however, somewhat swollen, although there was no pitting or other signs of serous œdema. The dissection of the tissues revealed a normal thickening of integument, with a peculiar gelatinous infiltration in the subcutaneous tissues. The muscles appeared normal, somewhat paler than usual. Not only the superficial but also the nerves deeper in the muscular tissue were swollen and bright red in color. The change in the appearance of these nerves was limited to the area of application of formalin externally, and did not extend above the upper margin of this application.

The microscopic examination of all the nerves, both superficial and deep, revealed a very extensive degeneration. The bloodvessels were markedly distended, and free blood was present in the interstitial tissues.

In the experiments with the weaker solution at the end of one week the same changes, only less marked, were present in the

subcutaneous tissues. The degenerative changes were also present in the nerves. The skin appeared perfectly normal. There was not even any reddening. This may be accounted for by the fact that the weakened formalin had been applied three days before the tissues were examined. And it is quite possible that a congested condition of the capillaries of the skin could easily have disappeared within this time.

Extensive microscopic studies of the tissues other than the nerves was not made. This will be left for a further contribution.

A study of the clinical manifestations of the results of the changes described yielded very deficient data on account of the necessary paraphernalia attached to the extremities of the rabbits.

A résumé of the experimental work may be stated as follows:

1. An intense and extensive degeneration, the result of an acute inflammatory process, was produced by the local application of formalin to the skin without destroying the continuity of or seriously interfering with the structure of the superficial tissues.

2. The action of hydrofluoric acid when locally applied does not differ essentially from other corrosive poisons. In weak solutions it may cause degenerative changes in the deep nerves, with minor necrotic lesions in the subcutaneous tissues without destroying the continuity of the integument.

3. The effect of carbolic acid in strong solutions is confined mainly to the superficial tissues, and it is only when these tissues are extensively involved (dry and hard, although there may be no blistering or ulceration) that the subcutaneous and deeper nerves become degenerated.

4. Acetate of lead produces irritative changes in the skin, somewhat similar but less intense than that produced by carbolic acid without involvement of the subcutaneous tissues or nerves.

Only two animals were used in this experiment, and the results are, therefore, inconclusive.

Clinical observations on human beings would seem to show that lead may penetrate the tissues and cause local changes. The above experiments were controlled by the examination of nerves from a distal extremity to that experimented upon to exclude the possibility of the constitutional action of the irritant through the respiratory system.

In all cases where paralysis is produced by poison, which may also have a constitutional effect, the differentiation between the location of such poison and the selective action upon particular nerves should be borne in mind. There is no evidence presented in the case under discussion to show that the inhalation of vapor of hydrofluoric acid had any selective action upon the nerves of the upper extremity. So that as far as the medical testimony was concerned it remained merely as a matter of differential diagnosis between the diseases above noted. It would, therefore, seem both from the conclusions in this case and from the results of the experimental work herein described that it is quite possible for certain poisons to penetrate the superficial tissues and cause inflammatory and degenerative changes in the deeper trunks without destructive lesions of the overlying tissues. The possibility of a constitutional effect of a poison locally applied and the difficulty of differentiating this condition from local manifestations is very well shown in a case of arsenical paralysis under the care of Dr. Riesman. In this case, which will be later reported in full by Dr. Riesman, Dr. Spiller was of the opinion that the paralysis was due to the local action of the arsenic. Both Dr. Schamberg and Dr. Riesman, on account of development of intestinal symptoms and paralysis in the distal extremities during the course of the disease, considered it a case of constitutional intoxication. I am indebted to Drs. Mills and Spiller for permission to use the case above described.[1]

[1] A discussion of the above case from the medico-legal standpoint, by Dr. J. Hendrie Lloyd, will be found in the last volume of the Twentieth Century Practice.

FAT CRYSTALS IN THE SPINAL CORD.

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Fat crystals in areas of secondary degeneration in the spinal cord of a case of compression of the spinal cord from tumor formation is so rare as to merit its being placed on record. The only other reference to the occurrence of such crystals in any part of the central nervous system is a short note by Eichhorst that they may be found in the neighborhood of acute plaques of sclerosis in the central nervous system in cases of multiple sclerosis. I have not been able to find them in the cases of multiple sclerosis I have examined, nor have I been able to find any reference to them in the reports of the pathological examination of cases of multiple sclerosis by other observers. The case from which the material used in this paper was obtained was admitted to the service of Dr. Charles W. Burr in the Philadelphia Hospital, to whom I am indebted for the material and the notes of the case.

J. C., a sailor, aged thirty-six years, was admitted to the hospital September 7, 1896. His previous history was negative, with the exception of a syphilitic infection in 1885, with typical secondary eruption, alopecia, etc. He was operated on for stricture in the surgical wards, and was afterward transferred to the nervous wards with spasticity and loss of power in the lower extremities, developing gradually after his admission to the hospital. There was intense girdle pains about the waist, almost constant jerkings of the legs,

incontinence or retention of urine, bed-sores on the buttocks, and loss of sensation from the waist down. The legs became very spastic and "locked," the pulmonary symptoms (tuberculosis) became very distressing, and the patient died August 20, 1897. Autopsy revealed pulmonary tuberculosis, general miliary tuberculosis, aortic stenoses, vesical calculus, spinal column normal.

The spinal cord on gross examination presented a very marked thickening of the dura from the ninth to the twelfth dorsal vertebræ. This thickening of the dura appeared to be internal to the dura itself, and was independent of any external irritation, the spinal canal being perfectly normal throughout. At the lower part of the thickening of the dura it became adherent to the spinal cord.

On microscopic examination the condition proved to be one of an internal pachymeningitis, fibrous in character, and infiltrated with typical tubercular areas. At the point of attachment to the spinal cord an infiltrating mass had almost completely destroyed the cord at this point. The infiltration here was likewise tubercular in nature, and had broken down at two points into a creamy liquid which appeared to be separated from the rest of the mass by a distinct capsule. Tubercle bacilli were not found in the membrane of tumor formation, but this is not surprising on account of the use of Müller's fluid as a preserving agent.

Above and below the destruction of cord substance typical secondary degeneration was observed, and differed from the usual secondary degeneration in that it presented a peculiar yellow color to the naked eye. The entire area of secondary degeneration (the posterior and direct cerebellar tracts above the lesion and the crossed pyramidal tracts below) was crowded with delicate acicular crystals arranged in clusters. These crystalline forms can plainly be seen in unstained glycerin mounts of the scraped degenerated areas. They stand out with especial prominence, and dominate the microscopic picture in specimens stained by the Marchi method (Fig. 1). They take a deep black stain by the osmic acid, but have a tendency to lose this after a few weeks of exposure to the air. These crystals are soluble in ether and alcohol; at least particles of tissue hardened in alcohol or placed in ether do not contain these crystals when stained by osmic acid or other stains.

Fat crystals occur elsewhere in the body, and are not infrequently

met with in the secretions (sputum, urine, feces, vomit, vaginal secretions, etc.), and are, according to von Jaksch, combinations of potassium and magnesium salts with the higher fatty acids. They may, however, be pure fat crystals, and these can be detected by their freer solubility in alcohol and ether.

Besides the fat crystals there was also free fat globules along the course of the degenerating nerves, around the vessels, in compound granule cells, and at times within the perivascular spaces.

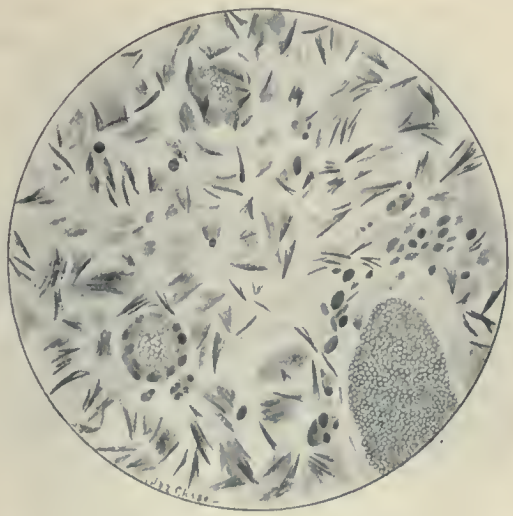

FIG. 1.—Section through the posterior column in the cervical enlargement of the cord. The fat crystals are seen throughout the section. The darker areas represent compressed granule cells about the bloodvessels.

At the area of compression what was left of the spinal cord revealed the same changes as are detailed above. The vessels at this point contained thrombi, and in some cases the thrombi were channelled by the blood current, and gave very striking appearances under the microscope (Fig. 2).

If the osmic acid stain were a selective stain for fat there would be little question as to the nature of the changes taking place when the nerve is sectioned. If a fresh nerve be placed first in distilled water or alcohol, and then in osmic acid, the myelin is stained black. If this same nerve is hardened in a solution of the chrome salts it loses its faculty for taking the osmic acid stain. A chemical com-

bination has taken place between the substance (lecithin) of the normal nerve which took the acid stain and the chrome salts. If a nerve be degenerated from any cause, after one or two days the myelin begins to clump in small balls along the course of the nerve within the sheath of Henle. After several days (even three to nine) these myelin balls take the osmic acid stain as a deep black. It has been the opinion of most pathologists that the substance staining

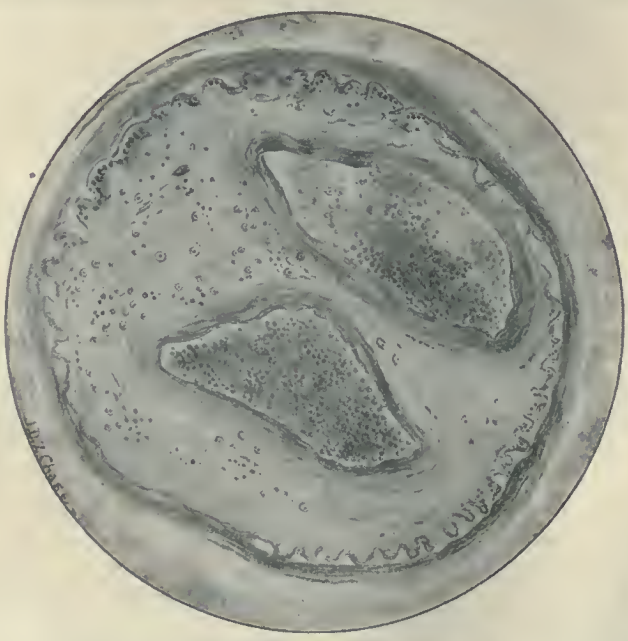

FIG. 2.—From section through thickened area of dura. There is a large thrombus in the artery. The wavy line shows the inner area of the vessel wall. The two areas containing blood corpuscles are where channelling of the thrombus has occurred.

black with osmic acid in degenerated nerves was fat. Exception has been taken to this statement, and different complex chemical compounds were blamed for it. The evidence presented in this paper goes far to prove that the substance is really fat, and that it has the property of either undergoing crystalline change by itself or possibly in combination with some of the potassium or magnesium salts of the body.

THE FORMATION OF HEMOLYMPH GLANDS FROM ADIPOSE TISSUE IN MAN.[1]

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(*From the William Pepper Clinical Laboratory, Phoebe A. Hearst Foundation,*)
(*Read before the Univ. of Pennsylvania, Hospital Medical Society, November, 1902.*)

Recent contributions to our knowledge of pathological conditions of lymphatic structures has led to a more careful examination and study of hemolymph glands. Our knowledge of these structures and their formation may be said to be the result, indirectly, of the early experimental work on the regeneration of splenic tissue. The investigations of Zambecari (1680), Gerlach, Eberhardt, and Phillipeaux upon this subject led to the work of Tizzoni and Filetti (1880), who still thought that the structures they described were newly formed splenic tissue. They noted the red color and increase in size of the retroperitoneal and thoracic glands and attributed these changes to a post-operative lymphadenitis. The fatty marrow of the long bones was transformed into red marrow, and in two of the splenectomized dogs spleen-like nodules were found in the great omentum. They believed this new splenic tissue to be formed directly from the adipose tissue by a process of absorption of the fat, conversion of the fat cells into a reticulum, followed by leucocytic infiltration and active proliferation of the smaller vessels into Malphigian corpuscles. A continued proliferation of the reticulum and cell elements led to the formation of a pulp-like structure containing red blood cells and about which a connective tissue capsule was formed.

Warthin in a recent paper states that Tizzoni's description of the formation of hemolymph glands from adipose tissue is confirmed in every detail by his (Warthin's) experimental work on sheep and goats. (Jour. Medical Research, May, 1902.) All stages of the process were seen, and he observes

[1] Received for publication March 7, 1903.

that if the blood sinuses persist the structure of a hemolymph nodule is presented; if the formation of the lymphoid tissue is so great as to reduce the sinuses to capillaries the node assumes the structure of a lymphatic gland.

In the two cases about to be described, the experimental work of the above quoted receives full confirmation in the human subject.

The first and most important of these cases has already been described as a case of adiposis dolorosa with Dr. F. X. Dercum.

Briefly, the clinical history is that of a male, aet. thirty-nine who had suffered for fifteen years from adiposis dolorosa, *i.e.*, a painful swelling of the subcutaneous fat tissue, with a tendency to induration and fatty tumor formation. He also suffered from epilepsy. Death occurred February, 1902, from erysipelas.

The autopsy revealed an adeno-carcinoma of the pituitary body, acute parenchymatous nephritis, and interstitial neuritis of the nerve filaments of the subcutaneous fat.

The subcutaneous fat on the trunk was four inches in thickness. For the greater part it was of normal color and consistence. Several large bright red nodes the size of an orange were present in the incision from the neck to the pubis. These nodules were surrounded by a firm capsule of connective tissue. This capsule, as was also its contents, was rich in nerve filaments and blood vessels. When this nodule was cut across it was found to consist of thousands of small ovoid fat bodies connected with each other by a delicate reticulum of connective tissue, and these joined to form thick gelatinous looking bands which fused with the capsule.

In the immediate neighborhood of these large nodules several small dark red bodies the size of a pea were found free in the fat. The microscopic examination of these smaller bodies revealed the typical structure of hemolymph glands. The gland tissue was surrounded by a capsule of fibrous tissue. At one end of the gland considerable reticular fat tissue was present. The rest of the gland was composed

of a dense fine meshed reticulum, the spaces of which were filled with small mononuclear cells. A comparatively large blood sinus filled with erythrocytes encircled the gland immediately beneath the capsule. Smaller sinuses extended in different directions through the reticulum. A striking characteristic of all the sections was the large quantities of granular blood pigment. Only a small portion of this pigment reacted to the test for hemosiderin. At the fat pole of the gland, the prolifieration of the capillary vessels was marked. Small nodes of small round cells were frequent along these new formed capillaries and especially at places where branching had taken place or were about to take place.

The hemolymph tissue was present in large amounts in the large fat nodules. The arrangement of the tissue was somewhat different from that described in the encapsulated gland. The lymphoid tissue here takes the type of an infiltrating character, mainly affecting the capsule of the fat nodule and the larger trabeculæ extending into the fatty ovoid bodies. The structure of the tissue here is the same as that above described, but is much more extensive. The several steps in the formation of the hemolymph tissue from the fat tissue can be carefully studied on account of the loose and open nature of the tissue and the extent of the involvement of the fat nodule.

The first step in the process is probably a chemical change in the fat preliminary to its resorption. Dr. Edsall found a distinct change in the acid values of this fat as compared to the free fat outside of the nodules. This process of resorption of the fat is also assisted by large round vesicular cells, analogous to the compound granule cells of the central nervous system. These cells filled with fat granules formed a striking picture in some of the sections from the second case to be described. The fat becomes lighter in color, the outlines of the cells become irregular in shape, and at the junction of the cells several nuclei are seen in a stellate mass of protoplasm. At the same time the capillaries of the capsule and trabeculæ have extended into this area and

large numbers of the proliferating vessels can be seen in a small space. Here and there accumulations of small round nucleated cells are noted around these vessels. As the process advances these accumulations of cells become larger and closer together; the capillary channels widen out; the loose fat reticulum assumes a closer type due to the proliferation of its own cells and the new formed blood channels; the spaces of the reticulum are now filled with the small nucleated type of cell, and the new tissue may be said to be completed as far as a functioning tissue is considered. In all such tissue described as functioning, large quantities of blood pigment in different stages of degeneration can be seen. Like the isolated hemolymph gland, only a small portion of this pigment gives the free iron reaction. While most of the cells followed the type of the lymphocyte, large plasma cells were occasionally seen and a type of cell which gave some of the staining reactions of nucleated red blood corpuscles. Dr. C. Y. White, who carried some of the sections through the differential blood stains, was inclined to regard them as the small mononuclear type of leucocyte, although he was not at all positive in this opinion.

The large vesicular cells filled with fat granules and pigment were more frequent in the infiltrating tissues than in the isolated fully formed hemolymph glands. The cell body was composed of a faint reticulum with an amorphous yellow substance between the fibres of this reticulum.

The second case which presented newly formed hemolymph tissue was also a case of adiposis dolorosa. She was thirty-six years of age, weighed over three hundred pounds, and presented clinically the symptoms of brain tumor. The pathological diagnosis was as follows: Glioma of brain involving the pituitary body, basal nuclei, filling up the fourth ventricle and associated with a dorso-cervical syringomyelia; chronic thyroiditis with calcification and acute localized inflammation of the thyroid gland; cirrhosis of the ovaries; interstitial nephritis in the fat nodules. The changes in the fat tissue were almost identical to those above

described. The large granular cells, with indistinct nuclei and filled with pigment granules, were present in large numbers in these tumors. This was especially true of those areas between the fully formed hemolymph tissue and the pale fat tissue. The same transition from normal fat into the hemolymph tissue could be easily followed.

The examination of the spleen in both the above cases gave the same result. The spleen was at least twice the size of the normal organ, the capsule was thickened and a dirty white in color, and was of a firm consistence. The microscopic examination revealed a marked cirrhosis. The trabecular tissue was thickened, and extensive masses of free red blood cells were without the vessel walls. The hemorrhagic extravasation, if it can be so called in a tissue so vascular as that under consideration, was so extensive in some of the sections as to completely overshadow the cellular network.

It is beyond the scope of this paper to consider the relation between the visceral lesions in these two cases, and the transformation of the fat tissue into hemolymph tissue. Whether it is secondary to the splenic lesions, or whether the latter is a part of a general disturbance of the lymphoid tissues dependent on a disturbance of the pituitary body, thyroid, testicle, ovaries, etc., cannot be definitely determined. There is much, however, in the findings here recorded to favor the latter view. Recent work upon the influence of the secretion of the pituitary body, thyroid, and testicle on tissue oxidation and metabolism and the well-known influence of the functional activity of the generative organs upon fat deposition also point to the same conclusion.

THE CLINICAL MANIFESTATIONS OF HYDROPHOBIA.*

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The usual text-book descriptions of hydrophobia give a clinical course of the disease divided into three stages. It is, however, difficult in practice to separate the clinical manifestations by any fixed rule.

The incubation period is usually about six weeks. In both the cases reported in this paper it was about that length. The onset of the disease is marked by several days of malaise, with slight fever, anxiety and, in a large number of cases, irritation at the seat of the infecting wound. The temperature at this stage is usually elevated one or two degrees, although it may remain at normal. This stage of irritation soon passes over to the convulsive stage. In some cases there is no convulsion or spasm, and the premonitory stage is followed by the paralytic symptoms. The symptoms of the second stage begin with more or less difficulty in the act of swallowing. Anything that excites the swallowing reflex mechanism causes an overflow spasm to the glottis, the muscles of the neck and, sometimes to the jaw muscles. As the disease progresses the local spasm is replaced by a general convulsion. The mental state is one of increas-

* Read at the Fifty-third Annual Meeting of the American Medical Association, in the Section on Pathology and Physiology, and approved for publication by the Executive Committee: Drs. A. Stengel, Winfield S. Hall and Frank B. Wynn.

ing anxiety, both as to the outcome and as to other conditions, until a maniacal condition supervenes, or much more frequently the mental state of a hallucinatory delirium.

The patient may die in the convulsive stage from exhaustion and heart failure or a paralytic group of symptoms supervenes. This so-called paralytic stage may occur in cases where there is very little spasm of the muscles. In these cases it is spoken of as dumb or paralytic rabies. The paralysis is usually one beginning in the lower extremities and later affecting the other extremities. In the delirium there may be passing of the urine and stools in the bed. Some authors include among the paralytic group of symptoms the evidence of cardiac and respiratory failure.

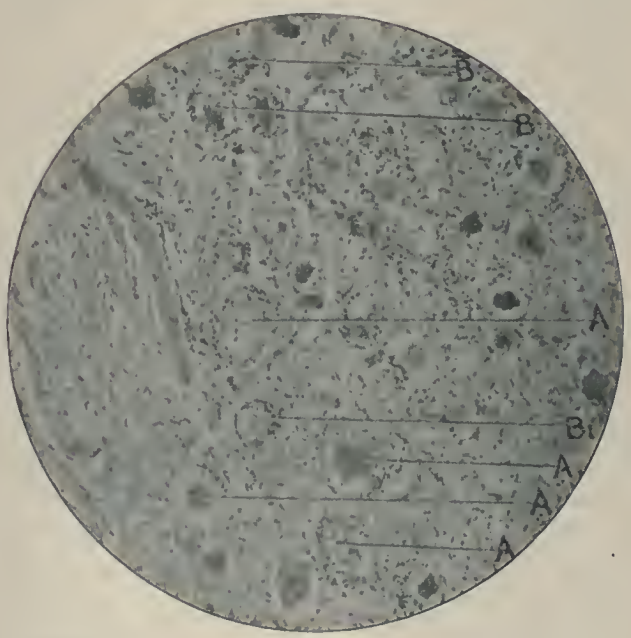
ILLUSTRATIVE CASES.

The following two cases give a picture of the disease as it is met in private and hospital practice.

CASE 1.—W. M., male, aged 5, had been perfectly well up to May 13, 1901. At that time he was bitten on the cheek by a stray dog. The wound healed and he appeared to be in good health until Saturday, June 15. During that night he cried during his sleep. The following day he was up and about, but did not appear to be well. He ate very little during the day. Citrate of potassium was administered by the mother; free purgation resulted. Sunday evening he did not appear to be able to drink, as he asked for water and then told them to take it away after attempting to drink it. Monday he was admitted to St. Joseph's Hospital, with a temperature of 101. He was very much frightened, according to notes of the case, evidently the irritative stage of the disease. He was tested as to his ability to drink. and every time he attempted to swallow there resulted a spasm of the glottis and the muscles of the neck and face. He refused to repeat the first attempt. After reassuring him, he again attempted to swallow a mouthful of water, but it came out through the nose by the spasm of the neck, throat and face muscles as in the first attempt. Later the nurse succeeded in getting him to swallow a portion of an apple. In attempting to wash him, he became nervous when his face was washed, but was still very nervous from the tests at swallowing. At 7:30 p. m. he succeded, with much difficulty and after much persuading, in drinking 6 ounces of weak coffee. Marked

spasms occurred with each mouthful of the fluid swallowed. Shortly after this general tonic convulsions ensued, the contractions of the legs being most marked. At 11 p. m. the pulse became very rapid, the patient became very restless, and in a short time delirium ensued. He imagined he saw his father under a sheet, with holes in it for eyes. The expression, which from the beginning was very anxious, now assumed a terrified aspect. At 11:15 he was pulseless, did not react to stimuli, and died at 12 m.

Autopsy.—The examination of the viscera showed nothing



Section of intervertebral ganglia of the cow (Case No. 1), showing the lesions of rabies. A. Marked vacuolation and degeneration of ganglion cells. B. Advanced capsular proliferation filling up the ganglion cell capsule with the proliferated capsule cells.

abnormal. The pons and medulla were markedly congested, and in some areas had the appearance as if some small hemorrhages were present.

The microscopic examination of the pons, medulla and cerebral crura showed a diffuse advanced degeneration of the ganglion cells by the Nissl method. Some of the nerve cells had entirely disappeared and in their place accummulations of deeply staining nuclei could be seen. These nuclei

of Babes were more frequent in the medulla than elsewhere. Around the blood vessels of the pons and medulla large accumulations of these same nuclei were present. Capillary hemorrhages were found in the upper portion of the medulla, or under the floor of the fourth ventricle.

The intervertebral ganglia showed marked changes. The cells were in a state of advanced diffuse chromatolysis. The capsules of all the cells showed more or less cell proliferation. Some of the capsules were entirely filled with the proliferated capsular cells. The peripheral nerves showed no degeneration.

This case is of special interest on account of its fulminating character. The patient was only sick three days. In reality only one day intervened between the development of the irritative group of symptoms and the boy's death. There were no paralytic symptoms noted. The intensity of the bulbar lesions could easily account for the rapid course of the disease. The perivascular lesions were in their extent and character more like those observed in the lower animals than those of the human being, where all the lesions, as a rule, are less in degree.

We take this opportunity of putting the following case on record:

CASE 2.—The patient was a girl, 8 years of age, who came under the care of Dr. Frederick Krauss on Aug. 12, 1900, by whom diagnosis of rabies was made, and to whom we are indebted for the history. Six weeks before, the child had been bitten on the right ear by a stray dog which she was petting because it seemed to be sick. The dog was put out of the house and lost sight of. The wound was cauterized with nitrate of silver by a druggist, and healed without suppuration. On August 11 the child complained of lassitude, but was restless, and on account of these symptoms her mother gave her a dose of castor oil. The next morning inability to swallow was observed, being attributed to "sore throat," and soon after her mother noticed that, on being touched with a wet towel or exposed to slight draughts of air, she was frightened and startled. Dr. Krauss was called in on this day. The temperature was 100, pulse 120. On giving her a glass of water, she would look at it with dilated pupils for a moment, then suddenly grasp it and quickly attempt to swallow a mouthful. Every trial was followed by severe tonic convulsive contraction of the pharyngeal constrictors and the more external muscles of the neck, lasting about fifteen seconds. Repeated attempts were made, always with the same result. In reply to a question, she said that she was

not afraid of the water, but it hurt her throat very much when she swallowed it. She shrank from the slightest current of air. Large doses of bromid of potassium and chloral with morphin were given, but without effect, and the symptoms grew more marked. She passed a sleepless night. On the morning of the thirteenth her temperature was 101.5, pulse rapid. Later in the day she developed a state of intense excitement. She would lie quiet and apparently conscious for a time, then without warning suddenly spring up to her mother, crouch down with short cries of fear, looking at the wall with an expression of great dread, and seemingly unconscious of her surroundings. After about two minutes she would wake as from a dream. Repeated hypodermic injections of morphin had no effect, and she was sent to St. Christopher's Hospital. After a short remission the convulsive seizures became so frequent that almost constant inhalation of chloroform became necessary. When this was left off, she would utter short and loud cries of fear, which might well have been mistaken for the bark of a dog, and attempt to spring out of the bed. Death took place on the morning of the fourteenth, at 6 o'clock.

Autopsy.—The examination revealed congestion of the brain and meninges and minute hemorrhages, while the severity of the convulsions was proven by rupture of the pleura. The train of symptoms left no doubt in the mind of the attending physician that the case was one of hydrophobia, and the diagnosis has been abundantly confirmed by the inoculation of rabbits, as well as by microscopic examination of the bulb and plexiform ganglia of these animals. The inoculations were carried through four generations, the rabbits all dying with typical symptoms of rabies, with the exception of one of the first generation, which died thirty-six hours after inoculation from septicemia. Besides the microscopic examination mentioned, full series of cultures were made, with the object of detecting any accidental infection during inoculation or after. These cultures remained sterile in every instance, so that we are able to exclude with certainty any known bacterial disease.

The clinical and microscopic evidences so far presented in connection with hydrophobia (human being) gives us as much right to regard it as a distinct clinical entity with a distinctive pathology as we have to regard syphilis or tuberculosis as distinct diseases.

EXAMINATION OF ANIMALS WITH RABIES.

We have had submitted to us for examination 105 animals suspected or known to be rabid, including 28 cases reported to the Pathological Society of Philadel-

phia Jan. 10, 1901. Of these 75 were dogs, 11 cows, 2 horses, 2 cats and 15 rabbits (experimental).

One of the cows and all of the rabbits were experimentally infected. In 83 cases the clinical symptoms and history were positive of rabies. Many of the dogs were sent to the Veterinary Hospital of the University of Pennsylvania and were under observation from one to three days before death. Forty cases were controlled by the inoculation of rabbits, a few being carried through four generations. In 60 both the medulla and the intervertebral ganglia were examined. In 36 cases only the ganglia were examined, in 7 cases only the medulla. In 2 cases neither could be examined.

In only two cases have we failed to find the lesion of Babes in the medulla when the changes in the ganglia were marked, but in several the bulbar lesion was slight. The vascular tubercle of Babes is much more often found than the one having the nerve cells as a starting point. While the vascular tubercle is frequently found accompanied by very slight changes in or about the nerve cells, we have not seen a case in which the reverse was true.

Of the 75 dogs examined 22 were killed and 53 died. In 44 the type of the disease was furious, in 9 paralytic and in 22 mixed or not reported. We have examined those animals which were killed with especial interest, since in practice we are asked to give a rapid diagnosis in a large number of such cases. The studies of Cuillee and Vallee in France have shown that in dogs experimentally inoculated, then killed at various times after symptoms of rabies have appeared, the changes in the ganglia may not be found, hence the advice is given to allow the disease to run its course, ending in death. Of the 22 dogs which were killed, in 7 we could give no opinion. In 3 of the 7 both the medulla and ganglia were examined. The importance of allowing the animal to die is manifest from this, since in at least one-third of the cases where the animal is killed prematurely no

diagnosis can be made except by inoculation with the attendant delay.

The value of the microscopic method is shown in the fact that in 87 of our 105 cases we were able to give a prompt diagnosis by examination of the ganglia alone, and in 94 by the ganglia or medulla.

In view of the fact that changes in the ganglia somewhat similar to those found in rabies have been described in other processes—endothelioma (Speller), diphtheria (Crocq), chronic alcoholism (Burr and McCarthy), forage poisoning (McCarthy and Ravenel)—the clinical history should always be taken into consideration in making the diagnosis. We know of no acute disease in dogs presenting the proliferation of the capsular cells and the tubercle of Babes, and would consider them as diagnostic of rabies in conjunction with a history of an acute clinical course of the disease.

Reprinted from The Journal of the American Medical Association, March 21, 1903

A PATHOLOGY FOR FORAGE POISONING, OR THE SO-CALLED EPIZOÖTIC CEREBRO-SPINAL MENINGITIS OF HORSES.[1]

(A PRELIMINARY REPORT.)

D. J. McCarthy, M.D., and Mazyck P. Ravenel, M.D.

(*From the William Pepper Clinical Laboratory (Phœbe A. Hearst Foundation), and the Laboratory of the State Live Stock Sanitary Board of Pennsylvania.*)

The disease known as infectious or epizoötic cerebro-spinal meningitis of horses is but little understood. In all outbreaks there seems to be a common cause, and there is little or no evidence that the disease is ever transmitted from one horse to another. In some cases the origin can clearly be traced to the food, and Dr. Leonard Pearson has produced the disease by feeding ensilage taken from a stable in which animals had been attacked. The influence of food is well illustrated by an outbreak which occurred in a large stable in Philadelphia. It began in December, 1901, twenty-seven horses being affected, of which ten died. A fresh supply of food was obtained, and piled on top of the old. No new cases occurred under the use of this feed, but in May, 1902, the old food was again reached, and soon after fifty-nine horses developed the disease, twenty-four of which died, and six were destroyed. From his experiments and observations Dr. Pearson has proposed the name "forage poisoning," a name which is more in accordance with the facts as we know them at present. The term "cerebro-spinal meningitis" is not justified by the clinical history nor by post-mortem findings.

While forage is no doubt responsible for many of the outbreaks, the actual pathogenic agent has not yet been discovered, though a toxic mold or fungus is supposed to be the cause. All attempts to find a specific micro-organism in the animals affected have failed completely, nor has microscopic examination of the tissues revealed any specific lesion. Gross examination usually shows hyperemia of the brain and cord, and their meninges, with increase of fluid in

[1] Received for publication July 29, 1903.

the subarachnoid spaces and ventricles. This fluid is clear, and we have been unable to discover any micro-organism in it by cultural methods.

Symptoms.[1] — The symptoms are referable to the central nervous system. In mild attacks there is loss of control over the limbs and tail, loss of appetite, and difficulty in swallowing. The inability to swallow is often a marked symptom in more severe cases, and the name "putrid sore throat" has been applied to the disease. There is stupor, apathy, extreme muscular weakness, or actual paralysis. A common symptom is contraction of the muscles of the neck, back, and loins, with more or less opisthotonos. Paroxysms of delirium occur, during which the animal will push against the wall, or show the disorderly movements due to meningeal irritation. Coma and paralysis come on, and death occurs in from five to forty-eight hours. In the most acute cases the animal falls and dies in convulsions.

It seems probable that several diseases which are characterized by similar clinical symptoms have been considered as one and the same by observers.

MacCallum and Buckley have found in the brains of horses dying of this disease areas of softening "in the frontal region on each side, anterior to the motor region of the cortex." This softening was practically confined to the white matter immediately under the cortex, the rest of the brain showing no abnormality. In these areas there was "complete destruction of the brain substance in which the anatomical elements are disintegrated, and largely replaced by a colloid-like material." The neighboring blood vessels were acutely inflamed, with exudation of leucocytes, and passage of the red corpuscles into the peri-vascular lymph sheath and adjacent tissues. In a second outbreak they failed to find the softened areas in the brain, but the condition of the blood vessels was such as to make them believe that they had the earlier stages of the same process.

[1] Moore. Pathology of the infectious diseases of animals.

They have given the name "Acute Epizoötic Leucoencephalitis." (Bulletin 80 of the Maryland Agricultural Experiment Station.)

The disease has engaged our attention at the laboratory of the State Live Stock Sanitary Board for several years, and examination by cultural methods have been made whenever possible, but always without result. We were led to the present investigation more than a year ago while making a study of the value of the rapid diagnosis of rabies after the method of Van Gehuchten and Nélis, in the course of which several horses and two calves, which had died of forage poisoning, were used as controls.

Pathological report. — With the exception of the lesions in the upper gastro-intestinal tract where the infection probably occurs, the only others discovered were confined to the central nervous system, and may be grouped for purposes of description as follows:

1. Lesions of the intervertebral and Gasserian ganglia. 2. Lesions in the cerebral and cerebellar cortex. 3. Lesions in the choroid plexuses of the lateral cerebral ventricles. 4. Lesions of the peripheral nerves supplying the larynx.

Fifteen animals have been studied. In the first six of these the intervertebral ganglia were not examined. In all the nine cases in which these structures have been studied the following changes have been found: In the normal ganglion the ganglion cells are enclosed in a capsule fitting closely around the cell. This capsule is made up of a single layer of endothelial cells. The supporting structure of the ganglion is composed of a loose areola of connective tissue, through which run the nerve fibers on their way to the spinal cord. All of these structures are affected.

The ganglion cells were the seat of extensive chromatolysis. The degenerative changes vary from a simple diffuse chromatolysis — a fusing together and loss of outline of the

fine chromatin points in the cell protoplasm — to complete destruction of the cell body and nucleus (Figs. 1 and 2). At times cells were found apparently normal, except for the accumulation of large amounts of a yellow pigment, staining black with osmic acid. In other cells, besides the diffuse chromatolysis above referred to, the nucleus was found displaced to the periphery of the cell. As the degenerative changes advanced, the cell protoplasm took the stain very strongly and appeared a deep blue by the Nissl method. Marked vacuolation of the cell protoplasm was present in two cases (Fig. 3). In four cases some of the ganglion cells were completely disintegrated, filaments of protoplasm remaining among the small mononuclear cells surrounding the capsule.

Capsular and pericapsular changes. — In all nine cases in which the intervertebral ganglia were examined a peri-capsular, small round cell accumulation was present (Fig. 2). In some of the degenerating ganglion cells a few nuclei were seen within the capsule in the degenerating cell protoplasm. The accumulation of nuclei around the cell capsule did not always assume a concentric shape, but was often eccentric extending irregularly into the stroma. The cells are all of the small type, the nuclei and protoplasm being about the size of a red blood corpuscle. There is no evidence that these cells are due to a proliferation of the original layer of capsular cells. Polynuclear cells, or cells with an irregular nucleus, were not present in any of the specimens examined. It is probable, inasmuch as these cells stand in no relation to the vessels of the ganglia, that they are the result of a proliferation of the stroma cells of the ganglion.

Cortical lesions. — The cortex of the cerebrum and cerebellum was markedly congested both to gross and microscopic examination. The meninges were normal. The ganglion cells were normal to the Nissl and other cell stains. Numerous capillary hemorrhages were scattered throughout the entire cortex of the cerebrum and cerebellum. There were also hemorrhages in the subcortical tissues. The basal

ganglia, pons, and medulla were perfectly normal. The spinal cord, outside of some congestion of the gray matter, was normal. The meninges showed no trace of an inflammatory process.

Lesions of the choroid plexus. — The choroid plexus in three of the cases was changed from a filmy membrane to a large triangular tumor-like mass. This mass was of a yellowish-red color, of firm consistency, and measured two and a half centimeters in transverse section. On microscopic examination the increase in size was found to be the result of a proliferation of the elastic tissue surrounding the vessels. By the Van Giesen stain the entire section was found to consist of whorls of delicate fibers starting from the neighborhood of the vessel walls and extending to the margin of the plexus (Fig. 4). These fibers were not nucleated, although numerous nuclei of the supporting tissue of the gland were present between the whorls. At the suggestion of Dr. Flexner, the Weigert elastic stain was used and the character of the tissue determined. The ependymal cells covering the villi were normal.

The peripheral nerves. — An examination of the nerves supplying the larynx and the neck by the fresh osmic acid method showed a slight but distinct degeneration. This was present in the nerve up to the ganglion, but was not present in the posterior roots, or the root of the fifth nerve. These lesions in the myelin corresponded to the presence of a marked degree of swelling of the axis cylinder in the substance of the ganglion. Hemorrhagic extravasation into the sheath of the pneumo-gastric nerve was present in one case.

Summary.—Hemorrhagic inflammation of the upper respiratory organs; degeneration of the peripheral nerves supplying these areas; toxic irritation of the intervertebral ganglion as manifested by intense degeneration of the ganglion cells, pericapsular round cell infiltration, and swelling up of the axis cylinders; widespread capillary hemorrhagic extravasation

of the cortical and sub-cortical tissues, tumor formation due to proliferation of elastic tissue of the choroid plexus of the lateral ventricles.

The ganglionar lesions above described closely resemble those described by Van Gehuchten and Nélis in rabies. In rabies, however, there is an active proliferation of the capsular cells with a marked tendency to extension within the capsule, while, as has already been pointed out, the tendency in this disease is to a pericapsular accumulation of cells. In advanced cases of forage poisoning the ganglion cells may entirely disappear and an accumulation of small round cells remain. Under these circumstances the picture cannot be differentiated from rabies by an examination of the ganglion alone. The perivascular round cell accumulation in the pons and medulla, which is rather constant in rabies, is never present in forage poisoning. There is no degeneration of the peripheral nerves in rabies. The clinical course of the two diseases is entirely different, and there should be no difficulty in separating the two conditions by the pathological lesions.

Professor Van Gehuchten, of Louvain, to whom we submitted the specimens from our first case (a calf), confirmed our opinion that there was a distinctive difference between the ganglionar changes in forage poisoning and in rabies.

Concerning the specimen sent to him he writes: "It cannot be denied that there is a sensible proliferation of the cells of the endothelial capsule, but this proliferation does not, however, appear to me to be as intense as in cases of rabies; so much so, that I would not make the diagnosis of rabies from the examination of the sections alone. I do not think that this animal had rabies. Rabies excluded, there remains a certain amount of proliferation, the cause of which escapes me; but in my opinion the degree of proliferation cannot be compared with that which occurs in rabies."

CONCLUSIONS.

1. The so-called epidemic cerebro-spinal meningitis of horses is not a true meningitis, and presents neither the gross nor microscopic lesions of true meningitis.

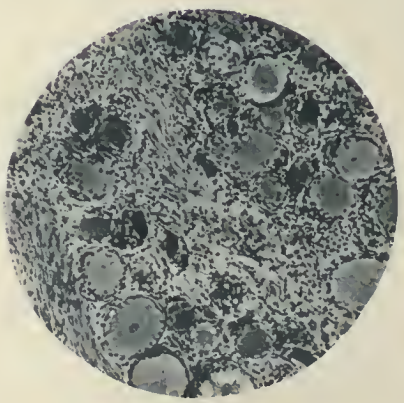


FIG. 1.

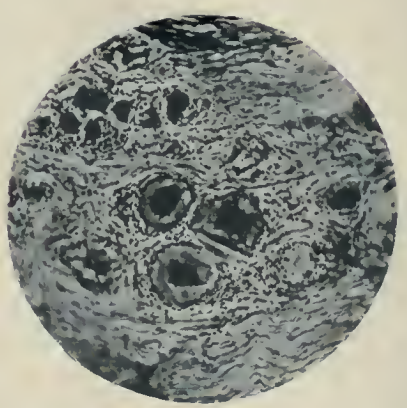


FIG. 2.

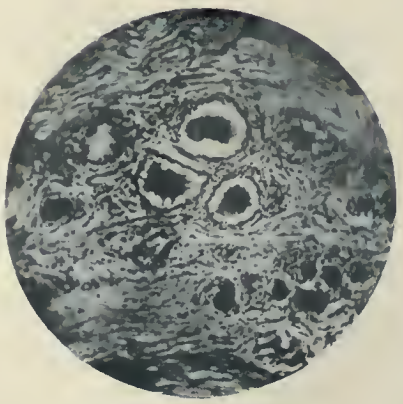


FIG. 3.

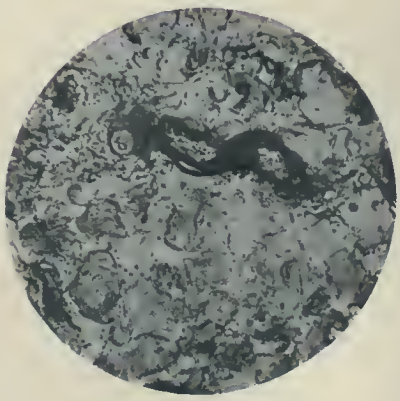


FIG. 4.

2. The evidence goes to show that all epidemics are caused by some poisonous substance contained in the forage. This is proven conclusively in the epidemic mentioned above, and in the experiments of Dr. Pearson.

3. The lesions in the intervertebral ganglia so closely resemble those described by Van Gehuchten and Nélis in rabies, as to offer the presumption that the pathological process in the two diseases is somewhat similar.

4. The differential diagnosis between forage poisoning and rabies depends upon (*a*) the absence from the medulla and pons in forage poisoning of the perivascular and peri-cellular lesions (Rabic tubercles of Babes); (*b*) in forage poisoning there is predominance of peri-capsular rather than intra-capsular round cell infiltration of the ganglion cells. (*c*) Lesions of the larynx and laryngeal nerves. The clinical history is always conclusive.

5. Forage poisoning is a much better and more comprehensive term than "cerebro-spinal meningitis," or than "leucoencephalitis," as proposed by MacCallum and Buckley.

EXPLANATION OF PLATE II.

FIG. 1. — Intervertebral gland of horse. Forage poisoning. x 210.

FIG. 2. — Gasserian ganglion. Cellular degeneration with peri-capsular round-cell infiltration. Forage poisoning. x 210.

FIG. 3. — Gasserian ganglion of horse. Forage poisoning. x 210.

FIG. 4. — Choroid plexus, occurring in two cases of forage poisoning. Van Giesen staining. x 210.

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REPORT OF A CASE OF TRANSVERSE MYELITIS IN A NEWBORN INFANT.

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and

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of Philadelphia.

(From the William Pepper Clinical Laboratory, Phoebe A. Hearst Foundation.)

William J. D., aged 3 months. Born February 7, 1902. The father is in good health, denies any history of syphilis, but at times uses alcohol to excess. The mother is in good health, but of a nervous temperament. The parents have had four children. The mother knows nothing of the first labor, as she was under ether when the child was born. It did not survive. The second child was born in what is said to have been a normal labor and is living and well. The third child was a breech presentation and lived but two weeks. The fourth child, the patient, was delivered feet first, and was only made to breathe after an hour's work by the physician in attendance. The mother says that the accoucheur had to make considerable traction upon the baby to bring it into the world. The condition of the child was not noticed by the mother until four weeks after its birth, as she herself was very ill. Her attention was first attracted by the baby's inability to move its lower limbs from the position in which they were put, and its seeming failure to notice when it was touched on this part of its body. I first saw the child when it was eight weeks old, and examination at this time revealed a fairly well nourished infant. As it lay upon its back it would move its head from side to side and throw the arms about, but the rest of the body remained as an inert mass. There were no respiratory movements of the thorax or abdomen, but at regular intervals there was a sinking in of the sides of the chest walls at about the region of the diaphragm. The abdomen was flaccid, flabby and sagged down on either side. There were no contractions of the abdominal muscles. The lower limbs were perfectly flaccid and there was absolutely no voluntary movement. The bowels were only moved by enema. The mother stated that the child passed its urine naturally. The bladder could easily be palpated. It was then about the size of a small peach. Later it could be outlined through the abdominal walls, its upper border reaching to within ½ inch of the umbilicus. Pressure of the hand caused an intermittent flow of urine; plainly an incontinence of retention. The knee jerks were absent, as were also the plantar reflex and the skin reflexes of the abdomen. There was no contraction of the abdominal muscles when the child struggled. Sensation of pin point was lost on the anterior aspect of the body as high up as the xiphoid cartilage. The only way to confirm this was by looking for expressions of pain on the child's face, or by noting some recognition of feeling. Up to the xiphoid there was certainly no sensation, but above this the baby would cry or move its head and arms. On the posterior aspect sensation was lost up to the second thoracic vertebra. The arm reflexes and the palmar reflexes

FIG. I. Shows flaccid Palsy of the legs; flaccid abdomen and scoliosis.

*Presented to the Philadelphia Pediatric Society, May 13, 1902.

were present. The pupils reacted freely to light. There was no evidence of cranial nerve palsy. There was no deformity of the spine, which may be considered straight, but for a tendency to a right-sided curvature, which was probably due to loss of power in the supporting muscles of the spine. The feet were warm; there was no atrophy of the legs or thighs, and the mother thought the legs were sharing in the general growth of the child.

The diagnosis lies between a transverse lesion between the second and third dorsal segments, and a stretching of the spinal roots.

This latter, however, can almost be excluded on account of the anesthesia up to the cervical segments. The possibility of such a condition must, however, be considered in explaining the flaccid type of paralysis.

The other features of the case pointed to a spinal cord lesion, completely transverse in character and high up in the dorsal cord.

While it is perfectly true that most cases of complete transverse lesions of the cord are associated with a spastic type of paralysis and increased reflexes, certain investigations, recently reported by William Alden Turner, of London, are important in the consideration of just such a condition as we have here. In a paper recently read before the New York Neurological Society, on an experimental study of the reflexes in total transverse lesions of the spinal cord, Dr. Turner* said: "The temporary abolition of the knee jerks was more commonly noted after high than low transections, but in no instance was complete absence observed. The influence of shock in laboratory transection was small, its effect being limited to distal parts. Many years ago, when working with Dr. Ferrier on experimental lesions of the cerebellum, he had noticed, in a case transected at the eighth dorsal segment, that the knee jerks were brisk and increasing immediately afterward, and that they lasted for months. He describes some recent experiments on rhesus monkeys, showing that the effect on the knee jerks was influenced by the level at which the section was made. If the section had been made at or below the fourth dorsal segment, the knee jerks were present as soon as the monkeys came out from the anesthetic. A patulous anus was rare. The limbs were in a state of flaccid palsy, rigidity and contracture occurring in time. In transection at the second or third dorsal segment some difficulty was experienced temporarily in eliciting the knee jerks, and they seemed to be quickly exhausted.

Transection at the first dorsal and the eighth cervical segments resulted in the knee jerks being temporarily obtained with difficulty, entirely failing after 15 or 30 minutes.

Various theories had been advanced to explain flaccid paralysis with loss of the knee jerks in man. The most commonly accepted explanation was the Bastian-Jackson theory, which ascribes the loss of reflexes to cutting off cerebral influences.

In no case in which the cord had been completely severed had any return of the reflexes been observed."

Dr. Turner reported a case in which dislocation of the fifth cervical vertebra resulted in complete flaccid paralysis and loss of the knee jerks. Post mortem examination showed that there was not complete transection, a thin bridge, about one mm. thick, persisting. This band was shown by microscopical examination to consist of degenerated white fibers.

G. L. Walton, of Boston, said that the present tendency in favor of cerebral reflex centers was largely due to Bastian's observations, but the reflex conditions found in disease were too varied to be explained by the acceptance either of cerebral or spinal centers. If the knee jerks were temporarily lost, it was because the cerebral reflex center was rendered ineffective by injury or functional separation from the lumbar region.

One point of divergence was in the newly born, in whom the knee jerks were faint or wanting and the cutaneous reflexes active. The other point of divergence of the knee jerks from the plantar reflex appeared in complete severance of the cord.

In order to elicit the knee jerks a certain degree of muscular tonicity is essential. Permanent loss of the knee jerks in cases of severance of the cord might be due to inability of the spinal centers for tonicity. In the prematurely born the spinal centers might not be able to act until the cerebral centers controlled the tonicity.

It will be seen that the symptoms in this case were fully consistent with a transverse lesion of the cord, which might be a hemorrhage, or even a temporary dislocation of the vertebra. The X-rays, however, showed no special bone lesion.

It would appear at first that the flaccid palsy was a result of a lumbar lesion or a traumatic lesion of the roots or leg nerves.

The absence of pain and of wasting were against a peripheral lesion. The character of the bladder and bowel paralysis was also that of a high lesion and pointed against a local lesion in the lumbar enlargements.

If the lesions were those of a lumbar nature, traction at birth might have been the cause.

The exact cause of the high lesion I am not in a position to say. I am inclined to believe, however, that the feet presentation had something to do with the condition.

Autopsy.—The spinal cord only was examined. Upon opening the spinal canal it was seen that the entire dorsal cord was flat. After the cord was removed, the collapse or flattening was found to extend from the second dorsal to the eleventh dorsal segment. (See Fig. II). The cervical and upper dorsal cord appeared to be

*Reported in Philadelphia Medical Journal, May 3, 1902.

normal. The lumbar enlargement was likewise normal in size, consistence and appearance. The pia mater over the collapsed area was thickened, and the superficial spinal vessels were distended and tortuous, which is shown very well in the photograph. (See Fig. III). The microscopical examination of the cord was very unsatisfactory on account of an accident to the cord during the photographing process. The cord became dry, hence it was only with difficulty that sections could be made and stained sufficiently well to obtain good results. The nerve-cell groupings, as well as the relation of the gray to the white matter, appeared normal. The ganglion cells stained black by the Weigert hematoxylin method; this, as has been shown in previous contributions, is due to the associated iron pigmentation or transformed blood pigmentation of the nerve-cells. The area of collapse of the cord was wider than a normal dorsal cord of three months. The

FIG. II. Shows a normal appearance of the cervical and lumber cord, with the flat area of the dorsal cord.

pia was intact, and some of the medullary tissue showed black by the Weigert hematoxylin. Masses of granular material stained a deep red with the eosin stain, and this was evidently extravasated blood, although it was impossible in the sections to recognize the individual red corpuscles.

It appeared at first that we had to do here with a defective development of the spinal cord, but a more complete examination leaves little doubt that the condition was the result of some assault to the nervous system after complete cord formation. The caliber of the cord, as evidenced by the pial tube in this area, suggests that the spinal cord had filled this tube in the normal process of development and as a result of a hemorrhagic process, softening of the cord and resorption of degenerated cord substance, there was a loss of contour of the cord, giving us the flattened cord so well shown in the photograph. It is quite possible, even probable, that this hemorrhagic condition and flattening of the cord occurred at birth, but it could not with any degree of positiveness be declared that the condition had not developed in the latter months of pregnancy, after the cord had attained its approximate size.

FIG. III. Anterior view of the spinal cord showing the size of the collapsed cord with the distended and tortuous anterior spinal artery.

A CONTRIBUTION TO THE CHEMICAL PATHOLOGY OF ACROMEGALY.

By David L. Edsall, M.D., and Caspar W. Miller, M.D.

(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

The chemical abnormalities that occur in acromegaly have been but little studied, though the tissue changes are so striking that one would expect that interesting and, perhaps, important results might readily be obtained. The observations that we are now recording were made chiefly on one case that met two important conditions of such a study, *i. e.*, the disease was exhibiting striking progress, and was uncomplicated; and, in particular, the man had no signs of diabetes. The results obtained, together with some control observations on a second case of acromegaly that was practically at a standstill, demonstrate some striking abnormalities of metabolism that offer certain interesting suggestions concerning the pathology of the condition, and also concerning some further lines of study of this disease.

Except for observations relating to the glycosuria that so often occurs in acromegaly, there are but two important records of the chemical disturbances in this disease with which we are familiar. Schiff (*Wien. klin. Woch.*, March 25, 1897) made observations on nitrogen metabolism and phosphorus excretion in a case of uncomplicated acromegaly, and in one of acromegaly with symptoms of myxœdema, and v. Moraczewski (*Zeitsch. f. klin. Med.*, Band xliii., Hefte 3 and 4) investigated the nitrogen, phosphorus, and calcium metabolism, as well as some other chemical features, in one case.

Schiff's observations, however, had less direct relation to the study of acromegaly itself than to the determination of the effects

of several of the organic extracts in persons with various diseases; and he took no account of calcium-metabolism or of phosphorus intake, matters that, because of the striking changes in the bones, are of much more direct interest in this disease than is nitrogen metabolism alone. The value of v. Moraczewski's results is made somewhat doubtful by the fact that his patient was regularly passing large amounts of sugar (100 grammes or more per day). The conditions of metabolism are, of course, wholly abnormal in diabetes; and, consequently, it is impossible, when acromegaly is combined with evidences of diabetes, to attribute any abnormalities found to the acromegaly alone. This is true of metabolic processes in general, and would influence the conditions relating to all three of the substances to which v. Moraczewski's work especially referred, *i. e.*, nitrogen, phosphorus, and calcium. But it is of special interest in connection with calcium; for, on the one hand, the condition of calcium metabolism is of particular importance in relation to disorders of the bones; and, on the other, calcium excretion usually exhibits striking abnormalities in marked diabetes.

It is of interest to note, however, that Schiff in his case of uncomplicated acromegaly found a nitrogen retention of about 2 grammes a day, while v. Moraczewski found a retention of as much as 7.6 grammes of nitrogen and of about 1.5 grammes P_2O_5 and 0.8 gramme CaO, a day; and in the latter case an abnormally large percentage of the calcium was, contrary to normal conditions, excreted through the kidneys instead of through the bowel. The latter point appears to us to be the most important that v. Moraczewski's figures demonstrated; but, as previously indicated, it is this point especially that might readily be explained by the diabetes.

Our own work was done on the two patients whose cases have, from the clinical standpoint, been reported in detail by Dr. W. G. Shallcross (*Philadelphia Medical Journal*, April 20, 1901). Both have for years been inmates of the Pennsylvania Training School for Feeble-minded Children. Their condition has not changed in any important regard since Dr. Shallcross' report, except for marked growth in the first case, as will be shown by the anthropometric tables that follow. These have been condensed from the records of the Training School, these records being regularly prepared under the supervision of Dr. Miller. The measurements were made by

the system of the American Association for the Advancement of Physical Education; the strength tests by the collegiate system.

The first patient, S. B., with whom most of our work was done, was temporarily transferred to the University Hospital, where, in order to insure accuracy in the experiment, he was put under the care of a particularly intelligent nurse, who had been especially detailed to watch him and give him the proper food and drink. He was put on a special diet for a metabolism experiment on December 13th; and this diet was continued until December 16th before work was begun. His food allowance was made very large because he had a very large appetite and had eaten extremely freely before admission; the caloric value of the food was made to correspond, as closely as we could arrange it, with his previous allowance. The daily ration was as follows: Bread, 550 grammes; butter, 100 grammes; beefsteak, 150 grammes; ham, 150 grammes; eggs, 4 daily; rice, 27 grammes (dry rice); milk, 1000 c.c. The food was weighed each day by one of us. The man took what he wished of this, which was usually nearly the whole amount; and any portions remaining, as well as the eggshells, were weighed by us and deducted from the amounts given. The figures for the food that we shall give are the net amounts for the individual days. He was allowed only distilled water, which he took freely, as he had a moderate polydipsia.

The amounts of P_2O_5, CaO, and nitrogen in the various foods were determined as follows: Four samples of bread were taken for P_2O_5 determinations; and five samples for both CaO and nitrogen determinations. The average of the P_2O_5 and nitrogen percentages in these samples, and the percentage of CaO in the total five samples, the latter being estimated *en masse*, were taken to represent the percentages of these substances in all the bread used.

One boiled ham sufficed for the whole experiment. This was freed, as completely as possible, from fat; and fifteen portions, five each for P_2O_5, CaO, and N determinations, were taken from different parts of the ham by means of a corkborer. As with the bread, the average percentage of P_2O_5 and nitrogen in the different portions, and the percentage of CaO in the whole of the five portions, were taken to represent the percentages of these substances in all the ham used.

	Case I.—S. B.			Case II.—P. K.		
	Oct. 15, 1900.	April 29, 1903.	Change, %.	Sept. 17, 1900.	May 2, 1903.	Change, %.
Age (years and tenths)	18.4	20.9	13.58	20.2	22.9	13.36
Weight	100.4	110.0	9.56	76.0	77.3	1.71
Height	193.4	195.0	0.82	181.5	182.0	0.27
" sitting	98.5	99.7	1.21	93.2	93.5	0.32
Girth, head	57.0	59.0	3.50	56.0	57.0	1.78
" chest	105.0	111.0	5.71	94.0	94.5	0.53
" ninth rib	108.3	108.5	0.18	96.5	98.0	1.55
" waist	94.0	99.0	5.31	79.0	81.0	2.53
" hips	107.5	114.0	6.04	91.0	91.5	0.54
" right thigh	56.5	60.0	6.19	57.0	57.0	0.00
" " knee	44.0	46.5	5.68	37.0	38.0	2.70
" " calf	38.0	39.5	3.94	39.5	40.0	1.26
" " ankle	24.0	25.0	4.16	23.5	23.5	0.00
" " upper arm	33.2	33.5	0.90	33.0	34.0	3.03
" " elbow	29.5	30.2	3.50	27.0	28.0	3.70
" " wrist	20.0	21.5	7.50	18.7	18.5	— 1.07
Depth, chest	27.5	29.5	7.27	20.5	20.5	0.00
" abdomen	25.0	26.0	4.00	19.0	20.0	5.26
Breadth, head	15.6	16.0	2.56	14.5	14.5	0.00
" shoulders	41.7	45.8	9.83	42.6	42.7	0.23
" waist	31.5	34.0	7.93	26.4	26.5	0.37
" hips	39.3	41.7	6.10	31.5	31.5	0.00
Length, right shoulder-elbow	43.2	46.6	7.87	35.0	35.5	1.42
" " elbow-tip	56.3	58.0	3.19	50.9	51.0	0.19
" " foot	30.2	31.0	2.64	28.2	28.2	0.00
Stretch, arms	212.0	215.4	1.60	190.0	190.0	0.00
Strength, lungs	130.0	120.0	— 7.69	135.0	100.0	—25.92
" back	140.0	85.0	—39.28	150.0	160.0	6.66
" legs	150.0	95.0	—36.66	190.0	180.0	— 5.26
" sum, both forearms	71.0	69.0	— 2.81	33.0	75.0	— 9.63

As to the steak, immediately after the nurse had broiled the day's portion, it was freed from fat; 150 grammes were weighed and set aside for the patient, and five other small portions were at once weighed as accurately as possible—two portions for P_2O_5, two for nitrogen, and one for CaO. The averages of the determinations of P_2O_5 and nitrogen represent the percentages that we give for these substances on the individual days. The CaO was determined by incinerating all the portions of steak taken for this purpose and determining the total CaO, and reckoning the percentage for the whole duration of the experiment from this.

The milk was analyzed daily, two determinations of both P_2O_5 and nitrogen being made each day, and the average being used as the figure for that day; while for the CaO 50 c.c. of each day's milk was placed in an evaporating dish; the total 350 c.c. was evaporated, dried in the oven, and ignited in portions. The total amount yielded was 0.647 gramme CaO. Reckoned for fresh milk, this represented 0.184 per cent.; and this figure was used for the milk of each day.

The figures for the butter, eggs, and rice were derived from the analysis of others. The composition of hens' eggs is very constant in a large series, as is that of rice; and the figures for butter and rice are so small that reckoning the percentages could not make any recognizable error in the result. All the figures for the rice were obtained from Blyth; the nitrogen of the butter from Koenig; the P_2O_5 and CaO of the butter from Richmond's *Dairy Chemistry* and all the figures for the eggs from Koenig. Our separate analyses and the figures for daily amounts of the individual foods, the percentages of P_2O_5, CaO, and nitrogen that they contained, and the total amounts of these substances in the daily food, follow:

The separate analyses of the bread were:

P_2O_5. I. = 0.1464 per ct., II. = 0.1442 per ct., III. = 0.1672 per ct., IV. = 0.1540 per ct.; average = 0.1529 per ct.

CaO. Five samples weighing 46,020 grm. were incinerated in portions. The total amount yielded 0.019 CaO=0.041 per ct.

Nitrogen. I. = 1.362 per ct., II. = 1.140 per ct., III. = 1.480 per ct., IV. = 1.129 per ct., V. = 1.218 per ct.; average = 1.265 per ct.

The separate analyses of the ham were:

P_2O_5. I. = 0.5672 per ct., II. = 0.5558 per ct., III. = 0.4335 per ct., IV. = 0.6161 per ct., V. = 0.5217 per ct.; average = 0.5388 per ct.

CaO. Five samples of ham weighing 11,794 grm. were incinerated in portions. The total amount yielded was 0.0046 = 0.039 per ct.

Nitrogen. I. = 4.228 per ct., II. = 3.372 per ct., III. = 3.698 per ct., IV. = 3.604 per ct., V. = 3.865 per ct.; average = 3.753 per ct.

The amounts of the different foods, the percentages and total amounts daily of P_2O_5, CaO, and nitrogen were as follows:

BREAD: Dec. 17th. Total amount 533 grm. P_2O_5, 0.1529 per ct. = 0.8149 grm.; CaO, 0.041 per ct. = 0.2185 grm.; nitrogen, 1.265 per ct. = 6.7424 grm.

Dec. 18th. 550 grm. P_2O_5, 0.1529 per ct. = 0.8409 grm.; CaO, 0.0410 per ct. = 0.2255 grm.; nitrogen, 1.2650 per ct. = 6.9575 grm.

Dec. 19th. 490 grm. P_2O_5, 0.1529 per ct. = 0.7482 grm.; CaO, 0.041 per ct. = 0.2009 grm.; nitrogen, 1.265 per ct. = 6.1985 grm.

Dec. 20th. 509 grm. P_2O_5, 0.1529 per ct. = 0.7782 grm.; CaO, 0.041 per ct. = 0.2086 grm.; nitrogen, 1.265 per ct. = 6.4388 grm.

Dec. 21st. 461 grm. P_2O_5, 0.1529 per ct. = 0.7048 grm.; CaO, 0.041 per ct. = 0.1890 grm.; nitrogen, 1.265 per ct. = 5.8316 grm.

Dec. 22d. 531 grm. P_2O_5, 0.1529 per ct. = 0.8118 grm.; CaO, 0.041 per ct. = 0.2177 grm.; nitrogen, 1.265 per ct. = 6.7271 grm.

Dec. 23d. 256 grm. P_2O_5, 0.1529 per ct. = 0.3914 grm.; CaO, 0.041 per ct. = 0.1049 grm.; nitrogen, 1.265 per ct = 3.2384 grm.

BUTTER: Dec. 17th. Total amount 96.5 grm. P_2O_5 0.045 per ct. = 0.0434 grm.; CaO, 0.030 per ct. = 0.0289 grm.; nitrogen, 0.080 per ct. = 0.0772 grm.

Dec. 18th. 88 grm. P_2O_5, 0.045 per ct. = 0.0396 grm.; CaO, 0.030 per ct. = 0.0264 grm.; nitrogen, 0.080 per ct. = 0.0704 grm.

Dec. 19th. 90 grm. P_2O_5, 0.045 per ct. = 0.0405 grm.; CaO, 0.030 per ct. = 0.0270 grm.; nitrogen, 0.080 per ct. = 0.0720 grm.

Dec. 20th. 96 grm. P_2O_5, 0.045 per ct. = 0.0432 grm.; CaO, 0.030 per ct. = 0.0288 grm.; nitrogen, 0.080 per ct. = 0.0768 grm.

Dec. 21st. 100 grm. P_2O_5, 0.045 per ct. = 0.0450 grm.; CaO, 0.030 per ct. = 0.0300 grm.; nitrogen, 0.080 per ct. = 0.0800 grm.

Dec. 22d. 85 grm. P_2O_5, 0.045 per ct. = 0.0382 grm.; CaO, 0.030 per ct. = 0.0255 grm.; nitrogen, 0.080 per ct. = 0.0680 grm.

Dec. 23d. 41 grm. P_2O_5, 0.045 per ct. = 0.0184 grm.; CaO, 0.030 per ct. = 0.0123 grm.; nitrogen, 0.080 per ct. = 0.0328 grm.

STEAK: Dec. 17th. Total amount 150 grm. P_2O_5, 0.388 per ct. = 0.5820 grm.; CaO, 0.0243 per ct. = 0.0364 grm.; nitrogen, 3.798 per ct. = 5.6970 grm.

Dec. 18th. 150 grm. P_2O_5, 0.5830 per ct. = 0.8745 grm.; CaO, 0.0243 per ct. = 0.0364 grm.; nitrogen, 3.8460 per ct. = 5.7690 grm.

Dec. 19th. 150 grm. P_2O_5, 0.7137 per ct. = 0.0705 grm.; CaO, 0.0243 per ct. = 0.0364 grm.; nitrogen, 4.538 per ct. = 6.8070 grm.

Dec. 20th. 150 grm. P_2O_5, 0.6148 per ct. = 0.9222 grm.; CaO, 0.0243 per ct. = 0.0364 grm.; nitrogen, 4.192 per ct. = 6.2880 grm.

Dec. 21st. 150 grm. P_2O_5, 0.6926 per ct. = 1.0389 grm.; CaO, 0.0243 per ct. = 0.0364 grm.; nitrogen, 4.505 per ct. = 6.7575 grm.

Dec. 22d. 150 grm. P_2O_5, 0.8095 per ct. = 1.2142 grm.; CaO, 0.0243 per ct. = 0.0364 grm.; nitrogen, 3.8690 per ct. = 5.8035 grm.

Dec. 23d. 150 grm. P_2O_5, 0.4976 per ct. = 0.7464 grm.; CaO, 0.0243 per ct. = 0.0364 grm.; nitrogen, 4.090 per ct. = 6.1350 grm.

HAM: Dec. 17th. Total amount 150 grm. P_2O_5, 0.5388 per ct. = 0.8082 grm.; CaO, 0.039 per ct. = 0.0585 grm.; nitrogen, 3.753 per ct. = 5.6295 grm.

Dec. 18th. 150 grm. P_2O_5, 0.5388 per ct. = 0.8082 grm.; CaO, 0.0390 per ct. = 0.0585 grm.; nitrogen, 3.7530 per ct. = 5.6295 grm.

Dec. 19th. 150 grm. P_2O_5, 0.5388 per ct. = 0.8082 grm.; CaO, 0.039 per ct. = 0.0585 grm.; nitrogen, 3.753 per ct. = 5.6295 grm.

Dec. 20th. 150 grm. P_2O_5, 0.5388 per ct. = 0.8082 grm.; CaO, 0.0390 per ct. = 0.0585 grm.; nitrogen, 3.753 per ct. = 5.6295 grm.

Dec. 21st. 150 grm. P_2O_5, 0.5388 per ct. = 0.8082 grm.; CaO, 0.039 per ct. = 0.0585 grm.; nitrogen, 3.753 per ct. = 5.6295 grm.

Dec. 22d. 150 grm. P_2O_5, 0.5388 per ct. = 0.8082 grm.; CaO, 0.0390 per ct. = 0.0585 grm.; nitrogen, 3.753 per ct. = 5.6295 grm.

Dec. 23d. 147 grm. P_2O_5, 0.5388 per ct. = 0.7920 grm.; CaO, 0.039 per ct. = 0.0573 grm.; nitrogen, 3.753 per ct. = 5.5169 grm.

EGGS: Dec. 17th. Total amount 175 grm. P_2O_5, 1.421 per ct. = 0 7367 grm.; CaO, 0.122 per ct. = 0.2135 grm.; nitrogen, 2.008 per ct. = 3.5140 grm.

Dec. 18th. 186 grm. P_2O_5, 0.421 per ct. = 0.7830 grm.; CaO, 0.122 per ct. = 0 2269 grm.; nitrogen, 2.008 per ct. = 3.7348 grm.

Dec. 19th. 171 grm. P_2O_5, 0 421 per ct. = 0.7199 grm.; CaO, 0.122 per ct. = 0.2086 grm.; nitrogen, 2.008 per ct. = 3.4336 grm.

Dec. 20th. 159 grm. P_2O_5, 0.421 per ct. = 0.6693 grm.; CaO, 0.122 per ct. = 0.1939 grm.; nitrogen, 2.008 per ct. = 3.1927 grm.

Dec. 21st. 136 grm. P_2O_5, 0.421 per ct. = 0.5725 grm.; CaO, 0.122 per ct. = 0.1659 grm.; nitrogen, 2 008 per ct. = 2.7308 grm.

Dec. 22d. 205 grm. P_2O_5, 0.421 per ct. = 0.8630 grm.; CaO, 0.122 per ct. = 0.2501 grm.; nitrogen, 2.008 per ct. = 4.1164 grm.

Dec. 23d. 149 grm. P_2O_5, 0 421 per ct. = 0.6272 grm.; CaO, 0.122 per ct. = 0.1817 grm.; nitrogen, 2.008 per ct. = 2.9919 grm.

MILK: Dec. 17th. Total amount 1000 c.c. P_2O_5, 0.270 per ct. = 2.7000 grm.; CaO, 0.184 per ct. = 1.8400 grm.; nitrogen, 0.5740 per ct. = 5.740 grm.

Dec. 18th. 1000 c.c. P_2O_5, 0.2700 per ct. = 2.7000 grm.; CaO, 0.1840 per ct. = 1.8400 grm.; nitrogen, 0.5516 per ct. = 5.5160 grm.

Dec. 19th. 1000 c.c. P_2O_5, 0.280 per ct. = 2.8000 grm.; CaO, 0.184 per ct. = 1.8400 grm.; nitrogen, 0 5936 per ct. = 5.9360 grm.

Dec. 20th. 1000 c.c. P_2O_5, 0.2328 per ct. = 2.3280 grm.; CaO, 0.184 per ct. = 1.8400 grm.; nitrogen, 0.5236 per ct. = 5.2360 grm.

Dec. 21st. 1000 c.c. P_2O_5, 0.2448 per ct. = 2.4480 grm.; CaO, 0.184 per ct. = 1.8400 grm.; nitrogen, 0.546 per ct. = 5.4600 grm.

Dec. 22d. 1000 c.c. P_2O_5, 0.2760 per ct. = 2.7600 grm.; CaO, 0.184 per ct. = 1.8400 grm.; nitrogen, 0.546 per ct. = 5.4600 grm.

Dec. 23d. 1000 c.c. P_2O_5, 0.266 per ct. = 2.6600 grm.; CaO, 0.184 per ct. = 1.8400 grm.; nitrogen, 0.5376 per ct. = 5.3760 grm.

RICE: The total amount was the same each day, being 27 grm. The percentages and amounts of P_2O_5, CaO, and nitrogen were as follows:

P_2O_5,	0.241 per cent.	= 0.0650 grm.
CaO,	0.0145 per cent.	= 0 0039 grm.
Nitrogen,	1.110 per cent.	= 0.2997 grm.

The urine while being collected was kept in a cool place in a vessel containing chloroform; and its reaction was tested each day, and was regularly found to be acid. These precautions were necessary in order to insure accuracy in the results for ammonia, volatile fatty acids, etc. The urine was analyzed quantitatively each day for P_2O_5, CaO, total nitrogen and ammonia nitrogen, volatile fatty acids, and preformed and ethereal sulphates; and qualitatively for phenol and acetone. The reasons for these various analyses will be mentioned later.

The feces were collected daily, placed in a large evaporating-dish on a water-bath, and covered with weak sulphuric acid. The total was evaporated to dryness on the bath and in the oven, weighed, ground fine, and well mixed; and portions were taken for P_2O_5, CaO, and nitrogen.

The methods used in the various analyses of foods and excretions were as follows: For P_2O_5, the method of Scholz and Pfeiffer; for CaO, the usual method of precipitation, as oxalate; for nitrogen, the Kjeldahl-Argutinsky method; for NH_3 nitrogen, distillation *in vacuo*, using Steyrer's apparatus; for volatile fatty acids, Blumenthal's method; for sulphates, the Baumann-Salkowski method; for phenol and acetone, the reaction of the distillate to bromine water and sodium nitroprusside, respectively.

The tables for the daily analyses of the urine and the separate analyses of the feces, and those exhibiting the daily and total balance of P_2O_5, CaO, and nitrogen follows:

URINE.

Date.	Amount.	P_2O_5.		CaO.		Total nitrogen.		NH_3 nitrogen	Volatile fatty acids.	Sulphates.			Phenol.	Acetone.
		Per cent.	Total amount.	Per cent.	Total amount.	Per cent.	Total amount.			Pre-formed. SO_3	Ethereal SO_3	Ratio.		
	c.c.													
Dec. 17	2265	0.1360	3.0804	0.0406	0.9196	1.0472	23.7190	1.3861	Lost	3.2924	0.3678	1 to 8.9	Negative.	
" 18	2605	0.1504	3.9179	0.0438	1.0410	0.9660	25.1643	1.3129	213.6	3.4567	0.6387	1 to 5.4	"	
" 19	1920	0.0760	1.4592	0.0238	0.4569	0.6048	11.6121	0.6666	123.8	1.7817	0.1536	1 to 11.6	"	
" 20	2910	0.1316	3.8295	0.0415	1.1276	0.8288	24.1180	1.1407	244.4	3.8843	0.3410	1 to 11.3	"	
" 21	2760	0.1464	4.0406	0.0398	1.0984	0.9100	25.1160	1.7310	Lost	3.5847	0.3897	1 to 8.4	"	
" 22	3195	0.1016	3.2461	0.0333	1.0639	0.7168	22.9017	1.4672	294.4	2.8528	0.3588	1 to 7.9	"	
" 23	2230	0.1408	3.1398	0.0348	0.7760	0.9520	21.2296	1.0989	303 2	3.3834	0.3683	1 to 9.1	"	
Totals			22.7135	. . .	6.4834	. . .	153.8607							
Average daily excretion			3.2449	. . .	0.9262	. . .	21.9801							

FECES.

No.	Amount weighed.	P_2O_5.		Amount weighed.	CaO.		Amount weighed.	Nitrogen.	
		Amount found.	Per cent.		Amount found.	Per cent.		Amount found.	Per cent.
I.	0.7138	0.0384	5.379	1.6606	0.0722	4.341	1.0314	0.06328	6.135
II.	0.7904	0.0396	5.010	1.5744	0.0712	4.522	0.9900	0.05600	5.656
III.	0.6432	0.0320	4.975	1.5986	0.0700	4.378	1.0048	0.05796	5.768
IV.	0.9246	0.0464	5.018	1.1292	0.0480	4.250	1 0860	0.06384	5.878
Average . .	.....	.....	5.095	.....	.....	4.372	.....	.....	5.859
Total amount in feces .		9.9390	.....	.....	8.5286	.....	.....	11.4294	.....
Daily average		1.41985	.....	.....	1.21837	.....	.....	1.63277	.....

Weight of total dried feces 195.075

P_2O_5 Balance.

Date.	Intake.	Outgo.			Balance.
		Urine.	Feces.	Total.	
Dec. 17	5.7502	3.0804	1.41985	4.50025	+1.24995
" 18	6.1112	3.9179	1.41985	5.33775	+0.77345
" 19	6.2523	1.4592	1.41985	2.87905	+3.37325
" 20	5.6141	3.8295	1.41985	5.24935	+0.36475
" 21	5.6824	4.0406	1.41985	5.46045	+0.22195
" 22	6.5604	3.2461	1.41985	4.66595	+1.89445
" 23	5.3004	3.1398	1.41985	4.55965	+0.74075
	41.2710	22.7135			+8.61855

Percentage retention . . . 20.88.

CaO Balance.

Date.	Intake.	Outgo.			Balance.
		Urine.	Feces.	Total.	
Dec. 17	2.3997	0.9196	1.21837	2.13797	+0.26173
" 18	2.4176	1.0410	1.21837	2.25937	+0.15823
" 19	2.3753	0.4569	1.21837	1.67527	+0.70003
" 20	2.3701	1.1276	1.21837	2.34597	+0.02413
" 21	2.3237	1.0984	1.21837	2.31677	+0.00693
" 22	2.4321	1.0639	1.21837	2.28227	+0.14983
" 23	2.2365	0.7760	1.21837	1.99437	+0.24213
	16.5550	6.4834			+1.54301

Percentage retention . . . 9.32

Nitrogen Balance.

Date.	Intake.	Outgo.			Balance.
		Urine.	Feces.	Total.	
Dec. 17	27.6998	23.7190	1.63277	25.35177	+ 2.34803
" 18	27.9769	25.1643	1.63277	26.79707	+ 1.17983
" 19	28.3763	11.6121	1.63277	13.24487	+15.13143
" 20	27.1615	24.1180	1.63277	25.75077	+ 1.41073
" 21	26.7891	25.1160	1.63277	26.74877	+ 0.04033
" 22	28.1042	22.9017	1.63277	24.53447	+ 3.56973
" 23	23.5907	21.2296	1.63277	22.86237	+ 0.72833
	189.6985	153.8607			+24.40841

Percentage retention . . . 12.86

There is one point that we would first note in explanation of the figures in the table of urinary excretions. On December 19th there was a marked reduction in the amount of urine and a remarkable drop in the amounts of all the substances estimated. This suggests, of course, that some of the urine had been lost; but this was nearly impossible, because of the rigid care used by the nurse and orderly in charge of the man, and it seems highly probable that it was due to a striking temporary alteration in excretion, for there was a reduction not only in the amount of urine, but also in the percentage excretion much below that of any other day. A similar though less marked condition is seen in v. Moraczewski's tables. Whatever the cause, it would make no material difference in the total results or in the main conclusions to be drawn therefrom.

The figures in general demonstrate a very striking retention of phosphorus and nitrogen, and a less marked retention of calcium—a condition of affairs that is somewhat remarkable when one considers the fact that in this disease the skeleton shows such notable changes. One would expect that if the changes in the bone consist merely of distorted overgrowth, as they are often said to do, the calcium would exhibit the most marked retention. Pathological reports, however, do not justify the statement that the bony change is a simple "overgrowth;" for while some observers claim to have proved that the microscopic appearances of the bones are normal, such statements are usually if not always based upon insufficient or inaccurate observation; and properly conducted examinations have usually shown more or less marked abnormalities of structure, and also evidences of absorption, as well as of deposition of bone-salts. Our calcium figures, as compared with the figures for P_2O_5 and nitrogen, are wholly in consonance with these facts; and they also strongly suggest that the chemical composition of the bone may show abnormalities, which, if determined, would be of interest, and would, perhaps, throw more light upon the nature of the process. We are at present making some examinations of bone from a case of gigantism with somewhat doubtful signs of acromegaly, and trust that we may have an opportunity to make similar investigations in unquestionable acromegaly. But examination of the bones alone, while important, will certainly not give very complete information concerning anything but a portion of the results of the process; for clinical and post-mortem observations have, of course, clearly demonstrated that

the disease is by no means confined to the bones; and our figures, together with those of Schiff and v. Moraczewski, emphasize this fact. The high degree of nitrogen retention found by v. Moraczewski and by ourselves is very noteworthy, and is almost undoubtedly pathological in our case, at any rate; for the man was already overnourished rather than undernourished at the time of the experiment; and there was, therefore, no question of a mere retention as the result of subnutrition. This seems to be quite clearly the expression of the abnormal growth of the soft tissues—a common feature of the disease, and one that was evidently present in this case, as is demonstrated by the anthropometric table. The strength tests, in this table, as well as common observation, demonstrate that this tissue growth is abnormal, since it is not accompanied by increase in muscular power, but by the directly contrary condition.

The figures for the phosphorus balance are still more suggestive, as they indicate a possible condition that is not demonstrated by ordinary clinical observation. The very large retention of phosphorus can be satisfactorily explained only by considering that it is used in constructing tissue especially rich in phosphorus, and this is particularly true when it is recognized that the nitrogen retention was relatively small. The first thought, naturally, is that the retained portion went toward increasing the large excess in the growth of bone; but this view is not supported by the figures for calcium retention; for the latter are relatively so low and the phosphorus figures so high that if a large part of the phosphorus had formed calcium salts, these would apparently be not insoluble bone salts, but the readily soluble and easily eliminable acid phosphates. The proportion of CaO to P_2O_5 in bone is about as 10 to 6. Putting aside, therefore, an amount of the retained phosphorus equivalent in this proportion to the whole retained calcium, a large part (7.7 grammes or 90 per cent. of the whole amount retained) still remains to be accounted for. This is likely in large part to have entered into the production of other tissue rich in phosphorus. It is probable that a number of organs rich in nucleoproteid, such as the pancreas and also the bone-marrow and other leucocyte-forming tissues, have a share in this, but this man exhibited no evidence of disease of any of these structures; and our pathological knowledge indicates the nervous system as at least one of the chief seats of this

deposit. Both clinical and pathological observations indicate that this overgrowth of nervous tissue that occurs in some cases of acromegaly is often, at least, not normal functionally, and the man we investigated is an imbecile. Our figures for phosphorus retention are so large as to suggest that the chemical constitution of this tissue is abnormal; for the retention was more than one gramme a day, and if this had continued for any considerable length of time the retention would, if in the form of normal nervous tissue, be relatively enormous.

The point in our figures that seems especially suggestive, however, is the relative amount of calcium excreted by the kidneys as compared with that excreted by the intestine. Under normal circumstances the amount of calcium in the daily feces is eight or ten times the amount in the daily urine. In this case the amount in the urine nearly equalled that in the feces. This is a condition frequently met with in diabetes mellitus, when acid intoxication is present. It has also been observed by v. Limbeck and others in acid intoxication, in a series of other diseases, and has been artificially produced in normal persons by Gerhardt and Schlesinger by merely making radical changes in the diet (strict proteid and fat diet). The large amount of urinary calcium excreted in our case was not due to the special diet of the experiment, for the amount of urinary calcium had been determined some time before the beginning of the experiment, and had been found to be more than one gramme; this was, indeed, one of our chief reasons for undertaking an exact metabolism experiment with the man. It was, likewise, apparently not due to a general excess of acids in the system. Our determinations of the ammonia nitrogen, volatile fatty acids, and acetone were made in order to attempt to settle this point. The volatile fatty acids having been found high in some preliminary observations, the ethereal and preformed sulphates and the phenol were investigated, in order to see to what extent the figures for the volatile fatty acids were due to intestinal decomposition. The figures for ammonia are, absolutely, somewhat high, but relatively to the total nitrogen they are not notably high, while the figures for the volatile fatty acids are decidedly excessive. The figures for the ethereal sulphates, however, indicate that both the ammonia and the volatile fatty acids were increased, partly, at least, by the generous diet. The constant absence of acetone bears out this view, and that this is

correct in regard to the ammonia is shown by figures obtained after the metabolism experiment was over and the man had been restricted to the ordinary ward diet, the results for two days were then 0.982 and 0.593 gramme. This is also certainly the chief explanation of the high figures for volatile fatty acids. Estimations made during six days while the patient was on ward diet gave the following figures: 95.3, 71.1, 176.9, 177.3, 132.0, and 114.4. These figures are much below those obtained during the metabolism experiment, but they are still high. A series of about 200 estimations of the volatile fatty acids made by Drs. Edsall, Fife, and Wile has shown the upper normal limit on this same diet to be about 80. We cannot say, therefore, that these acids had nothing to do with the peculiar calcium excretion, but they apparently cannot explain it all at best; and hence, they unfortunately do not demonstrate any clear cause for this peculiar excess of calcium in the urine. It seems probable, in any case, that it is directly associated with the progress of the disease, for, as stated, it was not dependent upon the diet; v. Moraczewski observed the same feature in his case (though in this instance it may have been due to the glycosuria); and, further, it was not exhibited by the second case under our observation, which was, as stated, one of acromegaly that was at a standstill. We were not able to make a complete investigation of this man's metabolism, since we could not have him sufficiently under our control. The CaO of the urine was, however, estimated, and the figures for seven days follow:

CASE II.—P. K. (URINE.)

Date.	Amount.	CaO.	
		Per cent.	Total amount
March 7	1450	0.0105	0.1522
" 8	1650	0.0285	0.4702
" 9	1520	0.0084	0.1278
" 10	1870	0.0076	0.1421
" 11	2550	0.0121	0.3085
" 12	2525	0.0156	0.3939
" 13	2190	0.0141	0.3087
Total in seven days			1.9034
Average per day			0.2719

The conditions in this man, then, were normal, or, at most, not far from normal. As far as observations have gone, therefore, this condition seems to be a part of acromegaly when the disease is progressing; and, if further observations bear this out, it would suggest a means of attack in the search for the nature of the condition. It would, *i. e.*, in connection with the knowledge that the bones exhibit evidence of absorption, indicate that there is in this disease some abnormality of metabolism that causes a solution of calcium from the bones at the same time that there is in other parts of the bone an abnormal deposition of bone salts. This does not appear to be the result of general acid intoxication, but is more probably due to the formation of some acid that combines with calcium with especial readiness. Some of the calcium is apparently carried off in solution. It may be that another portion is simply redeposited, and thus leads to the abnormal growth of bone; or the growth may be an entirely independent matter. As to this we have no knowledge, and the observations so far made offer no direct suggestions.

The observations that we report emphasize, however, the view that there is in acromegaly a growth of abnormal bone rather than a mere abnormal growth of bone, and that there are very marked abnormalities in the soft tissues, as well as in the bones; and they strongly suggest that chemical study of the bones, as well as chemical studies of the disease in general, may throw some light upon the disease and may demonstrate definitely that the alterations in the bones are the result of metabolic abnormalities rather than of a mere tendency to distorted overgrowth. While such metabolic abnormalities may be the result of disturbances in bone metabolism, *per se*, it is likewise possible that they may be due to general metabolic disturbances that only secondarily affect the bones. Mere general increase in the size of the bones would then be a part of a general gigantism, but the peculiar acromegalic deformities would be the result of metabolic disease.

In conclusion, we wish to thank Dr. Charles A. Fife for his kindness in making most of the estimations of the volatile fatty acids and the sulphates.

A STUDY OF TWO CASES NOURISHED EXCLUSIVELY PER RECTUM, WITH A DETERMINATION OF ABSORPTION, NITROGEN-METABOLISM, AND INTESTINAL PUTREFACTION.*

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and

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Grave gastric hemorrhage, intractable vomiting, and a number of operations provide imperative indications for stopping all food by the mouth. In œsophageal or pyloric obstruction the food taken is often wholly or almost entirely rejected, in which case the same absolute indication is encountered; and even if excessive vomiting does not occur, the amount of food that can be made to pass the obstruction is very frequently so small as to be quite insufficient for the maintenance of a nutritive equilibrium. In a considerable series of other cases of varied kinds it is desirable to limit the food by the mouth to a very low quantity or to substitute entirely other methods of feeding.

In any of these circumstances the only feasible method of supplying nutriment is by way of the rectum. Attempts have been made to administer food hypodermically; but while a very limited degree of success has been attained in this way, it is perfectly evident that such a method has very narrow limitations; and it is one that is exceedingly difficult to carry out, and that cannot be attempted except in case of very pressing need.

* Read before the College of Physicians of Philadelphia, June 4, 1902.

The value of rectal alimentation is often very differently stated by writers whose position and experience are such as to make them capable of forming a judgment concerning this question. For example, the late William Pepper always spoke of rectal alimentation as being disappointing and unsatisfactory. H. C. Wood's teaching is similar. Ewald admits that the use of nutritive enemata can ordinarily not be successfully carried out for any considerable period of time; but he, nevertheless, considers their nutritive value to be very considerable. Leube, at one time, spoke quite enthusiastically of the nutritive value of these enemata; but the last expression from his clinic, although not from himself personally, refers to the results as being "not particularly brilliant." Riegel speaks highly of nutritive enemata, and leads one to infer that by their use a nutritive equilibrium may be maintained for a long time. Fleiner, on the other hand, insists that it is impossible to maintain a nutritive equilibrium by this means; and that we must always consider, when using exclusive rectal alimentation, that the patient is partially starving.

In general it may be fairly said that the great majority of those who have directly investigated the absorption of nutritive enemata recognize that their value is limited, though different authors vary decidedly in the position that they would accord them. Some clinicians, on the other hand, on the basis of clinical observation alone, praise their use highly, and either state definitely or intimate that they can supply all needs for a long time; while other clinicians who are equally capable take a much more conservative view or even consider them almost valueless.

It must, of course, be granted at once that if any food is absorbed from rectal enemata, an important gain has been made over an entire lack of food. This needs no demonstration. The main question is to determine how much food can be administered and absorbed in this way, and how nearly it is possible to maintain an actual nutritive equilibrium when a patient is being fed exclusively or almost exclusively by the rectum. A recognition of the exact value of this form of alimentation is of much importance, because in many instances the period throughout which this form of feeding is continued must be determined by the general knowledge of its effect upon nutrition; and, frequently, a decision as to

the recommendation of operation or as to the period at which an operation should be undertaken will depend upon the same knowledge.

In a communication concerning this subject, one of us,[1] several years ago, presented some brief investigations which demonstrated the fact that in the patient then under observation nutritive enemata had been very imperfectly absorbed; and that the amount of nutriment actually received in this way was far less than enough to maintain a nutritive equilibrium, even in a patient so greatly reduced in nutrition as was that woman. Her nitrogen-excretion, also, was such as to indicate that she was practically in a condition of starvation. The present communication will serve as a further contribution to the literature of the same subject, and will, at the same time, direct attention to a factor that has been but casually referred to by previous investigators of this subject, and that should have some influence upon one when reaching conclusions.

The two patients studied were women with gastric ulcer, who were admitted to the University Hospital directly after the occurrence of very grave gastric hemorrhage—one of them in the service of Dr. Alfred Stengel, the other in that of Dr. John H. Musser. In both cases the indication for the exclusion of food by the mouth was imperative. Both were at once put upon three nutritive enemata a day. The total amount given in the twenty-four hours was 400 c.c. of milk and six eggs. In preparing each enema two eggs were added to one-third of the total daily quantity of milk; the whole was predigested with pancreatin; sufficient salt was added to make the percentage equal to normal salt solution, and three drops of laudanum were added to this mixture. In each case a cleansing enema of water was given an hour before the nutritive enema. The latter was always given through a long rectal tube, the patient having the hips elevated, and this position being maintained for an hour or more after the enema was given.

The first patient, H., never had the slightest sign of irritation from the enemata, and had no spontaneous stool during the whole time that the enemata were used. The second patient, N., did not retain the enemata well for the first day (this was five days before the study of her absorption was begun). After this, however, she also exhibited no evidence of irritation, and had no stool, except

after the use of the cleansing enemata. It is important to insist upon this point; irritation of the bowel could hardly have played any part in furnishing the results obtained.

Each patient was kept upon exclusive rectal alimentation for eighteen days. In each case our investigations were undertaken only after the patient had been on the rectal alimentation for five days, in order that the results might not be disturbed through the presence in the intestine of food-remnants from a previous period and in order that metabolism might have accustomed itself so far as possible to the unusual conditions.

The nitrogen of the milk was estimated daily; that of the pancreatin tablets was estimated in three samples and the average taken. The eggs were carefully weighed each day, the shells weighed after the eggs were used, and the difference taken as the weight of the egg-albumin and yolk; the nitrogen in the eggs was then calculated from the tables ordinarily given. The fat in the milk was estimated by the Leffmann-Beam process, that of the eggs was taken from tables. The total feces were collected daily, acidulated with sulphuric acid, and evaporated to dryness on the water-bath. The total dry and ground feces of the whole period was thoroughly mixed, and five estimations of the nitrogen and three of the fat were made. The nitrogen was estimated by the Kjeldahl process, and the fat by extraction in the Soxhlet apparatus. In each case the period of investigation was six days.

CASE I. PATIENT H. NITROGEN.

Nitrogen of Urine.

February 1st		11.160
February 2d		10.504
February 3d		10.5624
February 4th		10.856
February 5th		7.147
February 6th		9.9588
Total		60.1882
Nitrogen in eggs	34.7321	
Nitrogen in milk and tablets	13.5396	
Total food nitrogen	48.2717	
Fecal nitrogen	29.0254	
Nitrogen absorbed	18.2463 = 39.88%	

Total nitrogen absorbed (18.2463 grammes) equals 123 039 grammes protein in six days.

Nitrogen absorbed daily equals 3.041 grammes; this equals 19 grammes protein

Total fecal nitrogen	29.0254
Total urinary nitrogen	60.1882
Total nitrogen excreted	89.2136
Total nitrogen absorbed	18.2463
Total loss tissue nitrogen	70.9673

Equals loss of tissue protein 443.535.

FAT.

Fat in eggs	167.810	
Fat in milk	117.840	
Total fat in food	285.650	
Total fat in feces	246.770	
Total fat absorbed	38.88	$=13.61\%$

Total fat absorbed per day, 6.48 grammes.

CASE II. PATIENT N. NITROGEN.

February 6th		16.0599
February 7th		15.2105
February 8th		10.2028
February 9th		9.3586
February 10th		13.1022
February 11th		12.7270
Total		76.6610
Nitrogen in eggs	34.0843	
Nitrogen in milk and tablets	14.0307	
Total food nitrogen	48.1150	
Fecal nitrogen	25.261	
Nitrogen absorbed	22.854	$=47.5\%$

Total nitrogen absorbed (22.854 grammes) equals 142.837 grammes protein in six days.

Nitrogen absorbed daily equals 3.809 grammes; this equals 23.816 grammes protein.

Total fecal nitrogen	25.261
Total urinary nitrogen	76.661
Total nitrogen excreted	101.922
Total nitrogen absorbed	22.854
Total loss tissue nitrogen	79.068

Equals loss of tissue protein 494.175.

FAT.

Fat in eggs	164.688	
Fat in milk	120.072	
Total fat in food	284.760	
Total fat in feces	189.50	
Total fat absorbed	95.26	$=33.46\%$

Total fat absorbed per day, 15.87 grammes.

These results correspond fairly well with those obtained in the case previously mentioned; and in these two cases, as well as in the one previously reported, it is quite evident that rectal alimentation was an extremely insufficient method of maintaining nutritive equilibrium, even for a short period. The amounts absorbed in all the cases were far less than the demands of the patients, and the condition of the urinary nitrogen demonstrated that the tissues were suffering largely. The nitrogen in the urine, compared with the nitrogen absorbed, indicates a very marked tissue-loss; and, further, in Case I., as in the case investigated in the previous report, though to a less marked degree, the urinary nitrogen showed the same rapid fall that is exhibited by persons who are actually undergoing starvation.

That the food was insufficient was also clearly shown by the appearance of the patients. The patient of the previous report was, as stated, losing weight and strength so evidently and rapidly that investigation, which was begun late, had been continued only two days when it was considered necessary to give food by the mouth. Of the subjects of this report, only the second patient had her weight recorded before and after the eighteen days of rectal alimentation. During this time she lost forty-two pounds. The weight of the other patient before rectal alimentation was instituted was not known, but it was evident that she was losing weight rapidly. The figures given show that she absorbed less than the other woman, and it is highly probable, therefore, that she lost at least a similar amount of weight.

A fact of decided interest in this connection is that both patients persistently stated that the nutritive enemata greatly relieved their hunger. They said, however, that their hunger was much appeased within a few moments after each enema was administered. This

feeling of relief could, therefore, hardly have been due to anything but suggestion; and a comparison of the patient's own feelings with the figures given for absorption is sufficient to demonstrate the inadequacy of such sensations as a measure of the effect of the alimentation. Some authors insist rather strongly upon the fact that the enemata greatly relieve or entirely do away with any sensation of hunger.

Our figures in three cases, therefore, so far as they are an indication of general conditions, show that, at most, 40 to 50 per cent. of the nitrogenous food and, at most, one-third of the fat is absorbed. These percentage figures, in themselves, do not sound so unsatisfactory. If a fairly large quantity of nitrogenous and fatty food could be given per rectum, the absorption of 50 per cent. and 33 per cent., respectively, of these foods would furnish the patients with a very considerable amount of nutriment; and if their metabolic demands were already slight from prolonged disease and consequent prolonged subnutrition, it would serve to maintain them in a nutritive equilibrium and, perhaps, cause them to put on tissue. This, however, cannot usually be the case. We are, as a rule, limited strictly to comparatively small quantities of food, because the bowel will not retain more; and if an attempt is made to give larger quantities the percentage of absorption falls, and, indeed, it often becomes impossible to carry out rectal alimentation at all, because the larger quantities frequently cause severe irritation of the bowel.

If the actual caloric value of the food absorbed in our cases be reckoned, it will be found that patient No. 1 absorbed of—

	Grammes.	*Calories.*
Fat	38.88	361.5
Proteid	123.039	467.5
Total equalling		829.0

If the total milk-sugar, reckoned high (at 4.5 per cent.), be considered to have been absorbed and be added to this we gain 442.8 calories. The total possible food calories absorbed by this patient in six days would then be 1271.9. The total food calories absorbed per day would under these circumstances equal 211.9. The patient had a moderately excessive amount of body fat, and

may be considered as demanding only about 30 calories per kilo to maintain her nutritive equilibrium; she would then need 1800 to 2000 food calories per day.

In the second case the conditions were not quite so bad. The woman absorbed of—

	Grammes.	*Calories.*
Fat	95.26	885.9
Proteid	142.8	585.6
Total		1471.5

If the total milk-sugar be considered to have been entirely absorbed in this case, also, and be reckoned as in the other, we add 442.8 calories and get a total of 1914.3 possible food calories absorbed in six days. Her total calories per day would then be 319. This woman was larger and heavier than the other, and her demands, reckoned at 30 calories per kilo, would be 2000 to 2200 calories per day.

The first patient, therefore, received about one-ninth of the amount of food that would be sufficient to maintain her nutritive equilibrium; the second patient, about one-sixth or one-seventh. Even this, however, as we shall show later, is certainly more than either actually absorbed, owing to the error caused by bacterial decomposition; indeed, it is possible that these amounts are decidedly more than they should be in order to represent the actual absorption. This question will, however, be discussed after referring to the literature.

When our results are compared with the work of others it will be seen that there are notable individual differences, but that, on the whole, the literature indicates that the figures which we obtained for the absorption of protein are not unusually favorable; and there is an almost general agreement that fats are but slightly absorbed, and that their use in rectal enemata provides very little nutrition, and also, probably, tends to interfere with the absorption of other food, since they undergo decomposition and irritate the bowel. The question of the absorption of carbohydrates will be mentioned later. We made no attempt to determine the actual degree of absorption of carbohydrates in our cases, for reasons that will be noted.

First, as to the absorption of albumin. Voit and Bauer,[2] and

Eichhorst,[3] the first experimenters in this line, determined that eggs are practically not absorbed by the large intestine of dogs, unless salt be added to them; but that if salt is added, they are fairly well absorbed.

As to the effect upon human beings, the greatest influence in regard to this question has, undoubtedly, been exerted by Ewald[4] through the report that he published in 1887. It has been generally accepted by that author since then, and by numerous writers who have followed him, that eggs injected per rectum are very well absorbed. Ewald's results, given in graphic form, are very difficult to examine carefully, and are very confusing. The figures themselves have, therefore, largely escaped careful observation. It is, however, worth while to give them some attention. His results are, in the first place, those obtained on one patient alone, and that patient certainly showed conditions of absorption that are most unusual; for, if the amount of nitrogen ingested be compared with the quantity given as absorbed, it will be found that the loss of nitrogen in the feces was far below even that which is normal in persons fed by mouth upon readily assimilable food. Indeed, in some of the periods, even when milk in quantities of half a litre was given per rectum (and it is generally recognized that milk, when given by rectum, is ordinarily not well absorbed), the excretion of nitrogen per rectum amounted to as little as 0.11 gramme a day, which is less than is found when absolutely no food is administered; in other words, it is less than the amount that is customarily due to the secretions of the bowel wall and to the breaking down of intestinal epithelium. Indeed, in almost all of the periods presented the excretion per rectum was abnormally low. The figures obtained in this case, therefore, cannot be properly accepted, as they have often been, as indicative of the general results of the use of rectal enemata.

The chief stress is laid by Ewald upon the condition of the urinary nitrogen and the nitrogen balance in his case; and he directs especial attention to the fact that the urinary nitrogen was largely increased, in many instances, by the use of rectal enemata, and that a negative balance, or a slightly positive one, was transformed into a very marked nitrogen-retention. He himself notes, however, that the conditions varied greatly. In some instances

the use of egg-enemata caused only an extremely slight nitrogen-retention, and in others the nitrogen-retention rose as high as 17 grammes. The same was true of "peptone" enemata. The author attributes these results to differences in the assimilability of the food used, rather than to its readiness of absorption. The condition of the nitrogen balance varied, however, to an extreme degree when exactly the same enemata were given in different periods, and it seems rather more probable that a large part of the difference in the nitrogen balance was due either to variations in the metabolic processes not dependent upon the food that was being used, or to a possible technical error. The latter suggestion is made upon the basis of the fact that Ewald himself says that the feces in the different periods varied between 177 and 1844.5 grammes. It is certainly impossible, under such circumstances, to be sure that the feces of one period were properly collected in that period, particularly since no way of separating off the feces was used or could well be used under the circumstances.

The value of rectal enemata can evidently not be determined, however, by studying the urinary nitrogen. The most important point is to determine the actual absorption; and in this case, as stated, while the absorption was good it was so surprisingly good that the results must be considered to be wholly unusual.

Next to Ewald, the most satisfactory results have been obtained by Huber,[5] who insists from his work on human subjects, as did earlier investigators after animal experiments, that egg-enemata are much better absorbed if salt is added to the egg. Huber investigated three persons throughout a number of three-day or four-day periods, during which enemata of simply emulsified eggs and enemata of eggs and salt, or of peptonized eggs, were given, and these were compared with other periods during which no enemata were administered. His results varied greatly. In the first case the figures which he gives, and which refer exclusively to nitrogen, show, with simply emulsified eggs, only 11.9 per cent. of absorption; with the same in a later period, 17 per cent.; with eggs and salt, as little as 7.1 per cent. of absorption; in a later period of the same enemata, 49.1 per cent. absorbed; with enemata of peptonized eggs, 63.3 per cent. In this last-mentioned period the amount of nitrogen absorbed per day was slightly more than 3.5

grammes—a very considerable amount, although, of course, much less than was necessary to maintain a normal equilibrium.

In his second and third cases the results were much more satisfactory.

Huber's results also are difficult to understand, in the first series particularly, and to some extent in the third. The first patient showed almost constantly a nitrogen-retention; the third patient showed a nitrogen-retention throughout three of the periods; and yet, in spite of this, and in spite of the apparently very marked increase in the absorption of nitrogen when enemata were used, the urinary nitrogen showed practically no change. Under such circumstances the patient would normally almost certainly exhibit a marked increase in the excretion of urinary nitrogen; but this did not occur. The fact that it did not is hard to explain, unless there was a technical error; and, again, evidence of a technical error is, we believe, found by a critical inspection of the figures relating to the feces. In the second case, the daily feces in the period *when no enemata were given* varied in weight from 152 grammes to 611 grammes, and the nitrogen (of these entire periods) varied from 0.55 gramme to 5.21 grammes. In the third case, when enemata were not given, the weight of the feces ranged from 313 grammes to 2044 grammes, and the fecal nitrogen from 2.55 grammes to 12.88 grammes. During these periods, in each case, the food was exactly the same. It is, of course, possible that absorption did vary as largely as this, but even if it did, it makes the value of the investigation doubtful; and it seems to us that a frank acceptance of probabilities must unquestionably lead to the conclusion that the feces were not properly collected in the periods to which they belonged. The different periods were of only three or four days' duration, and when absorption is being studied for such a brief time, with a period of another kind preceding and one following directly after, it is especially essential that some method of marking off the feces belonging to each period be used. This is impracticable in studying rectal alimentation, and hence a wide range of error must be reckoned with. In Huber's second and third cases particularly, in which absorption and metabolism seemed especially satisfactory, the possible error is so large that it could readily make the figures

that he gives indicate directly the contrary of what actually occurred. We grant that the same error was operative in our own work. But it must have been far slighter than in Ewald's or Huber's work, for our subjects had been on the same alimentation for five days before, and no comparison was made with any other periods, while Ewald and Huber kept their subjects on different forms of alimentation only a few days, and included all these days in reckoning results. Any error from this cause that occurred in our work could have been due to only one cause—*i. e.*, retention of feces that should have been expelled during the period of study. In such case absorption was even poorer than our figures indicate.

On the basis of Ewald's and Huber's work there has been rather a general acceptance of the statement that eggs are very readily absorbed from the large bowel. We believe that facts by no means indicate that this is generally the case.

Aldor,[6] however, has claimed also that milk, when given in large quantities and when sodium carbonate is added to it, is well absorbed, and constitutes a better enema than any other as yet proposed. It is difficult to understand his reasons for recommending milk so warmly. His actual results were as follows: In the first period the patient whose absorption was investigated absorbed, at most, 38 per cent. of the protein of the milk and 35 per cent. of the fat; while in the second period he absorbed only 12.6 per cent. of the protein and less than 1.5 per cent. of the fat. These figures are scarcely convincing of the value of large milk-enemata.

Other investigators of the subject have not had as satisfactory results with either eggs, milk, or predigested foods.

Czerny and Lautschenberger,[7] investigating a case of colonic fistula, reached the conclusion that only about 6 grammes of protein were absorbed by the large bowel in a day. Markwald found that "peptones" were irritating to the colon, and that the irritation prevented free absorption; and he also found that egg-albumin, with or without salt, was but little absorbed. Plantenga[8] is also referred to as having obtained very unsatisfactory results, but his article could not be secured by us. Kobert and Koch[9] found in a patient with a fistula at the ileocæcal junction that very little of either eggs or "peptones" was absorbed.

Brandenberg[10] investigated the usefulness of nutrose as a rectal aliment, and found that at most about 40 per cent. was absorbed. He also gave enemata of eggs and milk, and found that of 16.5 grammes of nitrogen 10.36 were not absorbed. He reckoned from this that the absorption of eggs was at most about 50 per cent., and of milk still less.

Strauss[11] confirmed Brandenberg's results as regards nutrose. He states that he also administered eucasin per rectum to a patient with œsophageal fistula. His figures could not be given absolutely, because some of the fecal nitrogen might have come from the previous period; but he thinks that at most 40 per cent. of the eucasin-nitrogen was absorbed.

Plantenga,[12] in a second communication, contributes some investigations concerning the effect of somatose injected into the lower bowel of a dog. He found that only 10.8 per cent. to 24.1 per cent. was absorbed in six different investigations.

Finally, however, it may be mentioned that Kohlenberger[13] claims that all of Witte's "peptone" was absorbed when injected per rectum. He bases his statement purely upon the fact that lavage after the administration of albumoses per rectum brought forth nothing that gave the biuret reaction. This method is wholly unsatisfactory, as it entirely overlooks both the influence of bacteria and the possible conversion to amido-acids, etc., by digestive ferments.

As to the fats, the story is a much simpler one. Everyone that has worked on the question of the absorption of fat from the rectum has reached unfavorable conclusions, with the exception of Hamburger, whose work was theoretical rather than practical. Munk and Rosenstein,[14] investigating a case of fistula of the thoracic duct, injected fat per rectum, and found that the increase of fat in the chyle indicated an absorption of only 3.7 to 5.5 per cent. Plantenga[8] is referred to as having had similar results by studying the feces. Strauss[11] found that only about 10 per cent. of fat was absorbed. Aldor,[6] as stated above, found an absorption of 33 per cent. of milk fat in one period; while, with the same patient and the same enemata, in another period soon after the first-mentioned one, he found an absorption of less than 1.5 per cent. Deucher,[15] whose work on this question has been the most exten-

sive of any except that of Hamburger, found that the maximum absorption of fat per day was about 10 grammes, even when circumstances were favorable. The absolute absorption per day which he found varied only from 4.5 grammes to 9.9 grammes. He thinks that there is little value, if any, in giving the enemata frequently or in administering large amounts.

Directly contrary to these results are those of Hamburger,[16] who, from his experimental work on animals, considers that the large intestine absorbs quite as much fat as the small intestine, provided the fat is administered in proper emulsion. He says that the use of sodium carbonate or of sodium chloride solution in preparing an emulsion is wholly unsatisfactory, because these salts are soon absorbed, and the emulsion is consequently soon destroyed. He found that a solution of soap (*sapo medicatus*) was well adapted to this purpose. The soap was absorbed, and during the absorption was partially changed into fat, but the emulsion was well maintained, and the fat in the soap emulsion was remarkably well absorbed. As stated, however, these results must be considered to be theoretical rather than practical. The work was carried out under purely experimental conditions, and, further, it is questionable whether a soap-enema would be tolerated by the human bowel. Hamburger's method has not been tested with human beings. While it is worth trying, we must for the present consider that fats are absorbed only in very small amounts when administered per rectum, and, in contradiction of his views, it must be remembered that numerous investigators worked with the best of natural emulsions—*i. e.*, milk and egg-yolk.

We turn now to a brief consideration of the question of the carbohydrates. Until recently the general opinion has been that sugars are very quickly and freely absorbed from the large bowel; and that starches are slowly transformed into sugars, and in large part absorbed. Strauss,[11] indeed, has gone so far as to say that he has maintained patients in good condition, for one, two, or nearly three months, with enemata consisting very largely of sugar. The great difficulty with the use of sugar, in the experience of most clinicians, has been that it tends to cause marked irritation of the bowel, and soon interferes with the use of enemata. Strauss claims that 40 or 50 grammes of glucose can be used in an enema, and

the use of these enemata continued for a month or more without producing, in a large proportion of cases, any irritation. He seems to stand nearly alone in this view.

The work of investigators on the absorption of carbohydrates has been done almost solely by injecting carbohydrates into the bowel, and determining that little if any sugar or starch is subsequently found in the bowel-movement. It is difficult to understand why such a method of work has been considered satisfactory, as it is certainly possible for a large portion of the sugar, and even of the starch, to have been broken up by bacteria and to have been passed as products of bacterial action or absorbed as such, and thus to have furnished little or no nutriment to the patient. This fact has recently been strongly insisted upon by Reach,[17] and very important testimony that this probably often does occur was offered by him. He administered various sugars by mouth, and at other times the same amounts and kinds per rectum, and determined their effect upon the respiratory quotient, considering this method to be a direct and positive means of determining whether the carbohydrates used had had any influence upon the actual tissue-processes. He noted the usual increase in the respiratory quotient when the carbohydrates were given by the mouth. When administered per rectum he found little or no influence upon the respiratory quotient. He insists that carbohydrates in general are probably but little absorbed as such from the large bowel, and that the previous teaching has been the result of imperfect methods of study.

It was with the same thought in mind that we undertook in our cases a determination of the urinary sulphates for several days during the course of the absorption experiments. The figures obtained were as follows:

CASE I.

February 2d.	Preformed SO_3	1.091
	Conjugate "	0.175
	Ratio 1 to 6.2.	
February 3d.	Preformed SO_3	1.227
	Conjugate "	0.144
	Ratio 1 to 8.5.	
February 4th.	Preformed SO_3	0.806
	Conjugate "	0.162
	Ratio 1 to 4.9.	

CASE II.

February 7th.	Preformed SO_3	1.8838
	Conjugate "	0.4819
	Ratio 1 to 3.9.	
February 8th.	Preformed SO_3	2.0173
	Conjugate "	0.5536
	Ratio 1 to 3.6.	
February 9th.	Preformed SO_3	1.3854
	Conjugate "	0.4197
	Ratio 1 to 3.3.	
February 10th.	Preformed SO_3	1.5549
	Conjugate "	0.6555
	Ratio 1 to 2.3.	

The ratio of the preformed to the conjugate sulphates is of little consequence, particularly when so little food is being absorbed as in these cases. The absolute figures for the conjugate sulphates are, however, important. They show in Case I. about normal values; or, more correctly, if it be remembered that the patient was taking very little food they show that she was excreting a somewhat excessive amount of the conjugate sulphates. Case II., however, was excreting an amount that would be from two to three times the normal, even in a person on a full, ordinary diet. It is, therefore, probable that in Case I. an abnormal amount of putrefaction was taking place in the intestine, and it is certain that in Case II. an exceptionally high degree of putrefaction was present.

These figures are of interest and, we think, of importance if they are compared with the results of the study of absorption in the same cases. Case I., with but moderate evidences of putrefaction, was absorbing badly. Case II., with very active evidences of putrefaction, was absorbing considerably better. These results, particularly when considered in connection with the work of Reach, make it seem highly probable that the putrefactive processes going on in the intestine when rectal alimentation is used are frequently, perhaps always, excessive, and that a certain part of what has previously been considered to be absorption of food is bacterial decomposition of food. As far as the fats are concerned, under such circumstances a very considerable portion might be absorbed as either non-nutritious or actually toxic sub-

stances, and another portion, also considerable, might be excreted in the bowel movements in a form which would not appear in the ether extract. The amount of fat found in the feces, as compared with the amount administered, would then be altogether too favorable an indicator of absorption.

In the case of the proteid, since absorption is reckoned from the nitrogen, the influence upon figures obtained for absorption would be comparatively slight. It is possible, however, that the absorption would seem too great in this case also, as some of the nitrogen might, as the result of bacterial decomposition, be passed as ammonia, etc., and thus be lost. This portion is probably of small moment; but, on the other hand, it is wholly probable that a considerable portion of the nitrogen that we have previously recognized as absorbed nutriment has really been absorbed as bacterial products; most of these would be of little or no value in nutrition, and many are to some extent toxic.

If, then, the general results of various investigators be collated, it will be seen that occasionally, as in Ewald's case and in a portion of the different series described by Huber, absorption of albumins seems to be so satisfactory that a very large percentage of what is administered actually furnishes nutriment; but Ewald's case must be considered an extremely exceptional one, and Huber's work is only partially favorable, and is subject to criticism. The work of other investigators, which is, collectively, decidedly more extensive than that of Ewald and Huber, indicates that egg-albumin, whether given plain or predigested, with or without salt, is, in most instances, not more than half absorbed, and frequently much less than this; that preparations such as somatose, nutrose, and eucasin are still more imperfectly absorbed; and that, as a rule, albumoses (so-called peptones) are irritating to the bowel if given in such quantity as to furnish any considerable amount of nutriment, and are also not usually more satisfactorily absorbed than the other substances mentioned.

As to the fats, there is pretty general agreement with the statement of Deucher that the limit of absorption in one day is about 10 grammes. In exceptional instances, as in one of our cases, decidedly more than this is apparently absorbed. The question of the carbohydrates is as yet unsettled, but Reach's work demon-

strates that too much value has been placed upon this class of food, and that it is probable that a large portion of even the comparatively small amounts that can be administered per rectum is not absorbed.

If all these factors be taken into consideration it will be found that under ordinary circumstances the bowel can scarcely be expected to absorb an amount of food in twenty-four hours equal to more than six or seven hundred calories, and that frequently the amount is very decidedly below this. If, further, the factor of bacterial decomposition, which makes the results seem more favorable than they actually are, be considered, it must be recognized that even the amount mentioned is more than is really provided for the tissue needs. Since this is the case, it is perfectly evident that unless circumstances are exceptionally favorable the use of rectal enemata furnishes far less food than is sufficient to maintain the patient in nutritive equilibrium, and that, indeed, in very many instances the patient is, when nourished exclusively per rectum, relatively little removed from a condition of simple starvation.

Granting the correctness of this conclusion, there are certain facts which must be explained. It is frequently stated, on the basis of clinical observation, that patients can be maintained for a short, sometimes for a long, period in a good condition of nutrition upon exclusive rectal alimentation. The reasons that such statements are made are several: In the first place, in the large majority of cases they are made merely as the result of superficial observation and on the basis of the patient's statement that the enemata relieve hunger. They are often unaccompanied even by the weighing of the patient or by inspection of the amounts passed per rectum; and in such instances they have no real scientific value.

But there is one real factor, that is, as a rule, overlooked. In the article previously mentioned one of us insisted upon this factor as being of much importance, and it is especially emphasized by Strauss as being perhaps the matter of greatest importance in the use of rectal enemata. This is the absorption of water from the enemata. Maintenance of the weight exhibited at the beginning of the use of enemata, and even an increase in weight over a considerable period, may unquestionably, in a good many cases in

which rectal enemata are indicated, be due not to the absorption of food, but to the absorption of water. Patients who demand this form of alimentation, as, for instance, those with pyloric or œsophageal obstruction, intractable vomiting, and the like, are now generally recognized to be frequently suffering from lack of fluids quite as much as from lack of food; often even more. In such a case the administration of nutritive enemata or of fluids alone meets one of the most important indications in the case by furnishing fluids to the tissues; this relieves the patient's general symptoms very largely, and not infrequently causes him to put on a considerable amount of weight. In such cases, however, it must be recognized that the improvement is not due to the food, but to the water.

Granting, however, that the results that are considered extremely favorable are at times due to mere superficial observation, and at times to absorption of water rather than of food, it must still be recognized that a number of clinicians whose experience is wide and whose observation is accurate state that they have occasionally maintained patients in fairly good nutritive equilibrium for quite long periods with the exclusive use of rectal enemata. An explanation of such statements must be offered, and an explanation quite in consonance with what we have previously said in this article can be offered if we consider some of the more recent views concerning the variations in the absolute food-demands of the system under varying circumstances. It was taught for years, on the basis of Voit's work, that a normal person at rest — as these cases, of course, practically always are—demands about 1.5 grammes of albumin to each kilo of body-weight; and at the same time he demands that the total caloric value of his food should be about 40 per kilo, in order that he should not lose tissue. If this were absolutely the case under all circumstances we should necessarily be driven to the conclusion that in studies of the nutritive value of rectal enemata, either the results of investigators must be entirely wrong or the observations of those clinicians who claim that a nutritive balance is sometimes maintained must be wholly inaccurate.

Voit, however, modified his own statement later, and showed that about two-fifths of the amount mentioned was sufficient to maintain

a nitrogen equilibrium; and a series of other investigations, among which those of Rubner, Hirschfeld, Klemperer, Kumagawa, and Breisacher are prominent, demonstrated clearly that a tissue loss can be avoided if the caloric value of the food be kept high, when as little as 0.9 gramme to 0.4 gramme of albumin per kilo is being taken. More recently Siven and Albu have shown still more striking results, persons in normal condition maintaining a nutritive balance on an equally small amount of nitrogenous food when the calories were reduced to the normal point or even below the normal. Perhaps the most striking instance in which this has been shown by figures is the case recently reported by Albu.[18]

The person investigated was a female vegetarian, who for six years had lived exclusively upon a diet which had varied little from that which she was taking at the time of the investigation. It then consisted of 225 grammes of carbohydrate, 36.44 grammes of fat, and only 5.46 grammes of nitrogen, the woman weighing 37.5 kilos. The nitrogen metabolism was determined while this diet was being continued, and it was found that the woman was maintaining a nitrogen balance, and that her weight also remained practically constant. Her nitrogen absorption per day was only 3.30 grammes, which was equal to only 0.56 gramme of albumin per kilo. At the same time her total caloric absorption was but 33.8 per kilo. In spite of this the woman, even while doing moderately taxing intellectual work, maintained a nutritive balance, as was stated.

A striking collective statement of this question appeared recently in an interesting paper by Bernert and Steyskal.[19] The authors direct special attention to the fact that the minimal food intake consistent with the maintenance of a nutritive equilibrium has generally been placed far too high. They believe that it has been proved that it is possible to reduce the intake to 0.48 gramme of albumin per kilo, and at the same time to have the total caloric value of the food as low as normal, probably even lower, and yet nutritive equilibrium may be maintained. They, however, emphasize the fact that in order to accomplish this it is usually necessary that the patient should have gradually accustomed himself to a reduction of his food intake. It is certain that if the food is suddenly reduced from a large amount down to a very small

amount the patient will, for the time being, be thrown into a condition of practical starvation; if, however, it is gradually reduced he will gradually reduce his metabolic demands, and this can be carried down to a strikingly low point.

This is a brief explanation of the fact that patients may occasionally be maintained at a nutritive equilibrium with the use of rectal enemata, even though rectal enemata, at best and even if entirely absorbed, cannot provide a normal amount of food. The fact that man can reduce his absolute demands to so low a point would at first seem to indicate that we have been wrong in insisting that there is but a limited value in the use of rectal enemata. It does demonstrate that they have importance, for if a patient can be maintained in nutritive equilibrium, even though the point at which equilibrium is reached has been brought far below the normal by prolonged subnutrition, a very decided gain over any condition in which there is tissue loss has been made. It should, however, be very definitely realized, on the other hand, that a mere maintenance of equilibrium at the minimal point, or at a point approaching the minimum, is far from being an ideal condition, and is really only a makeshift. The reduction of food to the lowest point consistent with the maintenance of an equilibrium means that the patient is being put into a condition of subnutrition; and the mere fact that he does not lose weight under such circumstances does not by any means indicate that he is being normally nourished. Even though we have learned that a balance can be maintained on far less food than Voit's figures indicated, we must at the same time hold to the fact that his figures do indicate the amount that a normal person, living normally, takes. Hence, while a reduction of the quantity of food very considerably below this point, if gradually undertaken, may be consistent with the maintenance of a constant weight and of apparently fairly good health, such reduction must always be considered to mean a condition of subnutrition, and the more marked the reduction the more severe the subnutrition.

When this view is applied to the question of the use of rectal enemata we must realize that even if the utmost limit of success with rectal enemata be attained and a patient be kept from losing weight, we are at best not nourishing him properly. If as much

success as this be obtained, and it is in the case at hand merely a question of inability to take food by the mouth for a limited period, it is, of course, proper to continue rectal alimentation as long as needed. We believe, however, that such a degree of success is but rarely attained. If, on the other hand, it is a question of attempting to maintain a patient's nutrition and to improve it, in preparation for operation, in such cases as pyloric and œsophageal obstruction, it is perfectly evident that the limits of success are very narrow; in practically all cases it is impossible to improve nutrition in this way to any notable extent, and the chances are large that the patient will lose decidedly rather than gain. If we hope to do any good by operative procedures we should not delay long with rectal alimentation, but should intervene as soon as practicable. In other cases in which food by the mouth is withheld because of the danger of hemorrhage, etc., we must realize that the patient is usually being partially starved, and if a critical occasion arises we must consider well the relative importance of partial starvation and of the dangers associated with the administration of food.

In conclusion we would say, briefly:

Rectal alimentation in exceptional cases provides enough food to the tissues to prevent tissue loss. Even in such favorable cases the best that can be done is to keep the patient from losing ground when he is already in a condition of decided subnutrition.

Usually food administered per rectum is very imperfectly absorbed, and consequently rectal enemata, as a rule, supply only a very small part of the amount of food necessary in order to maintain a nutritive equilibrium.

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CONCERNING THE ACCURACY OF PERCENTAGE MODIFICATION OF MILK FOR INFANTS.*

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The most distinctively American principle of pædiatric practice is the accurate modification of milk for infants by percentage formulæ. The scientific propriety of this method needs no demonstration, and it is used in this country by almost all careful practitioners who have any skill in the feeding of infants.

In spite of the general use of percentage feeding, however, there is no record of any comprehensive study of the actual composition of the milk mixtures made by this method; and, except for Wentworth's analyses, which relate solely to laboratory modifications, there has been no extensive attempt to determine whether the mixtures actually correspond closely with the prescribed formulæ. That is, it has been customary to order a certain formula, and to proceed as if the infant were getting that formula, the accuracy and conscientiousness of the person making the modification being usually taken for granted; while the fat and proteid content of the milk and cream are considered to correspond to certain accepted average figures. In other words, the method is known to be theoretically reasonably accurate, the practical results have usually been taken on faith. A conspicuous exception to this laxity of method is found, in Philadelphia, in those that use "certified" milks; for the chemical constitution, as well as the bacterial content of these milks, is kept constantly under control by a commission of disinterested physicians. A further important method of avoiding inaccuracies is in the use of laboratory modifications. Certified milks are, however, not available in many cities, and are never available in the smaller towns or in the country, except when a city that has a supply of such milks is not far distant and the family can afford the very considerable expense of having certified milk shipped to them—a course that is impracticable in most instances. Laboratory modifications, also, are used only by a somewhat limited number of physicians. Hence, in the majority of instances the statement that the composition of the milks and creams used is unknown, is correct; for few practitioners determine for themselves even the percentage of fats.

We have undertaken a series of chemical examinations of milk mixtures, with the purpose of learning whether there are any important errors in the percentage method of feeding, as it is usually carried out; and if errors exist, to determine their sources and, if possible, the manner in which they may be corrected. Our purpose was to get some information concerning the results of several of the most important methods of percentage modification, and to determine which are the best and which are the least reliable. In carrying out this purpose we have analyzed 88 different milk mixtures.

Wentworth's figures relate solely to laboratory modifications, and throw no light upon the accuracy of home modifications. He gives a few analyses of modifications made by himself; but, since they were made up from milks and creams that he analyzed himself, the correctness of these modifications depended solely upon the care that he used in measuring and mixing, and they do not indicate the conditions that one would find in practice with milks and creams of more or less doubtful composition and with modifiers that may vary from extreme intelligence and devotion to utter stupidity and lack of conscience.

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The two important sources of error that at once occur to one have already been indicated. First and foremost is, of course, variation in the composition of different milks and creams; particularly in the fat content of the creams. We have, for instance, found ordinary market creams, sold as "20 per cent. cream," to be as low in fat as 13 per cent. and as high as 26.5 per cent.—a variation of over 100 per cent. from the lowest point to the highest; and this, of course, entails a similar variation in modifications made from these creams. We have also known the fat content of milk to range from 2.5 per cent. to 8.8 per cent. in ordinary market milk—a matter of equally serious importance when whole milk or top milk is used in modifications. The proteid is subject to far less marked variations in unadulterated milk, but variations do occur. We have seen a range, within a brief period, from 2.85 per cent. to over 4 per cent. in mixed milk from one dairy of extremely good general quality; and the effect of such a variation, or of even a somewhat less pronounced one, upon a modification is at once evident. The proteid of cream is sometimes said to be less variable; but this is not an accurate statement, for marked variations occur, and especially with decided variations in fat percentage, there are usually coincident contrary variations in the proteid.

The other chief source of error in modifying milks is undoubtedly to be found in the person who does the measuring and mixing. That carelessness may often be discovered if looked for, every one will admit. That confusion and lack of understanding, even in persons of the more intelligent classes, is an equal source of error, will, we believe, be shown by our figures.

In order to meet these chief opportunities for error and to determine their effect, we have analyzed milk-mixtures made by supposedly capable persons and by others of unknown reliability; and also mixtures made, on the one hand, from milks and creams known to be of reliable chemical composition and, on the other, of ordinary market milks and creams. We are indebted to Dr. Griffith, Dr. Hamill, Dr. Westcott, Dr. Hand, Dr. Ostheimer, and Dr. Davisson for furnishing us with a number of the samples of mixtures from hospital and private patients.

In a general way, our analyses fall into the following four series:

1. A series of home modifications made from milks and creams of known composition.

2. A series of home modifications made from ordinary market milks of unknown composition.

3. A small series of modifications made from Dr. Ladd's card, chiefly using top milk and the lower fat free milk.

4. A series of laboratory modifications.

In the first and second series, the modifications were made by persons of varying capability. In one or two instances, the infants' fathers, who are physicians, modified the milk themselves. Usually it was done by a trained nurse or by the mother, the intelligence of the latter varying, in the different instances, from a high degree down to that of a stupid dispensary patient. The third series we modified ourselves, chiefly to test the accuracy of modifications made from top milk and the underlying, supposedly fat free, milk.

In all cases we determined only the fat and the proteid. The sugar is of less consequence in digestive disturbances, and, furthermore, the amount is more directly under our control, since we do not use a natural product containing a varying percentage of sugar, as we do with the fat and the proteid, but chiefly dry milk sugar. The fats and the proteid are the important constituents, and these we estimated accurately.

The method used for the proteids was determination of the nitrogen by the Kjeldahl-Argutinsky method, the value obtained being multiplied by the factor 6.38. This gave the proteid figures. We always used the mean of two control estimations. The reading of the titration in the control estimations rarely varied 0.1 cc. ($^4/_{10}$ normal solution).

The fats were estimated chiefly by the Leffmann-Beam method, frequently controlled by ether extraction. In a few instances, the latter method was used alone. It is important to note that in using the Leffmann-Beam method we, in the first place, always warmed the mixture to be analyzed to 15° C., and used a carefully calibrated pipette in measuring. We always used exactly 9 cc. of concentrated sulphuric acid of constant strength; and the dilute sulphuric acid used was always of constant strength. Two control estimations were frequently made, and always corresponded within 0.05 per cent.; and the result can practically not be read more accurately than this. If a new stock of concentrated or dilute sulphuric acid or of the hydrochloric acid amyl-

alcohol mixture became necessary, the accuracy of this new stock was always tested by making control ether extractions. The ether extractions were always made in the Soxhlet apparatus after drying on asbestos (Babcock method).

In the following tables, we have introduced on the left the percentages of fat and proteid supposedly contained in the milk mixtures; on the right are those actually determined to be present. The letters L-B indicate the Leffmann-Beam process; eth. ext. indicates ether extraction.

Series I. contains mixtures made from certified milks:

SERIES I.—CERTIFIED MILKS.

Calculated.			Determined.		
			Fat.		
No.	Fat.	Proteid.	L & B.	Eth. Ext.	Proteid.
1	3.	1.50	3.2		Sample too small for estimation.
2	3.8	2.16	3.0	2 965	2.2151
3	4.16	1.50	4.4		1.3396
4	6.6	1.59	5.3		1.57
5	6 6	1.59	5.0		1.542
6	3.0	1.50	2.82		1.6335
7	3.0	1 50	2 80		1 555
8	3.1	1.60	2.85		1.429
9	3.1	1.60	2.80		1.597

Series II. were modifications of ordinary market milks and creams. The first ten were modified at the patients' houses, in all cases by the mothers. The remainder, the larger number, were modified in children's wards in hospitals by nurses especially trained in the care of children.

Series III.—Chiefly modifications made by ourselves from Dr. Ladd's card. Nos. 52 to 55 inclusive were made by using Baner's formula.

SERIES II.—MARKET MILKS MODIFIED AT PATIENT'S HOUSES.

Calculated.			Determined.	
No.	Fat.	Proteid.	Fat L. & B.	Proteid.
10	3.0	1.0	3.4	0.7146
11	4.0	2.0	5 6	1.375
12	4.0	1.0	4.3	0.857
13	2.7	1.8	2 9	1.75
14	2.5	1 0	2.3	1.071
15	4.0	2.0	4 5	1.804
16	4.0	2.5	5.4	2.006
17	3.5	2.5	3 95	2.009
18	3 0	1.0	2 8	1.036
19	2.0	0.75	2.35	0.7146

MARKET MILKS MODIFIED IN HOSPITALS BY TRAINED NURSES.

Calculated.				Estimated.		
				Fat.		
No.	Date.	Fat.	Proteid.	L & B.	Eth. Ext.	Proteid.
20	1.16	4.	2	3.6		1.822
21	1.16	3.56	1 25	2.4		1.750
22	1.17	3	1	2.4		.7503
23	1.17	4	2 25	2.9		1.786
24	1.20	4	2	2.4	2.28	1.6792
25	1.20	3	1.25	2.4		1.2147
26	1.20	4	1 25	2.7		1.6335
27	1.20	3	1		2.802	.9646
28	1 20	3	1 25		1.806	1.036
29	2.2	4	2.5		2.72	2.1794
30	2.16	4	2	3.2	3.18	1.8935
31	2.16	3	1	2.2	2.24	1.036
32	2.19	4	2	3.2	3.4	
33	2.19	2	0.5	1.30	1.28	
		3.5	1.25	1.9		1.435
34	3.12	3	1	4.3		.786
35	3.12	3.5	1.5	4.5	4.42	1.2862
36	3.12	2.5	1.5	3.1		1.1432
37	3.17	2.5	1.5	3.2		1.2861
38	3.19	3.5	1.5	4.2		1.1432
39	3.19	3	1.5	3.8		1.1432
40	3.19	4	1	3.8	3.75	.8574
41	3.20	2	3	6		2.286

Series IV.—Laboratory mixtures ordered for this purpose to be sent to a city address. A number of specimens of each modification were examined, since this would lead to more proper conclusions, whether favorable or unfavorable, than would the examination of single specimens. The percentages were run up rapidly, for the purpose of testing the results.

In interpreting these results, one must first realize clearly that *absolute* accuracy can never be demanded or expected in the modification of milk. Consequently, if figures obtained by the chemical examination of modified milks occasionally vary a few tenths of one per cent. from the calculated figures, and only a few tenths, one is not justified in condemning the mixture in any way; on the contrary, if these variations are only occasional, the mixtures should be considered to be excellently made. This statement is based upon the well-known fact that the composition of milk and cream varies more or less widely, even when the product of one excellent dairy is used. Therefore, modifications made from milk and cream will vary somewhat, no matter how great the care used in preparing them. It is common knowledge that the fat of whole milk, even when from a constant source, may vary widely within

a short time, and even from day to day. To quote our own results, we have, among others, several series of figures from estimations of the milk from one excellent dairy, made for days or weeks at a time, which show variations as marked as from 3 per cent. to 5.5 per cent. of fat within a very few days; and these figures are not at all remarkable. The Milk Commission of the Philadelphia Pædiatric Society allows the fat of the milks that it passes as "certified" to vary between 3.5 per cent. and 4.5 per cent.; and yet, although these milks are produced under conditions that are as nearly ideal as it is practicable to make them, the fats not infrequently pass these limits slightly, and require reexamination. An error of consequence would result from this in mixtures made from whole milk; and when fat free milk is used and the fat is obtained entirely from cream, an error of as much as 0.4 per cent. is possible in modifications with fairly high fat percentages. The fats of the Philadelphia certified creams are allowed to vary between 14 per cent. and 18 per cent. and do occasionally vary to this extent, even though they also are produced under most excellent regulations.

SERIES III.—MODIFIED BY THE AUTHORS.

No.		Calculated.		Determined	
		Fat.	Proteid.	Fat	Proteid.
42	Certified milk, "B" 4/12, 1903, presumably 10 per cent. cream, twelve hours standing. Determined fat percentage of cream, 7.6	2	1	1.2	.912
43	Same milk, 4/13	2	1	1.6	.928
44	Same milk, 4/14, 1903, presumably 10 per cent. cream. Milk stood ten hours. Fat percentage 11.1	3	2	3.25	1.929
45	Certified milk "A," presumably 10 per cent. cream. Milk stood twelve hours. 4/12, 1903	2	1	1.8	.9746
46	Same, 4/14, 1903	3	2	3	1.8578
47	" 4/15, 1903	4	2	3.9	
48	" 4/16, 1903	3	2	3	1.786
49	" 4/17, 1903	2	1	1.85	1.0003
50	" 4/18, 1903	3	2	3.15	1.9649
51	Milk of unknown fat percentage stood eleven hours, giving supposedly 10 per cent. cream	3	2	2.65	1.826
52	Certified (fat-free) milk and 16	2	1	1.8+	1.0003
53	per cent. certified cream.	3	2	3.1	2.036
54	Baner's formula	4	2	3.8+	1.929
55	Unknown market milk and supposed 16 per ct. cream. Baner formula	3.5	1.25	1.9	1.435

SERIES IV.—LABORATORY MODIFICATIONS.

No.	Calculated.		Determined.		
	Fat.	Proteid.	Fat. L & B	Fat. Eth. Ext	Proteid.
56	1.5	.75	1.3		.822
57	1.5	.75	1.3		.8217
58	1.5	.75	1.4		.8217
59	1.5	.75	1.2	1.3	.7503
60	1.5	.75	1.3	1.3	.7146
61	1.5	.75	1.1		.8574
62	1.5	.75	1.45		.8217
63	1.5	.75	1.30		
64	1.5	.75	1.50		.8574
65	1.5	.75	1.50		.9288
66	2.	1.25	2 2		1.2147
67	2.	1.25	1.9		1.2504
68	2.	1.25	1.9		1.2147
69	2.	1.25	2.4		1.2861
70	2.	1.25	1.6		1.036
71	2.	1.25	1.7		1.2147
72	2.	1.25	1.9		1.0717
73	2.5	1.50	2.4		1.2504
74	2.5	1.50	2.6		1.3891
75	2.5	1.5	2.6		1.2861
76	2.5	1.5	2.6		1.4098
77	2.5	1.50	2.2		1.143
78	2.5	1.50	2.6		1.3
79	3.5	1.75	3.55		1.6335
80	3.5	1.75	3.3		1.6335
81	3.5	1.75	3.3		1.544
82	3.5	1.75	3.25		2.2151
83	4.5	1.75	3.9		2.1794
84	4.5	1.75	4.2		1.544
85	4 5	1.75	3.5		1.536
86	4.5	1.75	3.8		1.7049
87	4.5	1.75	3.9		1.557
88	4.5	1.75	3.7		1.562

As to the proteid, it is often said that this varies but little—and this is true, as compared with the fat; but it varies enough to make an error of several tenths of one per cent. possible in modifications of moderate strength. The Philadelphia milk commission allows a variation of one per cent. in proteid, as well as in fat; and no narrower limit could be maintained. As to excellent market milks, we have figures for several hundred estimations, made by us, that show even wider variations. Among these figures are many that were made day after day in metabolism experiments; and these show variations even as great as 1.1 per cent., on two successive days, with thoroughly mixed milk from the same dairy.

It is evident, then, that in the modifications themselves, if they are of moderate strength, an extreme variation of as much as 0.3 per cent. in the proteid, and certainly quite as large a variation in the fat, may be due purely to uncontrollable variations in the milk and cream; and such variations are not subject

to criticism. Again, it may be properly said that a reasonably conscientious and careful modifier may often make an error of as much as one drachm in measuring, and this would often in twenty-ounce mixtures increase the fat error as much as 0.1 per cent. If a similar error were made in both milk and cream, it would add at least 0.05 per cent. to the total proteid error; and this would make the possible excusable error with the proteid as much as 0.35 per cent.

We wish it to be clearly understood that the statement that has just been made is not intended to indicate that wide variations of fat and proteid are constantly occurring, even in carefully prepared modifications. Such a wide range is permissible only in mixtures ranging from a moderate strength up to a high formula, and not in very low formulæ; and it is never permissible for them to occur very frequently. The latter would mean that poor dairy products were being used or that the modifier had been careless. We do mean, however, that in formulæ with fats or proteids running as low as 1.25 per cent. there may be an occasional entirely excusable error of fully 0.3 per cent. in either fat or proteid. In lower modifications, which are the most important from this standpoint, the excusable error would decrease in accordance with the greater dilution; in higher modifications, a somewhat larger error may be excusable. Errors as marked as this should occur only occasionally, because extreme variations in good milk are only occasional. The fats, however, show a wide range more frequently than do the proteids; consequently, moderate errors in the fats may be expected with some frequency with mixtures containing high or moderately high fats. The fats of milk or cream may go either up or down; consequently the error in the modification may do the same. The proteids not only do not vary so frequently, but when they do vary they will usually be below what they are calculated to be, because the figure generally used in computing the formula for proteid is 4 per cent., and the actual proteid is usually somewhat below that point and is much more likely to go still lower than to go above 4 per cent.

Considered from this standpoint, our figures show the following facts:

The first series of home-modifications, made under favorable circumstances—*i. e.*, from certified milks and creams and by persons of intelligence—show satisfactory accuracy, as far as the proteid is concerned, the widest variations above or below the prescribed formula being slightly within 0.2 per cent. The fats vary widely, there being errors of 0.8 per cent., 1.3 per cent., and 1.6 per cent. in this small series. These errors were almost entirely due to the modifiers, who were in these cases usually intelligent mothers. We analyzed the creams used in the last two instances and found them to be almost exactly of the percentage that they were supposed to be.

In the second series, the home modifications made from market milks and creams, the results are extremely erratic. The proteids vary from the prescribed formulæ as much as 0.8 per cent. downward, and 0.4 per cent. upward; while it is rare for the fats to come within 0.5 per cent. of the amount prescribed, and in a large proportion of instances the error is so large that the actual result scarcely shows any resemblance to the formula aimed at. The error in the fats is certainly due, in large part, to the cream used; and to some extent, to the milk. We analyzed the milks and creams used in the hospital modifications and the figures for the fat in the cream used in Nos. 20 to 33 of this series show 13.75 per cent., instead of the supposed 20 per cent.; and all these figures for fat in the modifications are too low. On the other hand, the fat of the cream used in Nos. 34 to 41 ran at 21.5 per cent. and 22.2 per cent., instead of 16 per cent.; and the fat of the milk, at 6.2 per cent. and 8.8[1] per cent., instead of 4 per cent. In all these modifications, the fat is too high. The results with the proteid are also partly due to the fact that the proteid of the milk and cream was running low; this is particularly true of the second set, in which the milk proteid was at one estimation 2.41 per cent.

The results cannot, however, be attributed entirely to variations in the milk and cream. The dates on which these modifications were made have been given, in order to demonstrate that the modifier was at fault. They show this clearly. On individual days, when exactly the same milk and cream was used in the several modifications made on that day, it may be seen that the different mixtures showed marked errors of very differ-

[1] It is probable that this "milk" was, in part at least, old cream watered, with perhaps some separated milk added. This is indicated by the very high fat, the low proteid (2.4 per cent.), and the fact that a bacterial count showed enormous numbers of bacteria. It came from a supposedly reliable source, but the milk supplied the public from the same source contained on several examinations about 3.6 per cent. of proteid and 4 per cent. of fat.

ent kinds. On January 20th, for instance, a supposedly 4 per cent. fat-mixture contained 2.7 per cent.; while a supposedly 3 per cent. mixture at the same time contained 2.8 per cent., and another 3 per cent. mixture contained 1.8 per cent. On March 19th, a supposedly 4 per cent. and a supposedly 3 per cent. mixture contained an equal amount of fat—3.8 per cent. There are several similar examples of the same thing. On March 20th, indeed, a mixture of odd proportions (2.6.3), which was ordered purely for testing the accuracy of the modification, showed 6 per cent. fat, instead of 2 per cent. As to the proteids, on January 16th, a supposedly 1.25 per cent. mixture contained 1.75 per cent.; on January 20th, a supposedly 2 per cent. proteid showed 1.67 per cent.; on the same date, a proteid calculated at 1.25 per cent. contained 1.63 per cent., another calculated at 1.25 per cent. was found at 1.03 per cent. The proteid of the milk used in the last-mentioned modifications we have repeatedly estimated and found to be regularly between 3.4 per cent. and 4 per cent.

The variations in the mixtures were undoubtedly due to the modifier, and were the result of either carelessness or confusion. Carelessness probably played a part, but we believe that a lack of clearheadedness had more to do with the results. The figures that we have referred to in detail are all from modifications made by nurses especially trained in the care of infants and children. We know the nurses that did this work, and know them to be reasonably conscientious and trustworthy; and yet the results are attributable to them. They can scarcely be considered to be due to anything but lack of clear understanding and to confusion in measuring off the various constituents of the mixtures. This is a matter of importance that will be briefly referred to later.

As to the third series, the time at our disposal prevented our examining many specimens; and we have, therefore, little right to speak concerning the accuracy of mixtures made from top milk. Dr. Ladd's extremely convenient card, with its formulæ ready made, is, in itself, evidently entirely accurate. When the top milk contained about the amount of fat that it was supposed to contain (Nos. 44 to 50), the mixtures corresponded closely with the calculated formulæ. With the first two mixtures made from certified milk "B," however, (Nos. 42 and 43) the results for fat (1.2 per cent. and 1.6 per cent., instead of 2 per cent.) show decided error; especially the first.

These results, few as they are, show that with one milk, such as certified "A," the results by the top milk method may be excellent over a series of days; while with other milk of fine quality the result may be decidedly erratic. The results that have been obtained by different investigators of the fat content of the top milk are somewhat confusing. Several authors agree that the fat content is reasonably constant, but give somewhat different figures for the same quantity of top milk. Others have no faith in the reliability of the method. Our own small series of figures and—much more than this—the knowledge gained from dairy-chemists of wide experience lead us to believe that the use of top milk is unsatisfactory, unless the fat content of the individual top milks used is controlled to some extent by fat estimations. Milks, in their natural state, certainly differ to some extent in the rapidity and completeness with which the cream rises. It seems probable, though it has not yet been definitely proved, that in most fresh milks this is sufficiently constant to give wholly satisfactory modifications. Other milks, in their natural state, probably yield their cream more slowly or more rapidly than the standard; and probably with varying rapidity at different times. At any rate, it is well known to dairy chemists that heating milk causes the cream to rise very slowly; and it is likewise well known that some milk dealers pasteurize their milk, either covertly or openly; this is nowadays often done at temperatures that cause no change in the taste of the milk, and it is therefore often not known that it has been done. Hence, this source of error in using top milk may be met with at any time in market milk, and is an important argument against the method. On the whole, we believe that it is a method of doubtful value, as our knowledge stands at present. It has, at least, been shown that it is not always reliable; and this means that if it is to be used with any confidence, the fat of the individual top milk in use should certainly be estimated once, and better, several times, in order to see how it is running.

We agree with many others that the most accurate method is to use a cream of known fat percentage from an entirely reliable source. The objection has repeatedly been raised that creams sold as containing a certain percentage of fats have been found, on analysis, to vary widely from this percentage. This is quite true of many market creams; it is, however, not true of creams from

all sources. The Philadelphia milk commission now certifies to several creams, and this means that analysis of these creams constantly shows that their fat-content runs within narrow limits. Equally reliable cream may be obtained in any of our large cities and in many smaller towns.

It is also asserted by some writers that in the process of separation the emulsion of the fat is altered, and that a milk modification made from it is less digestible than one made from a gravity cream. There is no good proof of the truth of this statement. If, however, it impresses one as being important, there is in Philadelphia a reliable (certified) gravity cream of constant 16 per cent. fat content; and such creams may be obtained elsewhere.

As to the fourth series, the laboratory modifications, the proteid variations in this series are slight, and are worthy of remark in only three instances: i. e., Nos. 77, 82, and 83. The variation of 0.36 per cent. in No. 77, in a proteid formula of 1.50 per cent., certainly falls within the limit of occasional unavoidable error. The errors of 0.46 per cent. and 0.42 per cent., with a proteid formula of 1.75 per cent., are perhaps a little beyond the range that is permissible; but they are only slightly so. That these errors may be attributed largely to unavoidable variations in the milk and cream is made probable by the constant way in which the other figures run.

The figures for the fat are a little less satisfactory; but all the figures are within the range of unavoidable error, except those for the 4.5 per cent. fats—those numbered 83 to 88. In this set, the fat regularly ran very low; except in No. 84, when it was 4.2 per cent. Some estimations that we made of the fat of the cream from the laboratory company at about the same time showed that it was running about 2 per cent. below its usual figure. This would explain the major portion of the fat error in the modifications, leaving the smaller portion still unexplained. On the whole, the results are excellent, particularly with the low formulæ, which are the more important. It is but fair to say, also, that by subsequent inquiry we learned that the regular modifier had been ill for a portion of the time during which we were making these estimations; and the results would perhaps have been even more accurate, had he not necessarily been replaced by a substitute, who, while trained in the work, was less accustomed to it.

These analyses of laboratory modifications are much more favorable than Wentworth's. The difference in our results may, perhaps, be due to the fact that the modifications examined by us were better prepared than those that Wentworth analyzed; but a more definite and satisfactory explanation may, we think, be found in the differences in the methods used. As already stated, we used various precautions in our Leffmann-Beam fat determinations, and frequently controlled them with ether extractions. Wentworth, who used the Babcock method, which needs similar precautions, makes no statement of having adopted these precautions; and particularly, did not use control ether extractions. The proteid we determined directly by Kjeldahl nitrogen estimations. Wentworth used the method of difference, which includes in bulk all errors made in the fat, total solid, ash, and sugar determination; and the error in sugar determinations, in particular, is likely to be considerable when the polariscope is used. We cannot emphasize this last statement more strongly than by referring to Stohmann, who, in his excellent article in Musspratt's *Encyclopädie der Technischen Chemie*, states that he cannot recommend polariscopy at all for determining the sugar in milk, as the error associated with it is likely to be even great enough to cover the whole amount of sugar in the milk. This very decided view is not shared by all dairy chemists, and the error in the special polariscopic method used by Wentworth is undoubtedly much less, but even that method is known[2] to be subject to considerable error, and polariscopy is always exceedingly untrustworthy unless one has extensive and continued experience in its use. The effect of a much less marked error in polariscopy than that attributed to it by Stohmann is evident and striking, if the method of difference is used in estimating a proteid of, for example, 1 per cent. Indeed, we are not aware that the difference method is considered reliable by any authorities.

The general conclusions that we believe our work justifies are: (1) Milk modifications, under the best of conditions, will often vary 0.2 per cent., occasionally 0.3 per cent. from the prescribed formulæ, with modifications of medium strength. With low modifications, the error will be correspondingly less; and with high modifications, correspondingly somewhat greater.

[2] Richmond, *Dairy Chemistry*.

(2) Home modifications are, within the limits just mentioned, trustworthy, if they are made by a clear headed and careful person, from milks and creams of a chemical composition that is known to be reliable.

(3) If the composition of the milks and creams used is not known, or if one cannot be sure that the modifier is careful and clear headed, home modifications are likely to vary greatly from the formulæ prescribed.

(4) Laboratory modifications appear from our figures to be satisfactorily accurate; and unless the milks and creams, as well as the person doing the modifying at home, can be fully trusted, laboratory modifications, when available, are much more reliable than home modifications.

Undoubtedly, the most satisfactory method of having milk modifications prepared is to have a thoroughly capable person make them at home, from milk and cream of reliable composition. In this case, the whole process can be kept under direct supervision. This means, however, that milks and creams that are constantly watched, as are the certified milks and creams in Philadelphia, must be used; and that a clear headed mother or trained nurse must do the modifying. To trust the modifying to a readily confused mother, trained nurse, or nursery governess, or to most nursemaids, would make the results very doubtful. We confess that our analyses, while not lessening our faith in the devotion of mothers and nurses, do make us somewhat doubtful of the accuracy of many of them in making milk mixtures. The analyses of their modifications demonstrate how important it is, in having home modifications made, to have all the small details and, above all, the amounts of the different ingredients, carefully written out, or filled out on printed blanks, in order to guard, as far as possible, against confusion. Nothing should be left to the modifier's judgment or memory.

The figures that we have given demonstrate, also, that it is careless practice to order a certain formula for an infant, and to take it for granted that this formula is actually being given to the child. It is, of course, difficult for those in general practice if they have not even the small facilities necessary in doing such work, to determine the fat content of the milk mixtures that are actually being given to the infants under their charge. It would, however, be very easy for many such physicians to have this done by an assistant. Those that are especially interested in pædiatric practice can hardly show proper interest in their work, unless they often do this or have it done. Simple centrifugal estimations of the fat are certainly quite sufficient for clinical purposes, as an indication of the accuracy of the mixtures; though an occasional proteid estimation, if one has facilities for it, will add to the effect. The knowledge that this is likely to be done at any time will necessarily have an excellent moral effect upon any modifier who has a tendency to carelessness; and the somewhat general use of such controls would go far toward eliminating any question as to the accuracy of percentage modifications, whether made at home or in a laboratory. At the same time, it would give one constant knowledge as to their accuracy in any individual case. The apparatus required is cheaper than that used for ordinary examinations of the blood; the method requires less time, and it gives good results. It is already occasionally used by some physicians, but is not often employed by any considerable number of them.

Finally, it is proper to insist again upon the fact that we have already repeatedly mentioned; *i. e.*, that there is a very great advantage, from the chemical standpoint, as well as from the hygienic, in the use of milks and creams that are under constant professional control, and are certified to by members of the profession as being reliable. Such milks are already available in a number of our cities; those interested in pure and reliable milk in some other cities are preparing to institute their use in those cities; and it may well be urged upon the members of the profession elsewhere that they should offer the same protection to their patients. These certified milks and creams have been received with a curious degree of skepticism by many physicians, but they stand the tests put upon them admirably. There are on sale in Philadelphia six certified milks, and three certified creams. We have made a large series of analyses of these products, and know that, except for occasional slight and inconsequential variations, they do not pass the narrow limits imposed upon them. They are therefore suited, chemically, for milk mixtures, as are few others in this city; and as no others are known by the profession to be. The records of the veterinarian and of the bacteriologist of the Philadelphia milk commission testify as to the care given these milks in their production and sale, and demonstrate their remarkable purity from the hygienic standpoint. The best indication of their condi-

tion as they reach the consumer is the number of bacteria that they then contain. The limit placed upon them is 10,000 bacteria to the cubic centimetre. They are not allowed to run above this limit; and are, indeed, usually much below it. Several of them regularly and consistently, at all the examinations made, have shown only a small fraction of that number. It should be remembered that most market milks show hundreds of thousands of bacteria to the cubic centimetre, and that, as delivered in large cities, most of them show millions. One of the latest additions to our knowledge concerning this matter is Wall's statement that Gehrmann recently found the average in fifty specimens of Chicago market milk to be over 2,600,000; and only three were below 100,000. Similar figures have been obtained in other large cities. Such figures demonstrate the wretched and dangerous hygienic conditions that attend the production and sale of most market milks; and, at the same time, they show that the strictest care must be used with milks that are not passed if they contain more than 10,000 bacteria to the cubic centimetre. Certified milks are not examined only once or occasionally, but at least once each month that they are sold. No one can rationally object, therefore, that these milks are not what they are intended to be; *i. e.*, of as constant a chemical composition as is possible, and—most important of all—free from dangerous contamination.

A CASE OF COLON INFECTION SIMULATING TYPHOID FEVER.

By Joseph Evans, M.D., and Joseph Sailer, M.D.

(From the service of Professor Musser, and from the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

The specific serum reactions have had a great deal to do with the development of a clear conception of the nature of infectious processes. For instance, we have learned to distinguish between typhoid and paratyphoid infections, although the clinical course of the two diseases presents many points of resemblance. The question naturally arises whether there may not be a type of disease resembling typhoid and paratyphoid infection, produced by the micro-organism most closely resembling the typhoid and the paratyphoid bacilli, that is, the colon bacillus. The blood serum of animals infected experimentally with different varieties of the colon bacillus will cause it to agglutinate promptly.[1] There seems to be good reason to believe that in certain forms of pyogenic colon infection the specific reaction with the colon bacillus has been obtained, but owing to the great variability in the different specimens of this micro-organism the results have been very confusing. The following case has been incompletely studied, and is therefore unsatisfactory, and yet it indicates that it is not impossible that some obscure cases of continued fever in which the blood does not react either to the typhoid or para colon bacilli, may be actually due to general colon infection:

The patient, a negro, aged twenty-seven years, and a laborer by occupation, without significant family history, states that ten or twelve years ago he had chills and fever, which lasted two weeks;

[1] The literature of "Diagnosis by Means of the Serum of the Blood" was recently reviewed by one of us. (Univ. of Penna. Med. Bulletin, August–September, 1902.)

otherwise he has been well. On February 6, 1903, he caught a cold that affected his throat, but he continued to work until February 12th. On that day, after dinner, he suddenly became weak and dizzy, and was compelled to give up working. His physician ordered him to bed, and the following day he had diarrhœa; his abdomen was sore; he had loss of appetite and gastric discomfort. He was admitted to the hospital on the following day, February 14th. The physical examination showed him to be a well-nourished, powerful man. The tongue was heavily coated and tooth-marked at the edges; the breath was fetid; the mucous membranes were pale; there was a soft, palpable, cervical gland on the left side. The right radial pulse was stronger than the left; the pulse was medium full and dicrotic, and the artery was slightly sclerosed. The apex beat was slightly diffused; the area of cardiac dulness was not enlarged; the first sound at the apex was dull and prolonged; the second sound at the pulmonic orifice was reduplicated and accentuated. The lungs were normal with the exception of slight interruption at the apex during inspiration, and slight increase of vocal resonance over the right lung. The liver was not enlarged; the spleen extended from the ninth rib at the midaxillary line to the costal border, and its lower border was distinctly palpable. The stomach extended about one inch below the costal border. The ascending and descending portions of the colon were dilated; there was gurgling in the right iliac fossa; the appendix was palpable, but apparently normal. The abdomen was scaphoid; the tenth rib was movable, and there was slight separation of the recti muscles. There was no tenderness over either twelfth rib. There were numerous rose-colored spots on the abdomen and back, disappearing on pressure and returning slowly. The muscles showed extreme mechanical irritability; the reflexes were normal.

The disease continued to run the normal course of a case of typhoid fever complicated by slight sore-throat, until March 6th, when the temperature was normal. In view of the negative reactions of the blood with the typhoid bacillus, it was supposed that he might have had influenza, and he was placed upon full diet. The temperature immediately rose, and the patient had a typical but mild relapse, lasting until March 16th. The blood and urine were repeatedly examined.

Blood.

February 15, 1903 Hæmoglobin, 85 per cent.; red blood corpuscles, 5,520,000; white blood corpuscles, 5900.

17*th*. White blood corpuscles, 10,480.

21*st*. Hæmoglobin, 88 per cent.

25*th*. White blood corpuscles, 7200.

March 9*th*. Hæmoglobin, 85 per cent.; red blood corpuscles, 6,000,000; white blood corpuscles, 7000.

Urine.

February 15, 1903. Contained a trace of albumin; the diazo reaction was positive; but otherwise it was negative.

17*th*. Specific gravity, 1026; trace of albumin; sugar, indican, and bile negative; diazo reaction positive.

25*th*. Specific gravity, 1024; still faint trace of albumin, slight reaction to indican, and doubtful diazo reaction.

March 19*th*. Specific gravity, 1020; still some trace of albumin; sugar, bile, indican, and diazo negative. No casts were found at any time.

The serum of the patient was tested on four different occasions for its agglutinative property with the Bacillus typhosus, with negative results, no agglutination taking place in a higher dilution than 1 : 10.

February 25*th* (the twentieth day of the disease), in addition to the test with the Bacillus typhosus, the serum was tested with four different cultures of the Bacillus paratyphosus (Cushing's, Gwyn's, and two of Longcope's). No reaction further than an incomplete agglutination in the dilution of 1 : 10 took place. A test was then made with the Bacillus coli communis, the culture being one isolated at the Pasteur Institute, having marked motility and producing abundant gas in the sugars. In dilution of 1 : 10 motility was immediately arrested, and in two minutes agglutination was complete. Agglutination was complete in dilution 1 : 50 in fifteen minutes. At the end of half an hour agglutination occurred in dilution of 1 : 100, but there was still some motility present.

27*th*. The tests gave the following results:

In dilution of 1 : 10. Incomplete agglutination with the Bacillus typhosus and the Bacillus paratyphosus.

In dilution of 1 : 10. Complete and immediate agglutination with the Bacillus coli communis.

In dilution of 1 : 50. No agglutination with the Bacillus typhosus and Bacillus paratyphosus.

In dilution of 1 : 50. Complete agglutination with the Bacillus coli communis in fifteen minutes.

In dilution of 1 : 75. Complete agglutination with Bacillus coli in twenty-five minutes.

In dilution of 1 : 100. Complete agglutination with Bacillus coli in forty-five minutes.

March 6th. The patient's temperature being afebrile, no blood cultures were made.

7th (the thirtieth day of the disease). The serum tests, made by Dr. S. S. Kneass, were as follows: In dilution of 1 : 10. Incomplete agglutination with Bacillus typhosus and Bacillus paratyphosus.

In dilution of 1 : 50. No agglutination with Bacillus typhosus and Bacillus paratyphosus.

In dilution of 1 : 10 and 1 : 40. Complete agglutination with Bacillus coli communis.

20th (the forty-third day of the disease) :

In dilution of 1 : 10. Agglutination of Bacillus typhosus and Bacillus paratyphosus.

In dilution of 1 : 50, 1 : 75, 1 : 100, 1 : 150. Complete agglutination of Bacillus coli within one hour.

In dilution of 1 : 200 and 1 : 250. Partial agglutination of Bacillus coli in one and a half hours, but no increase later.

In dilution of 1 : 300 and 1 : 400. No agglutination of Bacillus coli in twenty-four hours.

Further Tests. The same culture of the Bacillus coli communis was then tested with six sera, which gave positive reactions with the Bacillus typhosus in a dilution of 1 : 50. One serum agglutinated the Bacillus coli at a dilution of 1 : 40, but failed in dilutions of 1 : 75 and 1 : 100, in which dilutions it agglutinated the Bacillus typhosus. Two sera-agglutinated the Bacillus coli in 1 : 10 dilution, both being derived from cases which manifested symptoms of severe infection, and agglutinating the Bacillus typhosus in high dilutions. The other three sera gave no reaction with the Bacillus coli. The

sera from four cases of suspected typhoid fever, which persistently failed to agglutinate the Bacillus typhosus or Bacillus paratyphosus, produced no agglutination with the Bacillus coli. In two cases of typhoid fever, the sera of which persistently failed to give a reaction with the Bacillus typhosus until the twenty-first and nineteenth days of the disease, no reaction with the Bacillus coli was obtained either during the period of absence of the Widal reaction or after it had been established.

These tests tend to prove, first, that although typhoid sera will sometimes agglutinate the Bacillus coli communis, yet not in as high dilutions as the Bacillus typhosus; second, that this case was not one of simple continuous fever, but was really a colon infection; third, that it was not a case of typhoid infection with delayed Widal reaction.

We have noted in immunizing rabbits with the Bacillus typhosus that a serum of high agglutinative power which agglutinates the Bacillus typhosus in dilutions as high as 1 : 100,000 may cause very little agglutination in dilutions of 1 : 50 and 1 : 100. In these latter dilutions, however, the Bacillus coli may be strongly agglutinated, but this reaction is soon lost in the higher dilutions. Kraus states that he has often found this to be the case in sera of high power. To exclude such a condition a dilution of 1 : 200 with the typhoid bacillus was made in this case with a negative result.

Therefore, this case appears to be one of pure colon infection with the colon bacillus similar to that used in making the tests—the bacillus that was isolated at the Pasteur Institute in Paris. Unfortunately a blood culture could not be made, although we were very anxious to have one, and it cannot be known positively whether a similar micro-organism was present in the blood of the patient or not. Certain sources of error, therefore, must be considered to be theoretically possible.

1. It may have been a case of typhoid fever in which the serum reaction to the typhoid bacillus did not occur at any time during the course of the disease. Such cases have been reported. It is known, moreover, that in cases infected with the typhoid bacillus not infrequently a reaction with the colon bacillus is obtained, this reaction

being, as a rule, less pronounced than the reaction with the typhoid bacillus. No case has hitherto been recorded in which this combination occurred. We do not regard it as likely, but merely as a conceivable possibility.

2. It may have been a case of paratyphoid fever in which similar conditions existed. This we also must regard as an unlikely but conceivable possibility.

3. It may have been a case of some other infectious process, possibly influenza, the history of sore throat lending some color to this supposition. The clinical course of the disease did not resemble that of an ordinary anginoid infection; the roseola eruption, the enlarged spleen, and the history of diarrhœa resemble more closely typhoid fever. The fact that the patient promptly had a relapse when placed upon a semiliquid diet early in the course of convalescence from the first attack, and the persistence of the reaction long after final convalescence was established, would seem to prove that we were dealing either with typhoid fever or with a disease closely resembling it. Objection will probably be made that the culture with which the reactions were made may not have been a true colon bacillus. There is so much variability in this micro-organism, both in its cultural peculiarities and in its serum reactions, that it would be difficult to state positively whether the culture was a colon and not a paracolon bacillus. The present culture, however, was recognized as colon at the Pasteur Institute. It ferments all sugars; it gives a strong indol reaction, and therefore is identical with the colon bacillus according to all the usual differential tests. It is, however, actively motile. Moreover, the blood of the patient did not give any reaction with proved cultures of the typhoid bacillus, nor with four varieties of the paracolon bacillus. Therefore, the infection was presumably not typical of any of these forms. As a result we feel ourselves justified in concluding that the most reasonable hypothesis regarding this case is that it was one of infection with the colon bacillus, and resembled in its clinical course an infection with the typhoid bacillus. As far as we have been able to ascertain by a careful examination of the literature, it is the first case of this nature on record.

NOTE UPON THE AGGLUTINATION AND PATHOGENICITY OF THE BACILLUS SUBTILIS.[1]

By S. S. Kneass, M.D., and Joseph Sailer, M.D.

(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

The number of spore-bearing micro-organisms for which agglutination has been determined is comparatively small. Nicolle and Trainelle state that the tetanus bacillus does not, as a rule, agglutinate with the serum of infected animals. Under certain conditions, however, a slight agglutination can be obtained with the blood of a chicken into which large numbers of the micro-organisms have been injected. The anthrax bacillus also may show a slight agglutination with very powerful sera.

In the beginning of the winter we undertook a series of investigations upon the Bacillus subtilis, in the course of which it was necessary to determine whether or not this bacillus exhibited a distinct agglutination. As the results were positive, and as we have not yet been able to discover that the agglutination of this micro-organism has been recorded, we have thought it worth while to make a note of the fact. The animals employed were rabbits, and the method of producing the agglutinating serum was as follows: Cultures of the Bacillus subtilis were grown upon agar plates for twenty-four hours. At the end of this time the luxuriant growth was suspended in a sterile physiological salt solution and injected into the rabbit. Usually from two to four platefuls were injected each time, at intervals of from two to three days. We selected this method in order to avoid the confusion that might result from the presence of reactions with the proteid bodies found in ordinary bouillon media. Homogeneous cultures were obtained by filtering the twenty-four-hour bouillon culture through cotton. The micro-

[1] Read before the University of Pennsylvania Medical Society, February 20, 1903.

organisms were large and actively motile, and, as a result, the reaction was distinct and characteristic. Altogether five rabbits were employed. Of these, the first was injected three times subcutaneously, and developed a large lump on the surface of the abdomen. It was then injected intraperitoneally, and four days later died. The second rabbit was given a large injection intraperitoneally, and died the following day. On neither of these animals was it possible to make an autopsy. Other rabbits, however, that were kept in the same place had also died and we were not certain that the death of our rabbits was due to the injections. The third rabbit was injected subcutaneously five times in the course of eighteen days. On the eighteenth day a drop of blood was obtained from the ear, allowed to dry, and a positive reaction obtained in a dilution estimated to be about 1 : 40. Two days later the animal was killed and a series of tests made with the serum. In dilutions of 1 : 7 and 1 : 10 agglutination was complete and instantaneous. All motility was lost; the micro-organisms gathered in clumps, and the outlines of their bodies became less distinct. There was no bacteriolysis. In dilutions ranging from 1 : 300 to 1 : 1000 complete agglutination occurred in twenty minutes or less. The hanging-drops were kept in the incubator and examined at intervals of about ten minutes. In dilutions from 1 : 1000 to 1 : 2500 there was distinct reaction in the course of half an hour, but at this time some of the micro-organisms were still free and motile. Two hours later the agglutination was complete in all the specimens. In a dilution of 1 : 5000 there was very slight clumping at the end of two hours and a half. The specimen was examined later and showed no further change. In a dilution of 1 : 10,000 no reaction occurred at the end of four hours. Therefore, with the blood of this particular rabbit it was possible to obtain a positive reaction in dilutions as high as 1 : 2500. In dilutions higher than 1 : 5000 no reaction occurred. In none of the specimens was bacteriolysis observed.

Practically all the text-books on bacteriology state that the Bacillus subtilis is one of the most perfect types of a non-pathogenic micro-organism. There is even some doubt as to whether it causes fermentation (Lehmann and Neumann, Macé, Flügge, Migula, and Williams). Pernice, Scagliosi, Perles, and Lobanow have experimented with the micro-organism and reached the same conclusion.

Wyssokowitsch found that after intravenous injections the spores might be retained for a long time in the liver and spleen, and that cultures made from these organs several weeks after the injections have been given would still show positive results. The histological examination, however, failed to reveal any evidence of irritation caused by the presence of the spores. This exceedingly interesting observation, which apparently has some bearing upon the relation of the liver and spleen to infectious diseases, does not appear to have attracted much attention.

The fourth rabbit was given an injection of six plates of the Bacillus subtilis in suspension, subcutaneously. Eight days later it received a second injection of eight plates, and the following day died. At the autopsy a large mass of sclerotic tissue was found in the abdominal wall. The walls of this abscess were thick and very tense, and contained numerous pockets of pus. Smears and cultures of this pus showed only the presence of the bacillus subtilis. There was also a fibropurulent pericarditis, smears and cultures from which again showed only the Bacillus subtilis. A pure culture of this organism was also obtained from the heart blood.

The earliest recorded instance that we have been able to find of morbid lesions produced by the injection of the Bacillus subtilis is that of Charrin and De Nittes, who cultivated the organism on media containing blood, and then passed it through a series of animals until, finally, its virulence was so enhanced that from 0.5 to 0.75 of a cubic centimetre of a bouillon culture was sufficient to kill guinea-pigs. A local lesion was produced, but the pathological picture was that of intoxication.

Poplawska, in 1890, found a micro-organism resembling the Bacillus subtilis in eight of twelve cases of panophthalmitis. Cultures, however, could not be made because the eyes had been hardened in alcohol. Baenziger and Silberschmidt were the first to record, in 1902, a certain case of human infection due to the Bacillus subtilis. They found this micro-organism in pure culture in a case of panophthalmitis, produced by the penetrating wound made by a fragment of steel from a farming utensil.

More recently Kayser, of Freiburg, has reported two cases of panophthalmitis: The first patient, while working in the field, received a small piece of steel into the eye. Cultures made from the

conjunctiva showed the presence of the Bacillus xerosis. Cultures made from the piece of steel and from a piece of the iris, excised during the operation, showed only the Bacillus subtilis; and cultures and smears subsequently made from the interior of the eyeball after enucleation showed the same organism.

The second patient received a splinter of stone into the eye, and cultures of the contents of the eyeball showed in addition to the Bacillus subtilis the Staphylococcus pyogenes aureus and albus. The Bacillus subtilis was identified by cultures upon various media, and the diagnosis was confirmed by Dr. Erne, of the Hygienic Institute. It produced panophthalmitis when injected into a rabbit's eye, but no results followed its injection into the cornea. Injected into the anterior chamber it caused irritation without subsequent suppuration. Subcutaneous and intraperitoneal inoculations into rabbits produced no effect. Large quantities of a bouillon culture (2 or 3 c.cm.) injected intraperitoneally into guinea-pigs caused death, and the same result was obtained with white mice. Pure cultures were obtained from all the organs of these animals. Kayser remarks that there is considerable difference in the pathogenicity of different specimens of the Bacillus subtilis obtained from different sources.

It appears, therefore, that under certain circumstances the Bacillus subtilis may become pathogenic, causing death in the lower animals, and destructive inflammation in human beings. It gives a typical reaction of agglutination with the blood serum of animals into which it has been injected, and, owing to its size and motility, would probably be an excellent subject for the demonstration of this reaction.

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A REPORT OF A CASE OF CHRONIC ACETANILID POISONING, WITH MARKED ALTERATIONS IN THE BLOOD.[1]

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AND

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Miss R., aged twenty-five years, came under our observation on January 19, 1902. The following notes were recorded at the hospital:

Family History. Negative.

Personal History. The patient had the diseases of childhood, including scarlet fever, but not diphtheria. She had measles thirteen years ago, following which she had a "cold" and trouble with her eyes, and has never felt entirely well since; she would tire easily, had some shortness of breath, and was unable to attend school. When she did attend school she studied moderately hard; she was fond of out-door exercise. She has never lived in a tropical country.

History of the Dental Conditions. The patient first saw her dentist about four years ago, when she was suffering with pain in the lower right bicuspid teeth. One of the teeth was extracted, but was found sound, and the pain was only temporarily relieved.

[1] Read before the Medical Society of the University of Pennsylvania, October 17, 1902.

Other teeth were successively extracted in the lower and upper jaw until she had lost all on the right side. Some of the teeth were reported to have had abscesses at the roots, but most of them were in good condition. The pain in the jaw subsided temporarily at various times, but always recurred. Two years after the teeth had been extracted, plates were introduced, but after a little time these became painful and could not be worn. A small fistula was found in the gums of the lower jaw communicating with a small pocket under the jawbone. This was laid open and packed for some time, and later an opening was made on the outside, but no evidence of periostitis, which had been suspected, could be found.

History of Present Condition. She had malaria of six weeks' duration five years ago, following which she had marked anæmia and nervous prostration. She first noticed at this time a tendency to cyanosis; often felt faint and nauseated. At times she has been entirely free from the cyanosis. The present attack dates from Christmas, 1901, and she thinks she is worse since admission to the hospital. The faintness and nausea have been more marked during the past three years. She has had much gastric trouble, the stomach at times not retentive. She has had more or less œdema for the last three years. She had a marked attack in November, 1901, during which the legs were very tense; the œdema was not confined to the lower extremities. She has had insomnia for the past five years, usually from the dental pain. She was given chloral, hyoscyamine, and other drugs. She does not know whether she was given sulphonal or not.

The patient was brought to the hospital for treatment of the infradental neuralgia, but was transferred by Dr. Cryer to my service (S.) on account of the general condition.

I found her excessively cyanosed; her lips, finger-nails, and toe-nails were dark blue or almost black. The general color of her skin was a leaden one. The hands were a little cool, the feet scarcely at all. She was elevated in bed, but was not specially dyspnœic. I was struck by the acneous eruption on the face and dark rings of pigmentation around the eyes. She was thin, and there was not a trace of œdema anywhere discoverable. Her pulse was scarcely palpable at the wrist. The heart's action was

rapid and very weak. A soft purring thrill of uncertain time could be felt about the neck, especially to the right side, while just above the clavicle on the same side a continuous thrill was felt. On percussion the heart was found enlarged to the right and to the left, and a systolic murmur was heard over the whole præcordia. It was transmitted toward the left and to the back. The second sound was accented on both sides at the base of the heart. The liver was a little enlarged; the spleen was decidedly enlarged, and could be felt nearly two inches below the ribs. It was hard and smooth and not in the least tender. I was struck by the fact that the extreme cyanosis was unattended with dyspnœa, coldness, or œdema, and at once concluded that she was either suffering with some form of blood poisoning or with an abnormal commingling of venous and arterial blood.

Her appearance was so startling that I immediately ordered a venesection; 11 ounces of blood being withdrawn. This caused considerable relief in her cyanosis, though it was accompanied by some faintness, for which aromatic spirits of ammonia was given. Subsequently the cyanosis rapidly improved, and all traces of it had disappeared by the next day. At the same time the heart sounds changed in character, the dulness, especially on the right side, decreased, and the murmur almost disappeared, though it was still audible at the apex and running around toward the left side.

The suspicion of some form of hæmolytic poison was subsequently rendered almost a certainty by the examination of the blood. This was found at first examination to contain 3,040,000 red blood corpuscles, and 19,800 white corpuscles. Nothing remarkable was noted in the appearance of the corpuscles at this time. The urine, however, was found to be claret-colored, clear, faintly acid, specific gravity 1024, and it contained considerable albumin, but no sugar. The microscope discovered numerous phosphate and oxalate crystals, some epithelial cells, and a few dark and light granular casts.

The next examination of the blood showed 2,092,300 red blood corpuscles and 71,400 nucleated cells, and 35 per cent. of hæmoglobin. The latter estimation was difficult and doubtful. The enumeration of nucleated cells was first thought to indicate leuco-

cytosis only, but when the specimen was stained it was found that there were 32,323 nucleated red corpuscles per c.mm., the rest being leucocytes. Of these nucleated red corpuscles, 91.4 per cent. were normoblasts, many of which showed clover-leaf, fragmented, and irregular nuclei; 3.5 per cent. were megaloblasts, and 5.3 per cent. were free nuclei. The non-nucleated red corpuscles varied greatly in size, decided microcytes and poikilocytes being discovered.

At this time I wrote to the patient's brother, who is a physician, stating my belief that his sister was suffering mainly with the results of some form of poisoning, probably phenacetin, acetanilid, or the like, and asking for more details regarding her history.

He stated in his reply: "In regard to her history, she has suffered with pain in her jaw for over seven years, and the teeth have been extracted, one at a time, with some relief after each extraction. After all were extracted the pain continued, though it was somewhat lessened for a time last November, when she had artificial teeth made. Soon after beginning the use of these the pain set in and pus discharged from the jaw. This was found to be caused by some local trouble in the alveolar process.

"About seven years ago she had nervous prostration from overstudy and other work, and was also profoundly anæmic. The cyanosis has been present for over five years, and is not due to any drug. I have never examined her heart, but several other doctors have, and their opinions have varied. One said there was very little trouble there; another that there was a very bad valvular lesion; another thought there was possibly a mediastinal tumor causing the cyanosis; and a prominent diagnostician of New York stated there was a tear in the interventricular septum just below the auriculo-ventricular opening, and that this communication allowed the venous and arterial blood to mix and thus cause the cyanosis. This physician believed that the tear had resulted from a fall which she had sustained.

"She has not taken any medicine for her heart but has complained of pain over this organ at various times, and occasionally the pain has been severe.

"At different times during the last seven years she has had

neuralgia elsewhere than in the jaw, especially at the knee. For the last three years her general condition has been improving, and last fall it was at its best. The cyanosis has diminished during the last two years, and finally became hardly noticeable, but after using the artificial teeth, which caused an increase of pain, a discharge of pus from the jaw, with loss of appetite and of strength, the cyanosis returned to a marked degree."

After receiving this letter we continued the strictest watch over the patient to detect any attempt at taking drugs without the knowledge of the nurses, and, though several searches of her room were made, nothing was found. In the meantime her blood condition and her appearance improved. The leucocytic count rapidly fell, and in a few days was normal. The red corpuscles remained at about the same number, and the hæmoglobin, which could now be estimated somewhat more satisfactorily, registered at about 40 per cent. to 42 per cent.

Examinations of the urine and blood were undertaken at this time by Dr. D. L Edsall, and in his report, given us some time later, he stated that he could find hæmoglobin and hæmatin, but no methæmoglobin or hæmatoporphyrin.

On March 6th another slight attack of cyanosis occurred, and the blood count showed 2,290,000 red blood corpuscles, 31,360 nucleated cells, many of which were nucleated red corpuscles.

On March 9th the count showed 1,860,000 red blood corpuscles, 25,200 nuclear cells.

On March 12th, her condition having greatly improved, Dr. Cryer undertook the operation of resection of the infradental nerve. He began the operation under cocaine, but finally was compelled to use ether, and the operation was then only partly satisfactory because of hemorrhage. The immediate effects were well borne, and she stated that after the operation she was practically relieved of pain at the angle of the jaw, but still had some near the mental foramen. This Dr. Cryer explained by the assumption that some fibres of the inferior dental nerve were not separated.

The operation, though attended with considerable loss of blood at the time and subsequently in the form of secondary oozing, did not occasion any change in the appearance of the blood.

*

Her condition remained practically the same until March 22d, when another operation was performed. The inferior dental nerve in its anterior portion was cut and a considerable section removed. This was done under ether. After the operation she complained of some pain in the affected side of the face, but the anæsthesia was easily shown by her insensibility to deep pin-pricks and the like.

On March 24th a box of compound acetanilid capsules (containing acetanilid 3 grains, caffeine ½ grain, soda bicarbonate 2½ grains) was discovered in a package sent the patient by express. She denied taking this medicine, but she also denied having received it, so that her statement that the medicine was intended for a friend was doubted. The nurses recalled that she had previously received a very similar package.

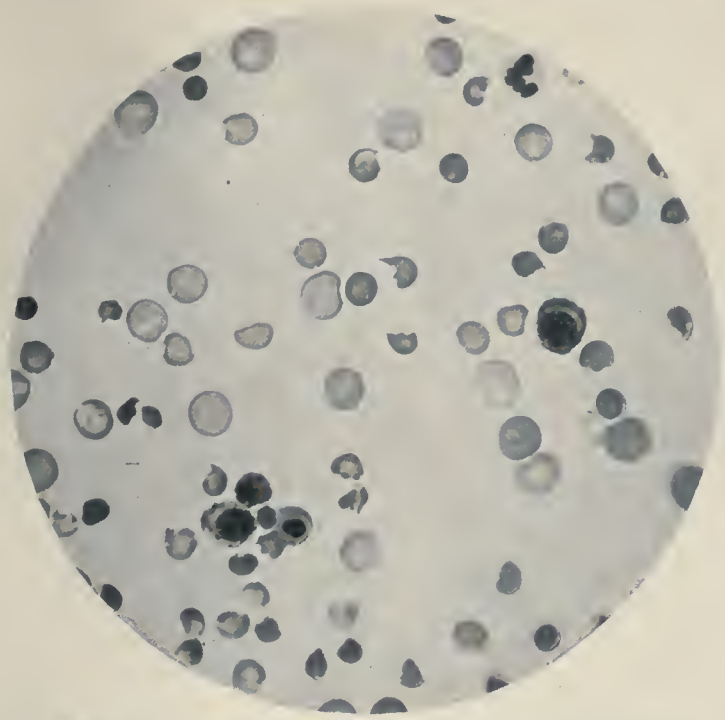
Subsequently the patient confessed to me that she had taken acetanilid capsules almost continuously since she was in the hospital, and that she had sometimes used as many as fifteen to twenty a day. She further admitted that she had been taking these capsules for the last four or five years in very large quantities. Prior to that time she took antikamnia and other forms of antipyretic anodynes. She claims, however, that her first attack of blueness appeared while she was still at school and before she had ever taken remedies of this sort.

April 3, 1902. At this date she had taken none of the antifebrin for several days, and her color was progressively clearing. The heart dulness had diminished, and her general appearance was very changed.

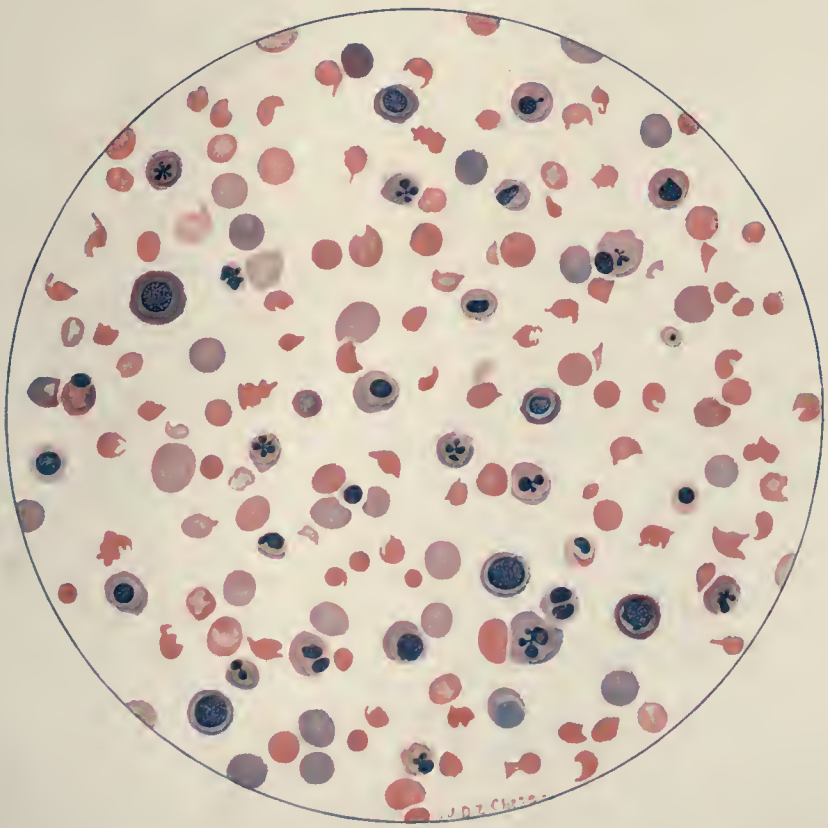
After this date the patient progressed steadily and had practically no untoward symptoms, though there was a little returning cyanosis for a few days, due to the inadvertent administration of a capsule containing phenacetin. The cyanosis disappeared when the medicine was discontinued.

The heart's action became steady. The area of dulness became practically normal. The sounds were entirely free of any murmur, and she complained of very little pain excepting at the left knee, where she believed a needle that she ran into her foot had become lodged.

May 5th. The needle referred to was located by a skiagraph,



Blood in a case of chronic acetanilid poisoning. Photomicrograph of an average field.



Blood in a case of chronic acetanilid poisoning. Composite drawing showing the degenerations of the red corpuscles and the different types of erythroblasts.

and was removed by Dr. Cryer under anæsthesia. It evidently had been in place for some time, as the surface was very rough from corrosion.

The patient remained in the hospital for some weeks after the above note was taken, during which time she was practically well in every respect. There was never any return of the cyanosis. The acneous eruption that first disfigured her very greatly disappeared, and she left the hospital practically well, though she occasionally had some headaches, to which she had been subject all of her life.

As the condition of the blood was of principal importance in the diagnosis of this case, the description of its microscopic features has been reserved for the conclusion of the report.

The histological examination of the blood in this case presented a remarkable picture.

On February 10th the following conditions were noted: The red corpuscles were markedly irregular in size, many cells being much above the average and others minute microcytes. Fragmented forms were very frequent, and many of the cells had lost their biconcavity. Shadow forms were found in some abundance and all intermediary stages between normal cells and distinct shadows, with but a rim of faintly staining protoplasm. Poikilocytosis was marked. Very few granular (basic) degenerative cells were seen. Polychromatophilia was conspicuous. The blood plaques were increased in number.

The most striking feature, however, of the blood at this time was the presence of abundant nucleated red corpuscles (erythroblasts) and free nuclei. Normoblasts preponderated, but there were considerable numbers of megaloblasts. Karyokinetic figures were found in many of the erythroblasts. The differential count of all nucleated cells, white and red, showed: polymorphonuclear, 72.4 per cent.; mononuclear, 5.4 per cent.; transitional, 6.6 per cent.; lymphocytes, 11.4 per cent.; eosinophiles, 0.8 per cent.; myelocytes, 3.4 per cent. Nucleated reds: normoblasts, 91.4 per cent.; megaloblasts, 3.2 per cent.; free nuclei, 5.3 per cent.

On March 1, 1902, an examination of the blood showed the red corpuscles for the most part normal in size and shape. A few

irregular forms were found. The leucocytes at this time were practically normal in appearance. The differential count gave the following figures: polymorphonuclear, 75.9 per cent.; mononuclear, 0.9 per cent.; transitional, 8.6 per cent.; lymphocytes, 13.4 per cent.

On March 20, 1902, the red corpuscles were found normal in size and shape and staining property. They appeared to be somewhat paler than before. The lymphocytes were practically normal in appearance.

There was much difficulty in arriving at a proper diagnosis in this case on account of the neurotic character of the patient and the practical impossibility of distinguishing between accurate and fictitious information. The recognition of the true cause of her trouble was rendered more difficult by the fact that her brother, a physician, believed he had full knowledge of her habits, and positively assured us that she had never used drugs.

When she first came under observation the marked cyanosis, with conspicuously little dyspnœa and with no coldness of the extremities, gave the case the appearance of one of cyanosis due to disorganization of the blood. Her condition, however, was apparently desperate, and without waiting to establish an accurate diagnosis we bled her, and the relief apparently afforded by this means was very considerable. This fact, together with the discovery of signs of cardiac disorder, and the history obtained from her that some congenital cardiac lesion was suspected, made us at the time incline to the opinion that the condition might be one of cardiac origin. This diagnosis, however, would not explain the peculiar features of the blood which were so characteristic of the action of a hæmolytic agent, and so resembled those seen in the few accurately reported cases of poisoning by aniline derivatives that we were strongly of the opinion that some such cause would be found, notwithstanding the patient's repeated denials of the use of any drugs, and the assurances of her brother, who was as much in the dark as ourselves.

The effects of acetanilid, phenacetin, nitrobenzol, and other poisons of the same nature are well known, but comparatively few cases have been reported with satisfactory studies of the blood.

Among the symptoms described are cyanosis, profound depres-

sion or collapse, and unconsciousness ; but, as a rule, dyspnœa and subjective symptoms have been slight or wanting. In many of the reported cases examinations of the blood have showed no morphological changes, but it must be recalled that the majority of cases are acute, while the case here reported is of a distinctly chronic type. In a few cases of subacute or chronic poisoning, like those of Ehrlich and Lindenthal, and Krönig, marked and characteristic changes in the blood were discovered. These consist in alterations of the red corpuscles, including such forms as shadow corpuscles, fragmented cells, poikilocytes, polychromatophilic cells, and particularly nucleated corpusles. The numbers of the latter have sometimes been exceedingly large. Thus, in the case of Ehrlich and Lindenthal, the relation of nucleated to non-nucleated red corpuscles was 1 : 56. In the same case it was noted that the nucleated red corpuscles were first normoblasts, but afterward megaloblasts appeared and finally preponderated. All forms of nuclear division were seen, but the cells in which such division was observed were generally more or less degenerative at the same time.

In addition to the above forms of altered red cells, attention should be called to the great variation in the size of the different cells and to the appearance of granular cells. Ehrlich has called attention specially to a form of granular or protoplasmic change in which the hæmoglobin seems to separate from the stroma and collect in a denser mass or masses as granular collections, the rest of the corpuscle being paler than normal. A more important change is the basic granulation of the red corpuscles described by Grawitz.

The blood plaques are usually increased in number so that aggregations of the plaques form a conspicuous feature in the blood picture.

The leucocytes are increased in number. Sometimes the leucocytosis reaches considerable grades. In the differential count the polymorphous neutrophiles are usually conspicuous. [This was not true of our case.] Degenerative changes in the leucocytes are not rare and evidence the fact that the hæmolytic agent, directly or indirectly, attacks the leucocytes as well as the red corpuscles.

We were much interested in the cardiac symptoms in our case. The fact that a distinguished specialist had diagnosed an interven-

tricular defect, together with our discovery of marked cardiac enlargement and the presence of a murmur, made us hesitate in excluding an organic lesion; but the progress of the case soon proved clearly that no such condition was present. In the intervals between the several attacks of cyanosis (which, in the light of subsequent knowledge, we know were caused by renewed use of the drug) the cardiac symptoms and physical signs rapidly subsided. Indeed, it seems remarkable, even now, that these signs could so completely abate with cessation of the drugging. No other interpretation than a pronounced cardiac dilatation can be offered for the cardiac enlargement and the murmur, but it is not easy to explain the rapid recovery of normal conditions when the drug was withdrawn.

The pronounced enlargement of the spleen was an interesting feature, which is easily explained by our knowledge of the relations of this organ to hæmolytic processes.

KARYOKINESIS IN THE MACROBLAST.

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

The first observation of indirect division or karyokinesis in the nucleus of a cell in the peripheral circulating blood was made by Luzet in 1891. The dividing cell was discovered in a stained spread of blood from a case of anæmia infantum pseudoleukæmica of v. Jaksch. The cell was a large microblast and showed the diaster stage of the cycle of the division. Other observations were reported soon after the discovery of this cell. Trope was able to demonstrate this form of the division of the nucleus in both the erythrocytes and leucocytes in a case of leukæmia. Baginsky found similar dividing cells in three out of five cases of v. Jaksch's disease, and he was inclined to believe that these cells were only found in this disease. Monti and Berggrün made similar observations in the same disease, and collected twelve other cases out of twenty reported instances of the same form of anæmia. In v. Jaksch's original case no observation of a dividing erythroblast was apparently made. v. Noorden saw a dividing nucleus in an erythroblast in a case of a severe anæmia which recovered. Schauman found similar dividing cells in two cases of bothriocephalus anæmia, one of the cases recovering. Similar observations have undoubtedly been made by other investigators. Askanazy was the first observer to find the karyokinetic figure in progressive pernicious anæmia, and perhaps the only observer who has ever been fortunate enough to watch the entire cycle in a fresh specimen of blood. In this observation the

dividing nucleus was first detected in about the stage of the mother-star or aster, and was carefully watched through the various stages until complete division of the nucleus and cell. The time required for the complete cycle was about two hours. The modern text-books upon blood mention the occasional finding of this form of cellular division in the macroblasts. They do not, however, more than mention the possibility of such a form of division. The usual stage observed in the reported cases has been the diaster.

This report is recorded to show the complete cycle of the dividing nucleus and cell and the probable significance of such observations.

The cells from which these observations were made were accidentally found in films of blood stained with hæmatoxylin and eosin, fixed by heat and prepared for routine examination and diagnosis. The cases furnishing the blood spreads from which the dividing cells were discovered were: three cases of splenomyelogenous leukæmia, three cases of progressive pernicious anæmia, one case of anæmia with an enlarged spleen and liver in a child, and one case of chronic acetanilid poisoning with peculiar blood changes. The cells containing karyokinetic figures are not present as a rule in great numbers in any one case. Rarely are there more than two or three such cells per cover-glass spread of blood. In one case only—a case of splenomyelogenous leukæmia—was this rule exceeded; in this case the spreads showed from ten to twenty of the dividing cells in the various stages.

From the number of the karyokinetic cells, probably fifty in all, observed in the various stages of karyokinesis in the nucleus of macroblasts, it would appear that the changes in the nucleus do not differ from similar changes in the nuclei of other cells of the body.

The process of indirect division of the cell has been divided into three chief stages, and each of these show several substages. The process is a continuous one, and the stages are described only for convenience of description. They are: 1. Prophases. This includes the changes preparatory to the beginning of the actual chromatin changes. 2. Metaphase. In this stage the actual division of the chromatin takes place. 3. Anaphases, in which the newly divided chromatin structure is rearranged.

The complete cycle, as observed in the cells forming this report, may be divided into the following periods:

1. The resting cell. This is seen in the accompanying plate (*a*) as a large erythroblast, which measures about four times the size of the accompanying normal erythrocyte. The cell consists of a relatively large nucleus and a small margin of protoplasm. The structure of the nucleus consists of dense interlacing of chromatin fibres which stain deeply with nuclear stains as hæmatoxylin. Between the fibres of the chromatin network are light unstained areas of achromatin. The presence of a nucleolus has never been described in a macroblast. The protoplasm surrounding the nucleus forms a distinct margin which is stained polychromatophilic. Usually the protoplasm does not contain granules, and only as an evidence of degeneration are granules present. The centrosome observed in some other cells, and which usually lies close to the nucleus, was not observed in any of the cells examined. These latter bodies play an important part in cellular division, and were in all probability present in each cell. From the fact that careful fixation and special staining were not employed in these specimens the technique used may have prevented the finding of such bodies.

2. From the stage of the resting nucleus the chromatin fibres change, becoming thickened and rearranged into convoluted loops. These loops are packed together in a dense bundle which forms the first important change in the dividing nucleus, and is known as the close or dense skein, or spirema. In the accompanying plate *b*. *c*. and *d*. represent the changes in such a nucleus. The nuclear chromatin of these nuclei is separated into distinct fibres, which are densely stained and closely packed into various convoluted figures. The protoplasm of all of these cells is distinctly polychromatic in character, and this is especially marked in *d*.

3. In this period the chromatin fibres of the previous stage become much thickened, less densely packed together, and the contortions of the loops are much less marked. This constitutes the loose skein stage and is represented in figure *e*. Here the chromatin fibres are seen to be greatly thickened and deeply stained and spread out in the surrounding protoplasm. The protoplasm is distinctly polychromatic.

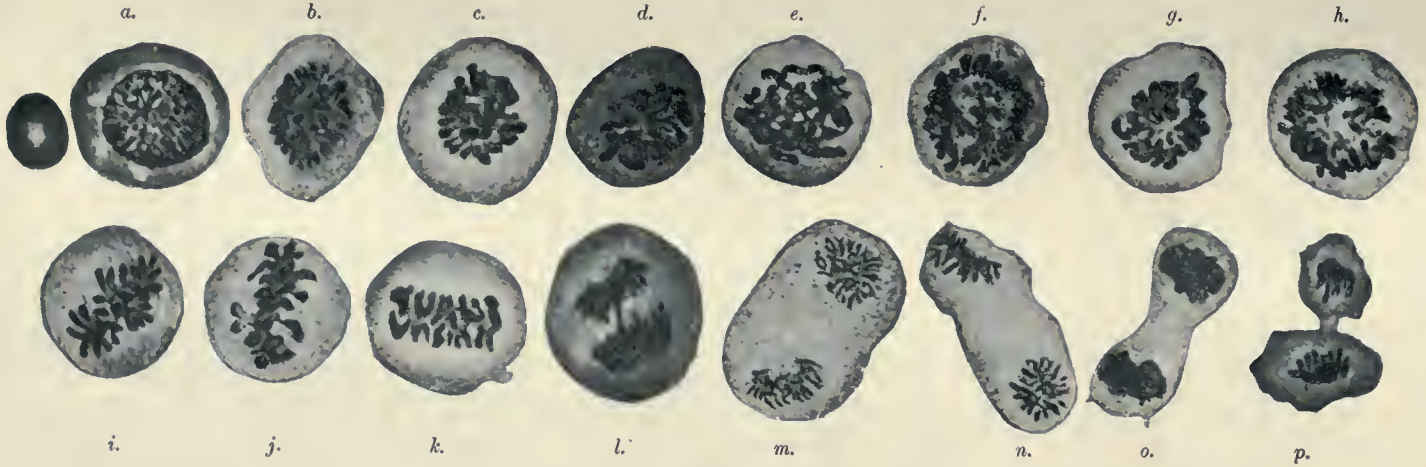
4. The convoluted chromatin fibres, which are loosely arranged in the preceding stage, divide at their peripheral curves. This causes the formation of a number of U-shaped fibres which have been

termed chromosomes. The looped or curved part of these chromosomes is directed inward toward a common centre. The clear space enclosed within these loops is known as the polar field. The chromosomes soon become much thicker and arrange themselves in a more or less wreath-like body around the polar field. While this part of the cycle has been taking place the nuclear membrane has disappeared, and the centrosomes, which very early divide, probably before the chromatin of the nucleus changes from the resting stage, have migrated toward the poles of the cell. It is to this part of the cell—the poles—that the divided parts of the nucleus will migrate before the cycle of changes has passed to the diaster stage. The chromosomes, which by this time have formed a complete wreath-like body in the centre of the cell, constitute that part of the cycle of division known as the mother-star or aster stage. This part of the cycle is represented in the plate by *f. g. h. i.* and *j.* The chromosomes as seen in *f.* and *g.* gradually form the typical mother-star or aster stage as seen in *h.* when viewed from the poles of the cell, or as is seen in *i.* and *j.* when it is viewed from the side. The chromosomes in these cells are stained very deeply, and the protoplasm shows a distinct polychromatic character.

5. In this stage the chromosomes very rapidly divide, after the preceding or aster stage is formed, into halves by splitting along their longitudinal plane, and making thereby twice the number of loops. The divided chromosomes rearrange themselves in the centre of the cell to a denser mass, with the curved part of the loop of each half of the segmented part directed to the opposite poles of the cell. This rearrangement of the loops is known as the equatorial plate.

The centrosomes, which have by this time of the cycle reached the poles of the cell, send out delicate achromatic rays. These rays extend toward the equatorial plate and are termed the polar striation. The rays by forming a spindle-shaped body have received (when both poles are considered together) the name of the nuclear spindle.

The equatorial plate separates transversely about the middle, and each half migrates toward the respective poles along the achromatic rays of the spindle as guides. When these halves move toward the poles delicate achromatic fibres connect the receding ends of the chromosomes and form the so-called connecting filaments.



Karyokinesis in a macroblast showing the changes of the nucleus from the resting stage to nearly complete division of the protoplasm into two separate cells.

This stage of the cycle is seen in the figure *k*. The equatorial plate here forms an oblong mass in the centre of the cell. The nuclear spindle was not observed in the cell. Through the centre of the plate can be seen an irregular space which marks the beginning of the separation of the two halves and their commencing migration to the poles of the cell.

The protoplasm of the cell was markedly polychromatic around the periphery, but immediately surrounding the equatorial plate was much paler than normal, and especially was this so in the direction of the poles.

6. The migrating halves in this stage on reaching the poles of the cell constitute the daughter-star or diaster stage. The several steps of these changes are noted in *l. m. n.* and *o.* The chromatin and protoplasm of these cells do not differ materially from that described in the foregoing cells.

The chromosomes upon reaching the poles of the cell repeat in inverse order the changes which thus far have already taken place and which bring the process back to the resting nucleus.

7. About the time of the diaster stage when the daughter nuclei have reached the poles of the cell the protoplasm begins to indentate, and finally a constriction separates the cell into two parts. The dividing protoplasm may be seen in *m. n. o.* and almost completely separated in *p.* The character of the protoplasm and newly-forming nucleus do not differ from what has been said regarding the staining properties of the preceding cells.

Significance of karyokinesis in the macroblast of the peripheral circulating blood: Karyokinetic figures in the nuclei of erythroblasts of the peripheral circulation are only found in conditions in which the blood shows a very marked degenerative condition of the erythrocytes. Accompanying the rare appearance of dividing cells one always find marked poikilocytosis, anisocytosis, polychromatophilia, basic or granular degeneration of the erythrocytes, and the presence of numerous erythroblasts, both normoblasts and macroblasts, and especially the latter. The dividing cells are, therefore, always associated with a grave condition of the patient. The prognostic value of such findings, however, may not be necessarily bad, as is seen in v. Noorden's case of severe anæmia and in one case reported by Schauman of bothriocephalic anæmia which recovered. In one of

the eight cases in which these cells were found in my own experience —a case of chronic acetanilid poisoning with peculiar blood changes —the patient made a complete recovery. In one case of splenomyelogenous leukæmia, and in one case of progressive pernicious anæmia of the same series, the patients were alive for some time after the discovery of these cells, but later succumbed to the disease. In the remaining five cases such cells were not discovered in the blood until the patients were in the final stage of their disease.

A NOTE ON THE HISTOLOGY OF VERNAL CONJUNCTIVITIS (FRUEHJAHR'S CATARRH).

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AND

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The conjunctival disease, to the pathological histology of which we desire to make brief reference, was first described by von Arlt, who regarded it as a variety of lymphatic conjunctivitis, and received from Saemisch, who called attention to the exacerbations to which it is subject during the warm seasons, the name Fruehjahr's catarrh, or vernal conjunctivitis, by which it is now generally known, in spite of the fact that this designation is singularly inappropriate, inasmuch as the affection is not in any sense a true catarrh.

Thomas M., aged thirteen years, from whom the specimens were obtained, the descriptions of which follow, was born in Philadelphia, and presented himself for treatment in the eye dispensary of the Hospital of the University of Pennsylvania in October, 1902. The boy's father and mother are living and healthy. One aunt died from phthisis; otherwise the family record is negative. There is no history of ocular disease in the family. The patient had scarlet fever in early childhood, and for a time some form of rhinopharyngeal disease, but in other respects has been healthy.

His ocular discomforts began in June, 1901, when his parents' attention was attracted to his eyes by the slight drooping of the lids

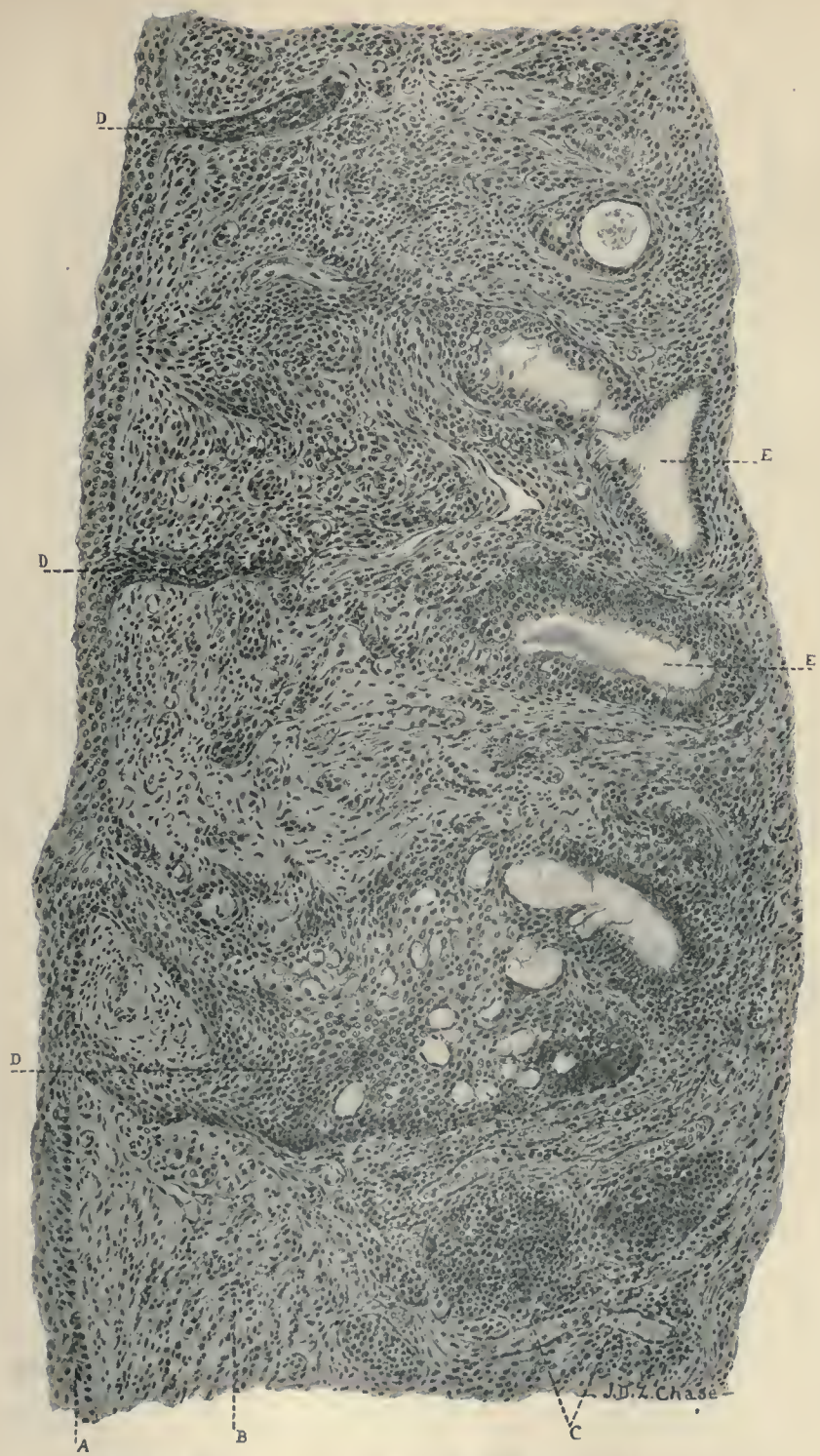
and his constant desire to rub them. He went, with more or less regularity, to one of the eye dispensaries of the city, and evidently had various astringents applied to his eyelids without improvement. Although his eyes were always worse during the warm season, they did not, as is frequently the case, clear up entirely during the winter months.

The eyes themselves were normal and possessed full visual acuity. The bulbar conjunctiva, although slightly injected, was free from disease. The tarsal conjunctiva of both eyes, particularly that of the upper lids, presented the characteristic lesions of so-called vernal conjunctivitis of the palpebral type, being covered with large, flattened granulations, containing deep furrows between them and overspread with a bluish-white film, which is so characteristic of the disease, and which has been compared by Horner to a thin layer of milk.

Ordinary treatment with the various astringents and antiseptic lotions was entirely negative in result. Expression with Knapp's roller forceps was equally without avail. On two occasions the most prominent masses of granulations were excised, with some improvement, but in recent times the boy has not presented himself for further treatment, and the ultimate result cannot be given.

The excised tissue was preserved in formalin solution and submitted to *microscopic examination*, with the following results: The sections of one of the growths excised from the superior tarsal conjunctiva measure 4 by 1.5 mm. They were cut in a direction perpendicular to the lid surface, so that the smaller diameter represents the thickness of the tissue. The structure consists essentially of fibrous connective tissue, covered with a thickened layer of epithelial cells which dip downward into the mass in the form of compact processes and proliferate there in the connective tissue stroma. The conjunctiva of the lid in this position is normally covered by a layer of cylindrical epithelial cells, two cells deep. On the surface of these small growths or so-called granulations, however, the cells have so increased in number that ten to sixteen layers are demonstrable, and instead of retaining their cylindrical form they have become distinctly squamous in type, like those on the surface of the carbuncle. (See Figure, *A*.)

The mass is divided into several lobules by clefts lined with epithelial cells, but in addition to these main clefts the surface epithe-



Transverse section of growth from the tarsal conjunctiva in Fruehjahr's catarrh. *A.* Thickened surface epithelium. *B.* Fibrous connective tissue, forming the body of the growth. *C.* Round-cell infiltration. *D D D.* Invaginations of surface epithelium, with cavity formation at *E E.*

lium sends inward a number of processes or invaginations which form nests of various shapes in the depths of the tissue, and give rise to an appearance which resembles very much that of carcinoma, except that the processes do not invade the lid proper (*D D D.*). The cells in the centre of these nests have undergone degeneration, leaving conspicuous spaces crossed by a fine reticulum, and the borders of the spaces are lined in places by cells which have a distinctly cylindrical form. Superficial examination of one of these areas suggests the acinus of a gland, lined with cylindrical epithelium and filled with a fatty, granular detritus about to be thrown off (*E E*). These processes, epithelial cells, and the nests make up the greater portion of the growth.

In addition to these cells, however, there is also a proliferation of cells which resemble those found in nævus of the conjunctiva and skin. They are flat in form, and instead of occurring in compact masses or alveoli, as do the epithelial cells, they are infiltrated through the reticulum of the fibrous tissue, and are separated from each other by fine fibrils of connective tissue. They stain well throughout, are mononuclear, and represent probably either a proliferation of the endothelial cells of the bloodvessels or of the fixed connective tissue cells. The deepest layers of the growth show also an infiltration with mononuclear leucocytes, indicating a moderate inflammatory reaction. The loose-meshed, fibrous, connective tissue stroma in which these various cellular elements are embedded is well supplied with fine bloodvessels.

W. T. Holmes Spicer's[1] investigations lead him to believe that the granulations or small growths of Fruehjahr's catarrh should be regarded as fibromas from their structure rather than papillomas, inasmuch as the amount of epithelium entering into their formation is not greater than that forming the normal conjunctiva of the lid. He thinks that his sections are in most respects identical with those that have been prepared by Schlub from lesions of the same disease when they occur at the corneal limbus, in the so-called limbus variety of the affection.

Terson,[2] who has reviewed the recent literature of spring catarrh,

[1] Transactions of the Ophthalmological Society of the United Kingdom, 1900, vol. xx. p. 64.

[2] Annales d'Oculistique, November, 1902, p. 335.

draws attention to the difference which sometimes exists between the so-called granulations of this disease when they occur at the limbus, and when they occur on the tarsus. In his preparations taken from the limbus, the thickened epithelium, markedly colored, was stratified pavement in character, and consisted of more layers than in the normal state, although he did not find the decided invaginations which have been described by many authors. The tissue contained some dilated bloodvessels and lymphatics, but was poorly supplied with cells. The connective tissue cells, flat and fusiform in appearance, were contained between large fascicles of connective tissue, and in point of fact the entire aspect of the section gave the impression of a mass of fibrous tissue. On the other hand, the tarsal vegetation contained a less abundant epithelium, and the invaginations were entirely absent. The general mass of the tissue was equally fibrous, but there was, in addition, a considerable infiltration of round cells and leucocytes.

Our findings correspond with the descriptions of the tarsal growths given by Vetsch, Horner, Uhthoff, Knies, Taylor, Schoebl, Haab, and Fuchs. Neither epithelium nor connective tissue elements especially predominates in our specimens, as each constitutes a definite portion of the new-growth.

ON THE HISTOLOGY OF BULLOUS KERATITIS IN GLAUCOMATOUS EYES.

By G. E. de SCHWEINITZ, A.M., M.D., and E. A. SHUMWAY, M.D., of Philadelphia.

(*With Text-plates V. and VI.*)

[From the William Pepper Laboratory of Clinical Medicine, Phœbe A. Hearst Foundation.]

ALTHOUGH the subject of bullous keratitis as it occurs in eyes the subject of iridocyclitis, interstitial keratitis and glaucoma has received much attention, the pathological histology of this condition is not definitely settled, and hence the report of the examination of two eyes thus affected is not unworthy of record.

Case 1.—M. B., a widow, aged seventy, a patient in the Hospital of the University of Pennsylvania.

Clinical History.—The patient presented herself for treatment on the 24th of October, 1901, with the statement that on the previous night pain had begun in the left eye, very severe in nature, which was followed by rapid deterioration of vision. She had used convex reading glasses for more than twenty years and convex glasses for constant wear for five years, and during this period had been much worried by inflamed eyes, lachrymation, photophobia, and conjunctival injection, for which she had from time to time received treatment from competent ophthalmic surgeons.

The vision of the right eye was $\frac{6}{24}$. With + 4 D., o. 75 was read at 23 *cm.* The cornea was slightly hazy, the conjunctiva injected, the optic disc round and contained a small cup. The field for white was normal. The vision of the left eye was $\frac{6}{60}$ and was unimproved by glasses. The cornea was exceedingly hazy and

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needle-stuck, the pupil semi-dilated and fixed, the fundus could be indistinctly seen, and a large glaucomatous excavation was visible in the nerve-head. The patient continued to attend the Eye Dispensary, and under treatment the glaucomatous symptoms which had been manifest in the right eye disappeared, but those in the left eye continued. Operation was not performed.

When Dr. de Schweinitz took charge of the service, in September, 1902, or nearly a year after she had first reported at the Eye Dispensary and six years after the first inflammatory signs had appeared in her eyes, she presented the following ocular conditions: O D, V = $\frac{6}{22}$. With suitable convex spherical correcting glasses vision rose to $\frac{6}{7.5}$. The field of vision was normal in all respects, the cornea clear, the anterior chamber of proper depth, and the tension normal. The left eye presented the appearances of advanced glaucoma. Light perception was absent, tension + 3, the cornea exceedingly hazy, the iris dimly seen and atrophic in appearance, the sclera discolored, and the episcleral vessels coarsely injected. The lens could not be studied through the opaque cornea, the surface of which was roughened. In both eyes there were well-marked follicular granulations in the conjunctiva, very abundant in the lower retrotarsal folds, doubtless due to the the unintermittent use of eserin for nearly a year. At periods varying from a few days to a week the patient would return on account of pain, great lachrymation, and great increase in the bulbar injection, these attacks always being associated with the formation of a large bulla in the centre of the left cornea.

Enucleation was advised, and on the 9th of October, 1902, Dr. de Schweinitz removed the affected eye in the usual manner, with prompt relief of all symptoms. Up to the present time there has been no sign of renewal of the glaucomatous symptoms, which are recorded on the case books as having been present in the right eye when the patient first reported.

There are no facts of interest in the patient's general history. In vague terms she has sometimes been rheumatic, but physical examination failed to reveal organic lesion. The urine was normal, but there were some signs of atheroma of the blood-vessels, not more marked, however, than would be expected in a woman of her age.

Macroscopic Examination.—The central part of the cornea and the area directly below the centre is occupied by a single large

FIG. 1.—Keratitis bullosa. Peripheral section, showing membranous formation on the surface, detached from Bowman's membrane and forming arches through the thickened epithelium.

bulla. On cutting the eyeball in half, the lens was found in position, the anterior chamber shallow, the retina thinned, allowing the choroidal pigment to show through it, and the optic nerve cupped.

Microscopic Examination.—The bulla on the centre of the cornea measures 2.2 *mm* in diameter. In sections in celloidin it has collapsed and the thin walls are folded and project laterally beyond the point at which the epithelium is reattached. Its anterior wall is composed of epithelial cells alone, which show a moderate amount of change. The basal cells are polygonal in form, instead of cylindrical, as is the case with the normal foot cells of the corneal epithelium. Those of the succeeding layers are swollen and frequently exhibit fine vacuoles surrounding the nuclei. The nuclei are distorted, displaced to one side, and show beginning fragmentation, particularly on the surface. In the centre of the bulla the number of layers is greatly increased. Laterally, however, the epithelium regains its normal thickness, although this is very variable, and the surface is made quite irregular by the removal of the superficial cells over numerous small areas. At the point of attachment the basement cells become cylindrical in form, and continue so to the periphery of the cornea. The intercellular spaces are widened, here and there broadening into vacuoles, which contain coagulated fluid and an occasional leucocyte. Towards the limbus the epithelium is separated from Bowman's membrane by many round cells, in which are imbedded a few vascular twigs—*i. e.*, pannus tissue. The episcleral tissue is œdematous and infiltrated.

Extending from the extreme periphery, between Bowman's membrane and the epithelium, is a membrane varying from 7 to 9 μ in thickness, which has a homogeneous appearance, except in places where it has been forced away from its adhesion to Bowman's membrane. Here it shows a distinct fibrillar structure, as it arches upward through the epithelial cells. It does not reach as far as the central bulla, and takes no part whatever in the formation of its wall. In sections cut some distance above the centre of the cornea, where the bulla does not appear, this membrane is present throughout the entire width of the cornea, and, as the drawing shows (Fig. 1), is in many places separated from Bowman's membrane by layers of epithelial cells, through which it forms distinct arches, the largest of which measures from 0.5 to 1.25 *mm* in diameter. In sections treated with Van Gieson

solution it stains a pinkish red color, brighter than that of the corneal lamellæ, and its fibrillar appearance is more apparent. Its peripheral terminations are continuous with fine fibrils of connective tissue passing out into the subconjunctival tissue beyond the limbus. The membrane evidently represents a condensed layer of connective tissue, originating at the limbus in the pannus tissue, and spreading inward toward the centre of the cornea.

Bowman's membrane is present undisturbed throughout all of the sections examined. The nerve canals which cross it as fine, dark lines, which are scarcely perceptible in the normal eye, are here unusually broad. The substantia propria is of normal width, and shows no decided signs of œdema. The endothelium on Descemet's membrane is considerably altered. The cells are flattened and are much farther apart than in the normal eye, spaces the width of two cells intervening in places between adjoining cells, especially in the periphery of the cornea. The posterior surface of the cornea is covered with a layer of coagulated fluid which fills up the space between the iris and the cornea, in the angle of the anterior chamber.

The iris is adherent to the cornea for a distance of about 1 *mm* in front of the opening of the canal of Schlemm, so that the filtration angle is closed all around. The iris is atrophic, and its fine stroma is replaced by thick, interlacing meshes of connective tissue, which surround and compress the thickened blood-vessels. There is an increased amount of pigment imbedded in the stroma in the form of irregular clumps.

The ciliary bodies show an atrophy of the muscular tissue and conversion of the vascular processes into solid cords of connective tissue, which has undergone hyaline change and contains a deposit of lime salts.

The lens is in position, and is normal in appearance.

The retina shows cystic cavities in its anterior portion. The membrane is much thinned, the ganglion cells have almost entirely disappeared, a few distorted cells with retracted processes alone remaining. Mueller's fibres are prominent and are spaced apart. The cells in the nuclear layer are thinned out; the rods and cones are also fewer in number than normal, their outer ends are degenerated, and the individuals tend to form in irregular tufts, between which small cavities are evident as the indication of a previously existing œdema. The retina is everywhere adherent to the choroid, but there is no proliferation of the pigment

epithelium. Here and there the cells are raised in small projections, apparently by the presence of fine droplets in the cells, as described by Wedl and Bock in beginning colloid change in the retinal pigment cells. The vessels have very much thickened walls, a point well shown in sections stained by Van Giesen. They contain red-blood corpuscles, but show no thrombi. The optic-nerve head is excavated to the depth of 1 *mm.* The nerve tissue is atrophic and the intervaginal spaces are broadened.

Diagnosis.—Absolute glaucoma; bullous keratitis; degeneration of the retina; excavation and atrophy of the optic nerve.

Case 2.—W. V., a man aged fifty-four, consulted Dr. de Schweinitz on the 18th of May, 1895.

Clinical History.—Seven years prior to this visit, while chipping a piece of steel with a cold chisel, something struck his eye which gave him some temporary inconvenience but of which no great note was made, although almost from the first muscæ were observed before the injured eye. Two months later vision failed markedly, and he consulted a competent ophthalmic surgeon, who informed him that the failure of vision was due to glaucoma and advised immediate iridectomy, which was successfully performed. Pain and inflammatory reaction in the eye, which had been present prior to the operation, stopped, and although there seems to have been no restoration of vision the eye gave him no serious inconvenience. He came for advice because of attacks of vertigo and some pain and inconvenience after the use of his eye.

Examination revealed the following conditions: Vision of O D nil; upward iridectomy with well-placed pillars of the coloboma; at the corneo-scleral margin at the upper part of the coloboma a small cystoid cicatrix. With some difficulty the lens was made out to be entirely opaque and presenting the ordinary appearances of black cataract; tension slightly +. V of O D with + 1.25^{c} axis 150, $\frac{6}{6}$; media clear; pupil prompt; disc round; small physiological cup; surface of the papilla slightly congested. The field for form and red was absolutely normal.

Suitable glasses were prescribed and the patient was not again seen until the 4th of September, 1902, when he returned with the following history: One year previously the cataract of the right eye had been removed by a surgeon whom he consulted, but his statement as to the exact character of the operation was not very clear, and it may be that no attempt was made to remove the lens but that the cystoid cicatrix was incised, for it is difficult to

understand why any surgeon would remove the lens from an absolutely blind eye of this character. Be this as it may, since this operation pain had begun in the eye and he constantly was worried with the feeling of a foreign body. The eye, previously quiet, became congested, the cornea very hazy, and on numerous occasions bullæ formed on it which were manifest at the time of the examination. Vision of the left eye at this time with suitable glasses was $\frac{6}{6}$ —, the discovery pallid, and a beginning pathological cup was evident.

The right eye was enucleated on the 12th of September, 1902, by Dr. de Schweinitz, with immediate relief of pain and discomfort, and suitable glasses and a weak eserin solution were prescribed for the left eye. The visual field of this eye was uncontracted for form, but there was distinct limitation of the red field.

Macroscopic Examination.—On cutting the eyeball in a vertical plane passing through the cornea and optic nerve, a small foreign body was seen in the outer half of the eye imbedded in the retina and choroid, about 10 *mm* behind the ciliary body. On application of the magnet to this, small particles of rusted metal adhered to the point. The crystalline lens had disappeared, the iris showed a broad coloboma above, the retina was in place and thinned, and the optic nerve showed a shallow excavation. This half of the eyeball was mounted in glycerin jelly.

Microscopic Examination.—The other half was imbedded in celloidin, and the microscopic sections show the following lesions: The surface of the centre of the cornea is occupied by two bullæ, respectively 0.5 and 0.62 *mm* in diameter, situated in close proximity. Their walls are composed of epithelial cells alone, and, as is shown by the sketch (Fig. 2), a thickened layer of the epithelial cells forms the wall separating them. At this point Bowman's membrane is destroyed, so that the epithelial cells are attached to the substantia propria below the surface. There is a similar area of old ulceration above, in which Bowman's membrane has been destroyed and the corneal tissue replaced by scar tissue into which the thickened epithelium sends irregular processes. Elsewhere Bowman's membrane is intact, but is separated from the epithelium by numerous small spaces, filled with fluid and leucocytes and at the periphery by considerable pannus tissue. There is no connective tissue over its surface, as in the first case.

The walls of the bullæ are very thin, in places being composed of only two layers of cells. These cells show vacuolization

around the nuclei, and the basal cells are all squamous in type. Laterally from the bullæ the foot cells are separated by fine lines, and those of the superficial layers are swollen, and in many places have been lost or are being detached so that the surface is very irregular.

At the limbus the subconjunctival tissue is œdematous and the blood-vessels widely dilated, full of blood, and surrounded by a round-cell infiltrate. These capillaries extend a short distance into the corneal substance. The lamellæ of the substantia propria are very distorted and irregular and the corneal corpuscles stain poorly. The upper part of the cornea shows the position of the old iridectomy wound. Here Bowman's and Descemet's membranes are both interrupted, and the surface epithelium dips downward into the cornea.

The iris is well clear of the wound, but is adherent to the cornea at the periphery all around for a distance of one-half a millimetre anterior to the position of Schlemm's canal, so that the angle of the chamber is obliterated. The atrophic ciliary bodies are forced backward, and a beginning intercalary staphyloma is thus formed. The processes contain widely distended blood-vessels. The endothelial cells of Descemet's membrane are very irregular, as in Case 1, especially at the periphery of the cornea, where they are flattened, spaced apart, and allow stretches of Descemet's membrane to lie exposed.

The iris stroma is not much altered. There are a few mononuclear round cells in the tissue, and the surface is covered with a thin layer of organized fibrous tissue, which is still quite cellular. The cross-sections of two blood-vessels of considerable calibre, running horizontally, form conspicuous projections above its surface near the pupillary area. The ciliary muscle is very much atrophied, especially above, in the position of the coloboma. The pigment layers of both iris and ciliary processes are proliferated and show several large cysts, formed between the separating layers.

There is no trace of the crystalline lens, either of the cortical substance or of the capsule. The choroidal vessels are hyperæmic, but the choroid as a whole is thinned.

The retina is cystic anteriorly; posteriorly its ganglion cells have disappeared entirely. Mueller's fibres are hypertrophied and form rounded arches, where the individual bundles have been forced apart and cavities formed by collections of fluid. The rods and cones are irregularly curved in the same manner, and

show minute cavities. The retinal blood-vessels are full of blood corpuscles and exhibit thickened walls. The pigment epithelium is normal and the retina is not adherent to the choroid, being artificially detached above in the imbedding process. The nerve-head shows a shallow excavation, 0.4 *mm* deep, embracing the entire nerve. Both edges are overhanging and the nerve is atrophic.

The eyeball is enlarged in all its dimensions, and the sclera is thinned, especially in the equatorial region, but it shows no evidence of scleritis. Sections treated according to Perl's method show a slight staining of the cells of the ciliary region, but no decided iron reaction, such as is usually found after the presence of a particle of iron in the eye for so long a time.

Diagnosis.—Foreign body in the interior of the eye; iridocyclitis; secondary glaucoma; bullous keratitis with corneal ulceration; iridectomy upward; atrophy of the retina; excavation and atrophy of the optic nerve; beginning intercalary and scleral staphylomata; blood-vessel formation on the surface of the iris.

The two cases illustrate the two most frequent conditions of the eye in which bullous keratitis occurs, mainly, absolute glaucoma of the primary variety, and glaucoma secondary to an iridocyclitis, in this case traumatic in origin.

The subject of bulla formation on the cornea, as upon the skin in herpes and pemphigus, is still involved in considerable obscurity. The first case to be anatomically described was by Albrecht v. Graefe in 1853.[1] He found that the anterior wall of the bulla consisted of three layers—epithelium, Bowman's membrane, and a thin layer of superficial corneal substance. Schweigger,[2] however, and later Saemisch,[3] claimed that it consisted only of epithelium, and in the majority of cases this has been confirmed by other observers.

Fuchs was the first who was able to make sections of the entire eyeball on which bullæ were present, and reported his results before the Heidelberg Society in 1879.[4] He said that in two cases, in addition to the epithelium, the wall was formed by a layer of tissue composed of parallel and apparently homogeneous fibres, about $\frac{1}{10}$ *mm* in thickness, apparently originating in the connective tissue accompanying newly formed blood-vessels which run from the periphery

toward the bullæ, between Bowman's membrane and the epithelium. He thought that Von Graefe had made the mistake of confusing this layer of connective tissue with Bowman's membrane, which it closely resembles, as he had been able to study only the wall of the bulla after its removal from the cornea. In a subsquent paper Fuchs[5] states that in some cases this layer of tissue is the result of the coagulation of an albuminous fluid forced through Bowman's membrane, just as a similar layer of coagulated fluid is often found on the posterior surface of the cornea. Such a tissue had been described by Leber,[6] Arlt,[7] and others, as a fine connective-tissue layer, differing from pannus in the greater absence of blood-vessels, and hence the lesser liability to absorption, from the surface of which fine twigs extended upward between the spaces in the epithelium. Brügger[8] and Birnbacher and Czermak[9] also mention this layer but do not say that it entered into the formation of the bulla.

In our first case, in which it is present, it does not extend to the bulla in the centre of the cornea, and so takes no part whatever in the formation of its wall, and apparently represents a continuation of the connective tissue from the corneal periphery. If this tissue is present at the site of the bulla it may of course form part of its wall, but it has been thus described only in exceptional cases, and the greatest interest, therefore, centres in the epithelium which is usually alone represented.

Thickening of the epithelial layers and a granular condition of many of the cells was noted by Graefe,[1] but it is to Leber[6] that we owe the most elaborate study of the subject. He described in detail the clefts between the cells, vacuoles surrounding their nuclei, the minute spaces between the epithelium and Bowman's membrane enlarging into tiny vacuoles filled with coagulated fluid, which were often in direct connection with the widened nerve canals passing through Bowman's membrane, and finally, the separation of the corneal lamellæ and the flattening of the corneal corpuscles. These appearances were fully confirmed by Fuchs,[5] and form a picture which since then has been recognized as typical of œdema of the cornea due to increased intraocular

tension. Very marked changes in the epithelium have also been sketched by Hess,[10] Nuel,[11] and Brügger.[8]

Nuel believes that many of the vesicles are produced by the local degeneration of the cells, especially of the middle layers, by the continued irritation of the epithelium. Brügger thinks that as a result of the lymph stasis there is an over-nutrition and consequent overgrowth of the cells, which, however, are not viable and soon degenerate, loosening their connection with Bowman's membrane. Birnbacher and Czermak,[9] on the other hand, believe that the degeneration is due to a neuritis of the corneal nerves—in other words, that it is an akantholytic process, such as is described by Lesser in herpes zoster and by Ausspitz in pemphigus. Panas[12] also thinks that by irritation of the corneal nerves, as in zona, the deeper cells may be liquefied and form the fluid contents of the bulla. The condition of the epithelial cells is therefore an important element in the production of these corneal bullæ, and while our two cases do not show the marked changes and bizarre forms described by Hess and Nuel, they illustrate a point which has not been sufficiently emphasized as a factor in the recurrence of the bullæ—*i. e.*, the change in the form of the basal cells. The corneal epithelium is much less firmly attached to the surface than the skin epithelium, because of the absence of the papillæ. In the normal eye the foot cells are cylindrical in form, and their basal plates fit smoothly to the surface of Bowman's membrane. Where the epithelium has been detached, however, the cells lose their cylindrical form and become small and irregular, and consequently are less firmly attached to Bowman's membrane and more easily raised by fluid forced through it. This factor must enter also in the recurrence of the lesion in the curious cases of relapsing traumatic keratitis bullosa, or traumatic keratalgia, some of which have been reported recently by de Schweinitz.[13]

The question as to the origin of the increased fluid in the cornea in œdema due to glaucoma has also been much disputed. Leber[8] believed that it was a pure stasis of the lymph circulation, and proved experimentally that fluid could not be forced into the cornea from the interior of the

eye by increased intraocular tension, as Descemet's membrane and its endothelial cells were impermeable. In this opinion he is upheld by Birnbacher and Czermak[9] and others. Birnbacher and Czermak believe that the increased fluid is to be ascribed to an increased transudation from the capillaries of the corneal limbus. Fuchs,[8] however, contended that, while under normal circumstances the endothelial cells are impermeable to fluids, under the pathological conditions which give rise to œdema of the cornea, changes in the cells, such as the loss of some of them, or in their form, whereby the interstitial spaces become broader, might render possible the passage of fluid from the anterior chamber into the cornea. Such changes, in fact, have been demonstrated by Panas[13] and are well shown in both of our cases, the cells being flattened and in places separated from each other by decided intervals. Greeff[14] thinks that in addition to this method there is a possibility that the fluid may come also from the capillary network of the corneal limbus. This increased fluid, which cannot be drained off laterally because of the obstruction of the lymph channels, forces its way through the widened nerve canals in Bowman's membrane, or, as Brügger believed, through parts of the membrane weakened by absorption, produces an interepithelial œdema which causes the cells to degenerate and loosen their hold on Bowman's membrane, and raises the epithelium in the form of bullæ. The irritation of the corneal nerves may also be a factor in causing degeneration of the epithelial cells, and when the bulla formation has once occurred, the weakening of the connection between Bowman's membrane and the cells by the substitution of flattened, squamous cells for the high cylindrical, basal cells makes the recurrence of the bullæ an easy one. After rupture of the vesicle, infection of the cornea may take place, and ulceration of the surface may be followed by panophthalmitis and total destruction of the eyeball.

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A PRACTICAL CLINICAL METHOD FOR DETERMINING BLOOD PRESSURE IN MAN, WITH A DISCUSSION OF THE METHODS HITHERTO EMPLOYED.[1]

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Before describing a new method for the estimation of blood pressure, a brief review of the instruments now in use and their underlying principles may be of value. From a mechanical standpoint arterial pressure is seen to be dependent upon (*a*) the heart, more particularly the left ventricle; (*b*) the arteries which, by their elasticity, transform the intermittent action of the heart into a constant one; (*c*) the peripheral resistance produced chiefly by the capillaries and small arterioles which are under control of the vasomotor system; (*d*) the quantity of blood. This latter factor varies so little under ordinary circumstances, and the vasomotor system possesses so great a power of accommodation, that this may generally be left out of consideration.

The pressure resulting from these factors is not a constant one, owing to the intermittent action of the heart, as is well shown by an ordinary pulse tracing which presents in graphic form the variations in the pressure but gives no reliable information as to the precise degree of pressure at different times.

[1] Read before the University of Pennsylvania Medical Society, December 19, 1902.

A study of such a pulse tracing shows (*a*) the abrupt rise which is the "beat," and (*b*) a more or less rapid and variously interrupted fall that continues until another beat begins the cycle anew. As to the meaning and origin of the highest point of the tracing—the apex—the belief is general that it represents the accession of pressure due to added force produced by the ventricular contraction, and need not be discussed further. Concerning the interruptions or waves on the descending limb of the pulse curve, opinions differ so greatly that it is impossible to draw many conclusions therefrom, but it is plain that the lowest point of the descending limb must represent the lowest pressure present in the artery, just as the apex represents the highest pressure. As these points in the pulse curve correspond to the phases of the cardiac cycle the pressure indicated by them may appropriately be called the systolic and diastolic pressures.

The systolic pressure, as indicated by the apex of the pulse wave, represents the entire work of the heart at each contraction, while the diastolic pressure as indicated by the lowest point of the descending limb of the pulse wave represents the resistance against which the heart must work. This is evident because no blood can be thrown into the aorta (and consequently no pulse be produced) until sufficient pressure is generated in the left ventricle to spring open the semilunar valves, which are held shut by the pressure present in the aorta during diastole.

The mean pressure lies somewhere between the high and low points, but just where is difficult to say, particularly if the value of the points in question is unknown.

The questions to be answered in measuring the arterial blood pressure in man are these: (1) Can we determine the systolic and diastolic pressure separately, and, if so, is their relation constant enough that the measure of one will give a satisfactory knowledge of the other, or (2) can we determine the mean pressure, and, if so, does this permit us to neglect determinations of high and low pressures as being sufficiently indicated by the mean pressure?

A brief review of the methods and theories by which these questions have been answered will serve to show our present knowledge of the subject of blood pressure determination in man.

1. The first estimations as to the circulation were made by counting the pulse. It was believed that, knowing the capacity of the heart and the rapidity of its action, the amount of work done could be calculated. The fallacy of this was soon evident, and the experiments of Stewart on animals may be quoted. Stewart[1] has shown that in animals the output of the heart per second may vary considerably, while the pulse rate remains approximately constant; and that the output of the heart per second may remain approximately constant while the pulse rate undergoes considerable variation. In the latter case the output per heart beat will vary inversely as the pulse rate. Jellinek,[2] with the Gaertner "tonometer," has found a similar lack of relation between the pulse rate and the blood pressure.

2. The most frequently used method is the estimation of the force exerted by the finger in obliterating the pulse, together with a similar estimation of the compressibility of the artery between beats, the rate and regularity of the heart's action being taken into consideration. The value of this procedure in the hands of skilled and experienced clinicians is undoubted; but, after all, it gives only an approximation, whose accuracy varies with the observer, hence the many efforts to devise a more precise method of determination.

3. The invention of the sphygmograph added greatly to the knowledge of the pulse wave and its variations, but the sphygmograph fails to give any data as to the actual pressure present.

4. Vierordt,[3] in 1855, by increasing the pressure on the spring of the sphygmograph measured the force required to bring about pulse obliteration.

5. Marey[4] in 1876 made the greatest advances along this line. He fastened the arm in a glass vessel resembling a druggist's percolator and then increased the air pressure within the vessel until the skin became pale, believing that in order to bring about pallor the air pressure must be somewhat greater than that present in the arteries. He then lowered the pressure until the color once more appeared, and noted this pressure as being somewhat below the arterial pressure. Therefore, a pressure midway between the points of pallor and flushing must equal the arterial

pressure. Using the same form of apparatus he replaced the air by water as a compressing medium, and connected the glass vessel with a mercury manometer. By increasing the water pressure the changes in the size of the arm due to arterial pulsation were seen in the oscillations of the mercury column, and the greatest of these Marey evidently thought represented the exact arterial pulse. The obliterating pressure was determined by increasing the water pressure until no more oscillations were seen in the manometer. This belief is incorrect, as shown by von Basch, and later by von Recklinghausen, because pulsations are transmitted to the manometer from the artery lying above the point of compression.

6. Roy and Brown[5] in 1878 found that the pressure could be applied by air or water enclosed in a membrane, instead of directly to the skin.

7. Von Basch[6] in 1881 produced the first instrument that could be used clinically. He demonstrated the possibility of measuring the blood pressure by recording the pressure required to occlude an artery—the pressure being applied at a point at which the artery lies on a solid support. The inventor adopted the method of Roy and Brown, and used a hollow capsule of rubber, connected with a mercury manometer, to compress the radial or temporal arteries. The pressure on the capsule (and by it on the artery) forced the air out, and accordingly displaced the mercury in the manometer, and thus the pressure was recorded in millimetres of mercury. This instrument attracted much attention, and was variously modified by different observers, among whom may be mentioned Potain. Many sources of error were soon discovered, and the apparatus is now seldom used.

8. In 1895 Mosso[7] demonstrated that when pressure on the two sides of a membrane is equal, the membrane being in a condition of no pressure is capable of making its greatest vibration or oscillation. Applying this principle to the measurement of the blood pressure in man, he assumed that if a measured pressure by a medium capable of transmitting pulsation could be applied to an artery, the greatest oscillations would occur in the compressing medium when the external pressure just equalled the mean pressure within the artery. The apparatus constructed by Mosso is too

complicated for clinical use, and need only be mentioned. The correctness of the principle will be discussed in describing the other instruments, in the use of which the greatest oscillations are considered to indicate the arterial pressure.

9. In 1896 Hürthle[8] invented an apparatus on the Marey principle, but its complexity prevents its clinical use, and it need not be described.

10. In the same year (1896) Riva-Rocci[9] brought forward a new idea, in that he applied external pressure by circular constriction of the arm, thus being always certain that the pressure was applied at right angles to the artery and thereby avoiding the worst error in the von Basch. At the same time the application to so large an artery as the brachial gave a better measure of the central pressure.

11. In 1898, Hill and Barnard[10] adopting the Mosso principle, applied it by the Riva-Rocci method to the upper arm and claimed to measure the mean pressure by recording the point at which the greatest oscillations occurred.

12. In 1899 Gaertner,[11] having made a finger bloodless by forcing over it a rubber band, applied to it a pneumatic ring connected with a manometer. He recorded as the mean pressure the point at which the finger regained its color.

13. In the same year Oliver,[12] using a small rubber capsule filled with liquid to compress the artery, transmitted the pulsations directly by a straight rod to a spring manometer and recorded as the mean pressure the point at which the greatest oscillations occurred.

14. In 1901 von Recklinghausen[13] published a diagram of a modified Riva-Rocci which differed from the original in that the compressing surface was broader; water instead of air was used as a compressing medium, and the oscillations were recorded by a Hürthle rubber manometer on a revolving drum. Many of the principles advanced in this method are good, but the apparatus has not as yet been manufactured.

As many of the instruments are complicated, only those capable of being used clinically will be described. These are the Riva-Rocci "sphygmomanometer," the Gaertner "tonometer," the Hill and Barnard "sphygmometer," the Oliver "hæmodynamometer."

The Riva-Rocci sphygmomanometer (Fig. 1) consists essentially of three parts. A flat rubber bag, or tube about 40 cm. in length and 4 cm. in width, covered on the outer surface with canvas to prevent expansion outward. One end of this tube is kept permanently closed by the special clamp (Fig. 2), while the other end is pressed together by a lever worked with a screw adjustment after the tube has been properly fitted to the upper arm of the patient. A metal tube passing through the clamp serves to connect the interior of the tube with the remainder of the apparatus. The second part is a mercury manometer, the scale of which will register at least 300 mm. The third part is the air pump, which, in this case, is a rubber syringe of the type furnished with a thermocautery. These three parts are connected to three limbs of a four-way glass connection. To the fourth limb is attached a short rubber tube closed with a spring clip, by means of which the air can be allowed to escape after the pressure has been determined.

The rubber armlet is fitted smoothly to the arm above the elbow, taking care that the muscles are relaxed and that the constriction is on a level with the heart. With the left hand on the radial pulse, the right hand establishes pressure within the closed system. As the air enters, the inner surface of the armlet bulges inward (the canvas held by the clamps prevents outward expansion) and compresses the arm with a force that is measured by the height of the mercury column, and this compression is transmitted through the soft tissues to the artery. As the pressure increases certain changes occur in the radial pulse, which finally disappears. Either the point of disappearance or, what is rather more easily distinguishable, the point at which the pulse reappears after compression is read off the manometer scale as the pressure.

The accuracy of this instrument has been investigated by Hensen,[14] and more particularly by Gumprecht.[15] The latter proved that the pressure recorded on the manometer was really the same as that exerted on the arm, a point of importance concerning which there is no difference of opinion. Whether the pressure applied externally to the arm is directly transmitted to the artery without loss, or whether some of the pressure is lost in the intervening tissues, is a disputed question. Gumprecht experimented on the arm of a cadaver, using arteries of rubber, and concluded

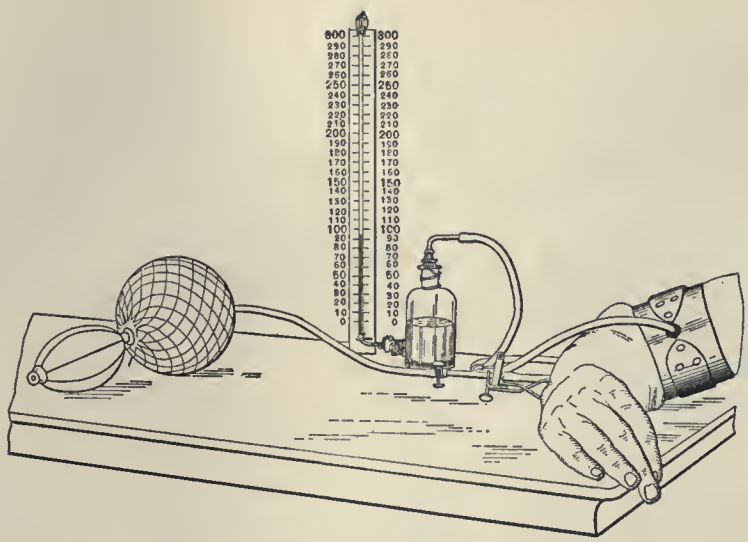

FIG. 1.—Riva-Rocci sphygmomanometer. (From JANEWAY.)
The arm attachment is that of a Hill and Barnard.

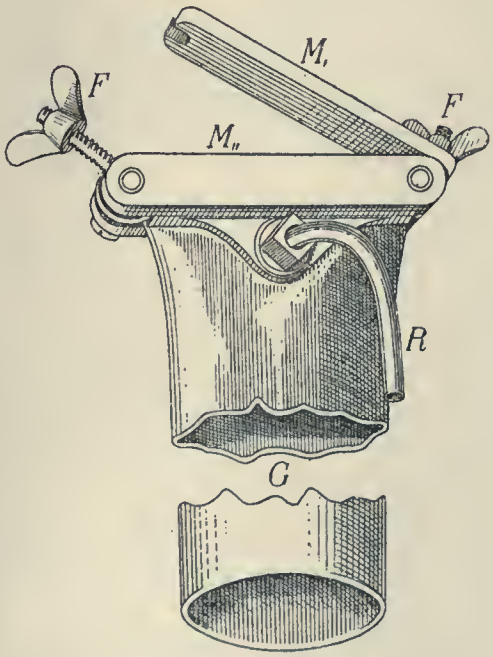

FIG. 2.—The special clamp of the Riva-Rocci.
(From GUMPRECHT.)

that the absorption of pressure by the tissues amounted to about 30 mm. in cases with average pressure, and with higher pressures the loss may amount to 40 or 50 mm. This experiment is open to the objection that dead tissues are much less elastic than living ones, hence his experiments are hardly conclusive. Hensen considers this elastic error as of little importance. He mentions, however, that when the disproportion between the width of the compressing surface and the circumference of the limb is great, a considerable part of the pressure is lost and the readings will be high. This disproportion explains the fact that with a Riva-Rocci a higher pressure is found on the thigh than on the arm. Von Recklinghausen reports a similar increase in the reading with a narrow armlet, and accordingly advises a much wider one than is ordinarily used in the Riva-Rocci. With a wide rubber cuff this observer made simultaneous measurements from the thigh and arm of a patient, and found the results to be practically identical. From this he argues that the soft tissues are perfectly elastic, providing the compressing surface is of sufficient width in proportion to the circumference of the limb. My own results correspond with those of von Recklinghausen. With the narrow cuff one obtains like readings whether it be applied to the arm or the forearm; but on the thigh, unless the patient be very thin, the reading is higher.

With the wide cuff, measurements made from the arm, thigh, and leg, on a patient of moderate development, were practically the same. This perfect elasticity applies only to healthy tissues. In cases of œdema the results are inaccurate.

Besides the soft structures of the arm the wall of the vessel may offer resistance to the compression, and thus increase the reading. The experiments of von Basch[6] are usually accepted on this question. Working with arteries dissected from a fresh cadaver this observer found that the normal arterial wall required an excess of from 2 to 3 mm. above the internal pressure to bring about occlusion. In sclerotic arteries this excess is increased to 5 mm. Von Basch mentions the increased rigidity of dead tissues, and says that these figures may be too high.

It is evident that the pressure measured by this apparatus is the maximum or systolic pressure plus any possible loss due to

transmission, and this possible loss we have seen is so small as to be negligible. Therefore, the conclusion seems to be justified that circular compression of the arm by the Riva-Rocci method gives an accurate measurement of the systolic pressure, provided the width of the compressing armlet is properly proportioned to the circumference of the arm. The mechanical objections are the narrow armlet and the clamp. This latter is difficult to keep in order, and soon wears out the rubber compressing tube.

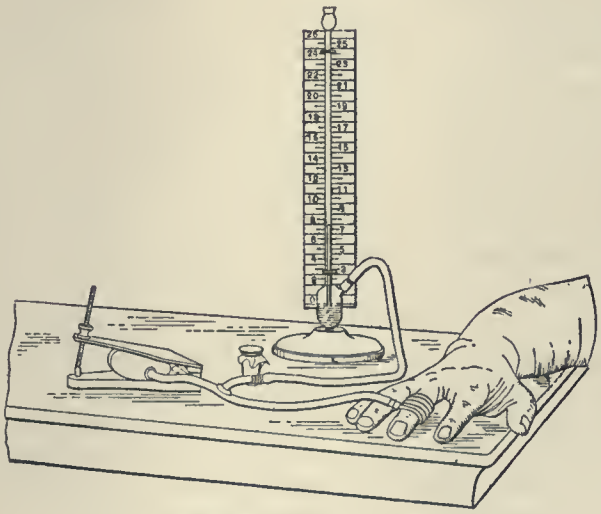

FIG. 3.—Gaertner tonometer. (From JANEWAY.)

The Gaertner apparatus (Fig. 3) consists of a rubber bulb connected at right angles with a rubber tube, on one end of which is a metal ring covered on the inside with thin rubber membrane, while the other end is attached to a metal or mercury manometer. This constitutes an air-tight system, and when pressure is made on the rubber bulb the displaced air bulges inward to the membrane lining the metal ring with a force that is measured by the displacement of the mercury. The procedure is as follows: Selecting usually the middle or ring finger, the ring is adjusted over the second phalanx and the first joint is made bloodless by forcing a rubber band over it. By compressing the bulb a pressure is established in the system which is greater than that expected to

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be present in the digital arteries, and the rubber band is removed. If the pressure in the ring is greater than that in the finger, the first phalanx remains pale. The pressure is now slowly reduced until the finger suddenly flushes, while at the same time the patient perceives a distinct throb.

The point read from the manometer is supposed to represent the mean pressure. That the "tonometer" gives the mean pressure has been disputed by many observers (von Recklinghausen,[13] Fränkel,[16] Janeway,[17] and others), and justly. While it seems plausible that no flushing of the skin can occur until the external pressure is below that within the artery, it is likely that the apices of the pulse waves will break through and cause the flush at a higher level than the mean pressure. Without going into a discussion, my personal belief is that the flush of the "tonometer" gives the same idea as to pressure in the digital arteries as the reappearance of the pulse by the Riva-Rocci method gives of the brachial pressure. This belief is based upon the result of a number of comparative measurements, made with the two forms of instruments, which will appear in a subsequent paper.

The compactness of the "tonometer," its ease of application, the fact that the pressure was determined by sight, and because it gave, or was said to give, the mean pressure, led to the belief that it offered many advantages over the Riva-Rocci, but my experience of more than a year, during which the two instruments were used side by side, has proven the contrary.

It was found to be difficult to define exactly the point of flushing, as in many instances this occurred gradually, and the pressure at which the flush appeared seemed to be dependent on the degree of primary pressure—a high primary pressure giving a lower flushing point. In negroes, and in all cases where artificial light was used, the exact level at which flushing took place was hard to estimate. In many instances it was practically impossible to get two successive readings to correspond with each other, and frequently a variation of 20 mm. or more between the high and low points was found in a series of ten successive tests on the same patient. These variations are explained on the ground that the arteries from which the pressure is taken by this method are so near the vessels under vasomotor control that the vasomotor

changes are shown in the pressure reading. This explanation is borne out by the fact that in cold hands almost no pressure is recorded by the "tonometer," while in conditions of peripheral relaxation the pressure is higher by the Gaertner than by the Riva-Rocci. Generally speaking, the palpation of the pulse reappearance by the Riva-Rocci was to me a more easily perceived and sharply defined criterion than the recognition of the flush.

The remaining instruments to be described are based on the theory of Mosso, that the greatest oscillations occur in the arterial wall when an external pressure is applied that just equals the mean pressure. The experiments on which this theory is based were not done on animals (Howell and Brush), and the statement that the point of greatest oscillation represents the mean pressure has been objected to by Sahli[22] and others, and rightly. So long as life is present there is pressure within the arteries, and so long as there is pressure the arterial walls are in a condition of tension, and, as the amplitude of vibration is proportional to the degree of tension, it is evident that the greatest vibration would occur at the time when the pressure within the artery was lowest—diastole. Before the pulsation can be recorded on the manometer a portion of the compressing medium must be displaced, and it is plain that when the external pressure equals the diastolic pressure every part of the arterial pulse wave can act to bring about this displacement. On the other hand, if the external pressure equals the mean pressure, during a portion of the time the arterial lumen must be occluded, and a part of the pulse wave is lost in restoring the calibre to the artery before it can come to act on the compressing medium.

This theoretical reasoning has been clearly proven by the work of Howell and Brush.[18] Experimenting on dogs, they found that the diastolic pressure as measured by a minimum valve attached to one carotid just equalled the base-line (lowest point) of the greatest oscillations recorded on the manometer attached to a plethysmograph surrounding the other carotid. From this it is evident that the "greatest oscillations" record the diastolic pressure (contrary to the belief of Mosso), and that the instruments constructed on this principle do not give the mean pressure.

The Hill and Barnard[10] (Fig. 4) "sphygmometer" is the best of this type of instrument. It consists of a rubber bag of the same dimensions as the Riva-Rocci, which is kept from expanding outward by a cuff of stiff leather. This rubber bag communicates with a specially constructed metal manometer that magnifies the pulsations, and with a small pump resembling a bicycle pump. The armlet is applied above the elbow, using the same precautions as to muscular relaxation, etc., as advised with the Riva-Rocci, and pressure established in the apparatus. As the pressure increases the needle of the manometer begins to oscillate, and the oscillations grow larger up to a certain point, and then diminish in size and finally cease. The pressure at which the greatest

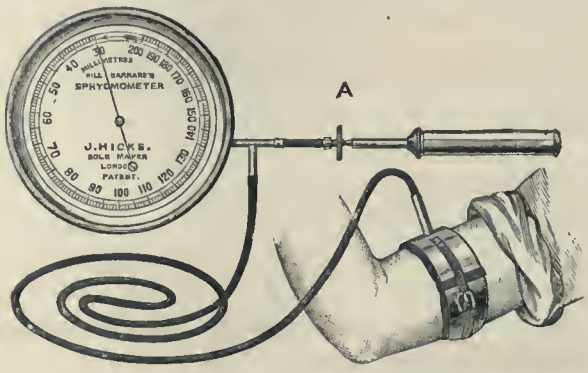

FIG. 4.*—Hill and Barnard sphygmometer.

oscillations occur is noted—erroneously, as we have seen—as the mean pressure. That the point where oscillations cease represents the systolic pressure is incorrect, as pulsation may be transmitted to the manometer long after the radial pulse has disappeared.

As the width of the compressing surface and the mode and site of application are exactly the same as in the Riva-Rocci, the anatomical considerations are similar and need not be discussed. The chief mechanical objections are the narrow compressing surface and the metal manometer. It has been impossible so far to construct a metal manometer that is reliable and will remain so for any length of time. With use the spring loses its strength,

* Cut from Oelschlager Bros., New York.

and instead of the indicator pointing to zero when at rest, it gradually comes to hold a higher position, so that the needle at rest may indicate ten or more millimetres, which must be deducted from the reading. Frequent comparisons with a mercury manometer are necessary in order to learn the degree of error in the metal instrument, and in this comparison it is often found that they agree while the pressure is increased, but that with diminishing pressure the needle of the metal manometer fails to fall with the same rapidity as the mercury column, so that after each diminution of pressure a distinct interval intervenes before the needle

Fig. 5.*—Oliver hæmodynamometer.

reaches the same level as the mercury. Under such circumstances it is impossible to gauge the error, and for these reasons I have given up all attempts at using the metal manometer in my blood pressure estimations. The length of the rubber tube leading from the pump and the degree of its elasticity will influence the size of the transmitted pulsations to a greater or less extent; for the more rigid the walls of the transmitting tube the more accurate will be the transmission of oscillation.

The Oliver[12] "hæmodynamometer" (Fig. 5) is a return to the original principle of von Basch. It consists of a very delicate

* Cut from the A. H. Thomas Co., Philadelphia.

spring manometer, from which runs a short, straight rod, terminating in a flattened extremity, which in turn is in contact with a small rubber capsule, filled with liquid. Any pressure on the capsule is transmitted by the fluid to the rod, and through the rod directly to the spring of the manometer. Being careful that the instrument is at right angles to the course of the vessel to be investigated (usually the radial), the capsule is pressed against the artery. As the pressure increases, the pulsations are transmitted to the indicator of the manometer. These vibrations of the indicator grow larger as the pressure increases until a maximum is attained, and then decrease in size. The pressure at which the maximum oscillations occur is read off the manometer as the mean pressure.

The objections to this method of applying pressure are those which caused the von Basch to be discarded, and need not be discussed. The delicacy of the spring manometer makes it even more liable to error than the ordinary metal manometer. My own experience with the Oliver was very unsatisfactory, and I have been able to find no reports on its use except those of the inventor.

It is evident from the preceding that there are two types of blood-pressure instruments—the one type giving, with more or less accuracy, the systolic pressure, under which are included the Riva-Rocci and the Gaertner; the other type registering the diastolic pressure, under which are mentioned the Hill and Barnard, and the Oliver. The mean pressure is thus still undetermined.

An effort was made by Hensen[14] to prove that the systolic pressure was a reliable guide to the condition of the mean pressure. He proceeded as follows: Selecting a patient with thin abdominal walls in whom the abdominal aorta could be compressed, he immobilized one arm and attached to it a sphygmograph. After a few pulse waves were recorded by the sphygmograph, and while the instrument was still in action, he compressed the abdominal aorta until pulsation disappeared in both femorals. The pulse waves recorded on the sphygmogram during compression of the aorta showed a higher level than those recorded before compression, and this higher level is attributed by Hensen to the increase

of blood pressure brought about by aortic compression. Applying his Riva-Rocci to the patient's other arm, Hensen measured the systolic pressure before and during compression of the aorta, and believed that the pressures obtained gave him the value in mm. of mercury of the apices of the pulse waves recorded by the sphygmograph at these periods. Knowing the value of these two levels, similar abscissæ were constructed, and in this way Hensen thought the entire pulse wave could be measured. He estimates the variation in pressure due to the pulse wave at from 5 to 20 mm. in normal individuals, an amount of such small importance that in such cases the systolic pressure of the Riva-Rocci is considered by him a reliable guide to the mean pressure. In pathological conditions, as aortic regurgitation, the pulse wave variation is much greater, and the systolic pressure is no longer a trustworthy indicator of the mean pressure. The difficulty of this procedure is so evident, and the fact that it cannot be used in all patients, according to the author's own statement, renders a discussion of its many sources of error unnecessary.

It is plain from this that the systolic pressure cannot be used as a guide to mean pressure. Concerning the instruments using the greatest oscillation as a criterion of the mean pressure, I have been unable to find any investigations as to the relation between the pressure found by them and the systolic pressure.

Various methods have been devised to obtain the two levels of pressure in the human artery.

1. Gumprecht,[15] after determining the systolic pressure by the Riva-Rocci, connected the apparatus with a mercury manometer provided with a float, clamped off the air syringe from the remainder of the instrument, and thus was able to secure pulsations in the manometer which were registered by the float upon a revolving drum. These oscillations were registered at varying degrees of pressure, and the pressure at which the oscillations showed the greatest amplitude was looked upon by Gumprecht as representing the mean lateral brachial pressure. The difference between this pressure and the systolic pressure was believed by the author to show the loss in pressure between the axillary and brachial arteries, and he thought this loss was due to the many large branches given off in the axilla. Since it has been definitely

proven that the pressure in all the large vessels is practically the same (von Recklinghausen,[13] Hürthle,[19] Tigerstedt,[20] and others), the pressures found by Gumprecht must be looked upon as systolic and diastolic brachial pressure. The author says that a comparison of these pressures would be of value if they could be made sufficiently close together.

2. Von Recklinghausen[13] adopted the same principle as Gumprecht, but used a wider compressing surface; while with water as a compressing medium the oscillations were transmitted to and recorded by a Hürthle rubber manometer. Determining the systolic pressure by noting the recurrence of the pulse, from the tracing made by the manometer—the so-called "treppencurve"—he constructs the true pulse in all its variations. A glance at his illustrations will show that the base-line of the reconstructed pulse corresponds to the lowest point of the greatest oscillations recorded. This apparatus must be very expensive to construct, and the disadvantage of an instrument using water as a compressing medium is evident. As already stated, this instrument has not as yet been manufactured.

3. Janeway[17] attempts to find the systolic and diastolic pressure as follows: Having attached a sphygmograph to the wrist in such a manner that the lever works freely, he applies a Riva-Rocci above the elbow on the same arm and determines the systolic pressure by noting the point at which the pulse recurs. "The maximum arterial pressure having been determined, successive tracings are taken at intervals of 10 mm. pressure from a pressure below that which first produces any effect on the curve up to the point of obliteration of the pulse." He records the pressure at which the secondary waves no longer appear in the pulse tracing, and thinks that the disappearance of the secondary waves denotes some degree of compression of the artery. The author states that considerable skill is required to carry out this method, and as after each tracing the pressure must be reduced to zero and the effects of venous congestion allowed to disappear, the examination must require a considerable time. This method is very ingenious, but the results in my hands have not been satisfactory.

It is open to the objection that a considerable interval inter-

venes between the two determinations, while the effect produced on the secondary waves by the long-continued pressure of the sphygmograph and the intermittent pressure of the armlet is difficult to estimate. Thus, in taking tracings by this method not only was the character of the secondary waves changed, but the systolic pressure in one case was increased from 122 mm. before tracing to 132 mm. after the tracing. With any sphygmograph but a Jaquet this method would require two people to carry it out.

4. Uskoff[21] has suggested that the Riva-Rocci be used in conjunction with the Gaertner in the determination of blood pressure. The former gives the systolic pressure, while by the latter the peripheral resistance can be estimated. My own results with the two instruments have already been mentioned, and it is my belief that the Gaertner gives information as to the systolic pressure and shows peripheral resistance only in so far as its readings are affected by vasomotor changes.

The results of Hensen's[14] investigations, and the fact that so many means have been devised to determine the two levels of arterial pressure, is sufficient evidence that the determination of the systolic pressure gives no reliable information as to the mean pressure or as to the diastolic pressure. At the same time the instruments using the greatest oscillation as the criterion of mean pressure give no reliable data as to the systolic pressure, nor do they, as we have seen, show the mean pressure. That the diastolic and systolic pressures do not bear the same relation to each other in every individual is patent to every physician when he examines a case of aortic regurgitation. The throbbing pulse and forcible heart action is indicative of the high systolic pressure, while the capillary pulse, moist skin, and almost empty arteries between the pulse beats evidence the low diastolic pressure. The maintenance of the circulation in compensated cases is clinical proof that the mean pressure is practically normal.

In this connection may be quoted the work of Howell and Brush.[18] They were able to produce variations in the high and low pressures of a dog without affecting the mean pressure; and, even more important, they showed that the mathematical mean of the systolic and diastolic pressures approximately equalled the mean pressure.

Therefore, in order to gain a complete idea as to the arterial pressure in man, it is necessary that both systolic and diastolic pressures be estimated, for only in this way can we obtain information as to the work of the heart, the degree of peripheral resistance, and the condition of mean pressure. Dealing with so changeable a quantity as the arterial blood pressure, it is necessary, as Gumprecht insists, that the measurements be made at practically the same instant; while in order that the determination can be of value to the clinician, the instrument employed must be simple in construction, easy of operation, and transportable. Bearing these necessities in mind, and also the fact that at the present time no instrument for determining blood pressure is made in this country, I submit this apparatus, which seems to possess most of the qualifications mentioned. Fig. 6 illustrates the working model which has been used for some months in Dr. Stengel's wards in the University Hospital.

The rubber armlet used in compressing the arm is three and one-quarter inches wide and sixteen inches long, and closed at both ends. This width of compressing surface (more than twice that of the Riva-Rocci or the Hill and Barnard) is selected because it is the widest that will permit of smooth adjustment to the average-sized arm. This rubber is prevented from expanding outward by a cuff of leather or double thick canvas, reinforced by tin strips. To the centre of the rubber cuff is cemented a rubber valve stem (of the kind used on the inner tube of a bicycle tire) through which passes a glass connecting tube, its extremity being flush with the inner surface of the armlet. A piece of very stiff-walled rubber tubing, about one-quarter inch in calibre, connects the glass tube in the valve stem with one end of the horizontal limb of a glass "T," while a similar piece of tubing joins the other extremity of the horizontal limb to a mercury manometer. The vertical limb of the "T" is connected by softer tubing with a small foot pump.

The procedure is as follows: The rubber armlet is fitted to the arm above the elbow by overlapping the ends, and it is held in place by adjusting the external cuff in a similar manner. The arm muscles should be relaxed, and the armlet should be on a level with the heart, to avoid the effect of gravity. The cuff

should fit smoothly, but no pressure must be exerted. The connections having been made, and the manometer placed securely, the left hand finds the radial pulse, the right hand catches the soft tube leading to the pump just below its attachment to the glass "T," and the right foot works the pump. Air is forced

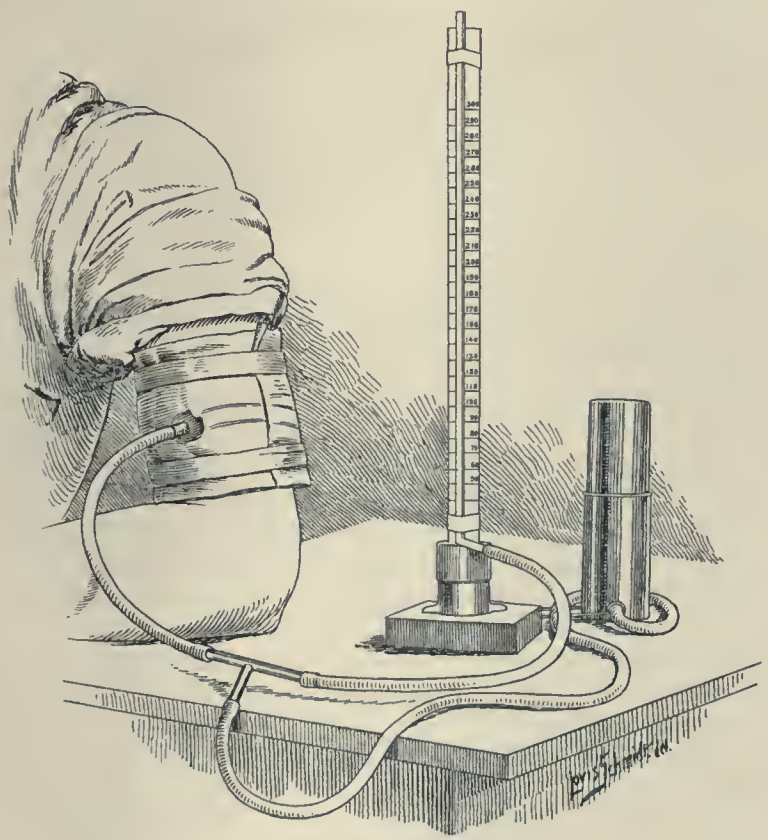

FIG. 6.—Author's model.

into the apparatus until the pulse is no longer palpable. The thumb and forefinger of the right hand now compress the soft tube, forming a most efficient valve. The air is then permitted to escape gradually until the pulse reappears, and this point mentally noted as the systolic pressure. The pressure is now reduced

a few mm. at a time, and the pulsations in the mercury column will increase in size until a maximum is obtained, and then diminish. The base-line of these maximum pulsations is noted as the diastolic pressure. The mean pressure is the mathematical mean of the two pressures obtained. The air is allowed to escape from the apparatus by disconnecting the lower tube. In this manner the systolic and diastolic pressure can be determined within a half minute of each other—a period so short that variations are hardly likely to occur.

It will be noted that after the fingers close the tube leading to the pump the armlet is connected directly with the manometer by a tube composed entirely of non-distensible rubber and glass, in this way avoiding any error in the transmission of the oscillations.

The manometer shown in Fig. 6 is one made after the plan of the Gaertner, is transportable, with some difficulty, and is presented simply to illustrate the method.

The Arthur H. Thomas Co., of Philadelphia, are constructing for me a simpler form of mercury manometer that will permit of easy transportation, which will be furnished with the apparatus they are making after the model shown in the cut.

The pump used is simple in construction, and when closed measures two inches in diameter by four inches in length. The one shown has been in constant use for nearly a year, and is still perfectly satisfactory.

The mode of fastening the rubber armlet around the arm avoids any wear, and I have cuffs that have been in use more than six months which are still air-tight.

In this article no tabulations of the pressures found in clinical cases will be included. Of special interest have been the results of blood pressure measurements in cases in which the vasomotor system was chiefly at fault, and the work now being done along these lines will form the subject of one or more subsequent papers.

In conclusion I wish to express my thanks to Dr. Stengel, at whose instance this work was undertaken, for his many suggestions and for the privilege of his wards in the University Hospital.

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THE PRESENT CONCEPTION OF DERMOID CYSTS OF THE OVARY, WITH THE REPORT OF A CASE OF TERATOMA STRUMOSUM THYREOIDEALE OVARII.[1]

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

Wilms' investigations in 1895 did much to settle the true nature of dermoid cysts of the ovary. While his deductions have been disproved in part, his demonstration of the anatomical peculiarities of these tumors has been generally accepted. Previous to that time ovarian dermoids had been regarded as essentially of an ectodermal type—hence the name dermoid. Their chief characteristic seemed to be the cutaneous structures of which they were largely composed, and the significance of other tissues sometimes found in them was not appreciated. Wilms showed that these ovarian dermoids were complicated teratomata, and that they contained derivatives from all three layers of the blastoderm. He called them embryomata, thought they were peculiar to the ovary, and believed they resulted from the development of an unimpregnated ovum (the parthenogenetic theory of Pfannenstiel, Geyl, and others). Wilms' paper excited a great deal of comment. His views were endorsed by some and rigorously opposed by others. Bandler attempted to show that dermoids of the ovary differed in no respect from dermoids in other regions,

[1] Exhibited before the Pathological Society of Philadelphia, June, 1903.

and that they never contained entodermal elements. He ascribed them to inclusions from the Wolffian duct, which he believed to be of ectodermal origin. Bandler's position is untenable, because the Wolffian duct is not of ectodermal origin, and because entodermal products do occur in ovarian dermoids. Bandler was wrong when he said that the entodermal structures found in "dermoids" were but "dream pictures" of the microscopist.

Bonnet showed that embryomata of the ovary differ essentially in no way from embryomata found elsewhere. He disproved the possibility of their parthenogenetic origin and with Marchand agreed that they are best explained by the inclusion theory of Cohnheim. They do not adopt the ideas of Cohnheim in every particular, but, in the main, their views correspond to those expressed by him years ago. At the present time Wilms agrees with Bonnet and Marchand, and in 1902 published the third part of his work on mixed tumors, in which he discusses the entire question in a very convincing way. Dermoid cysts of the ovary are mixed tumors that contain, as a rule, ectoderm, mesoderm, and entoderm. As they, therefore, possess structures derived from each of the three layers of the blastoderm, they are called embryomata. Embryomata are not peculiar to the ovary, but are found in other parts of the body. Mixed tumors containing but two of the blastodermic layers are designated as bidermome to contrast them with mixed tumors of the more complicated type (embryomata), which are called tridermome. Going higher in the scale, there are embryomata so complicated, or in which the resemblance to mature organs and tissues is so striking, that they are spoken of as fetal inclusions. Still higher there are parasitic formations and monstrosities. There seems to be a distinct relation between all of these growths, and their origin is referred to phenomena occurring during the early development of the ovum. Two theories have to be considered here. Either the embryomata originate from (1) a coincidently impregnated polar body, or (2) the development of a blastomere separated during division of the ovum and not participating in the formation of the fœtus proper. Which of these two possibilities is probable? That a polar body may be impregnated is, upon the basis of comparative embryology, accepted by Marchand and by Bonnet. Although it

has never been directly observed in man, its occurrence in invertebrates and vertebrates justifies the belief in the possibility of its occurrence also in the human. Polar bodies are abortive ova, and it is surely possible that such ova may be impregnated by the spermatozoön. Polar bodies, after their impregnation, may lie upon the surface of the ovum at different points. In their further development they may, as Marchand has observed, be implanted in the medullary furrows or crevasses, and after the three embryonal layers have differentiated they may constitute parasitic formations or inclusions with fetal envelopes more or less developed. If we believe these embryomata to be the result of impregnated polar bodies, then we must suppose that (but two of them are present in nearly all vertebrates) there would not be more than three embryomata in one individual; yet Sänger has a specimen in which there are five embryomata in a single ovary, each of which contains ectoderm, mesoderm, and entoderm. Another argument against the polar body theory is the fact that many embryomata contain parts of but one-half of the body; thus a specimen in the Giessener collection shows a beautifully developed temporal bone and upper jaw of the same side of the body. Bandler observed that the teeth found in embryomata of the ovary were always those which corresponded to that side of the body from which the tumor originated.

The blastomere theory seems to be less antagonistic to anatomical facts. Through the experiments of Driesch, Herbst, and others, Bonnet says it has been shown that by agitation in sea water free of chalk, blastomeres from ascidian and echinoderm embryos can be developed into complete but smaller embryos. Wilson found the same in amphioxus, Morgan in shell-fish and frogs, O. Hertwig and O. Schulze also in frogs, and Herlitzka in triton embryos. It is known, Bonnet further says, that the division of the ovum in suckling animals is irregular and that in some blastomeres there are mitoses, while in others there are not. Now it is manifest that if separation of a blastomere occurs very early—*e. g.*, after the ovum has been divided into sixteen blastomeres—it is capable in its further differentiation of a much more complicated structure than if it is separated later, perhaps one of several hundred blastomeres then differentiating into the three

blastodermic layers. This view reconciles the varying structure of tumors originating from the same cause. Wilms had difficulty earlier in explaining why, if embryomata of the ovary were to be explained on the blastometre theory, which he accepted for teratomata elsewhere, there was such a preponderance of these growths in the sexual glands; but Bonnet has explained this satisfactorily by observing the very large proportion of the embryo that consists of urniere (Wolffian body), from its earliest development until the sexual glands are differentiated. The possibility of blastomeres becoming implanted within this structure is, therefore, very great.

Roux and Keibel have made similar observations, and Wilms agrees with them.

Wilms believes that double monstrosities, fetal inclusions, and embryomata all come from the same origin, viz., a disturbance in early ovular division. Either the separated germinal elements may grow equally, or one may cease after a time, or one may remain quiescent entirely. Thus Wilms says there may be:

1. Development of two blastoderms out of one ovum, with partial attachment. We may have then:

(*a*) Symmetrical double formation (if both blastoderms grow equally); or

(*b*) Asymmetrical double formation (if one early ceases to grow); or

(·) Parasitic inclusion (if one is enveloped by the growth of the other).

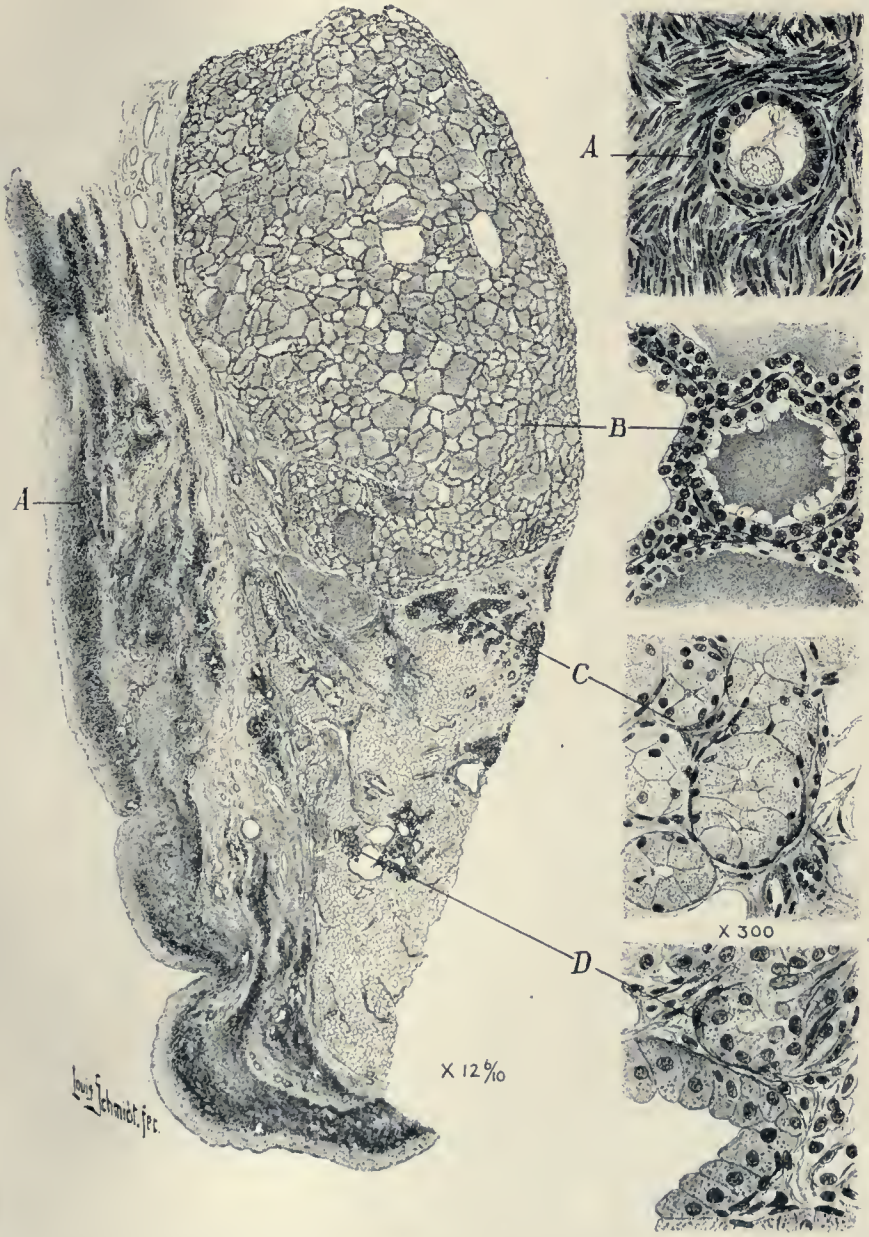
2. Development of one blastoderm from the ovum with displacement of the blastomeres.

Then follows either

(*a*) Evident embryomata or inclusions at birth (if the blastodermic cells have grown); or

(*b*) Deposit of blastodermic cells in the body which may at some future time give origin to embryomata.

Within the past year Schlagenhaufer and Pick have reported cases which seem to throw additional light upon this subject. Schlagenhaufer, in a testicular tumor, and Pick, in a so-called ovarian dermoid, found chorio-epithelial elements. Pick, indeed, found chorion villi. Marchand believes that parasitic formations



Section through "dermoid prominence" in author's case of teratoma strumosum thyreoideale ovarii. *A.* Premordial follicle in ovarian stroma. *B.* Struma colloides. *C.* Mucous glands. *D.* Sebaceous glands.

are derived from fecundated polar bodies, whereas the embryomata of the sexual glands are derived from displaced blastomeres. Bonnet attributed all embryomata to blastomeres, because (until the past year) portions of the ovisac had never been found therein. Schlagenhaufer has demonstrated their presence, and therefore he would divide embryomata into two classes: (1) those containing ovisac elements (these spring from fecundated polar bodies), and (2) those without ovisac elements (these spring from displaced blastomeres).

That this is a false conclusion Pick believes for the following reasons:

1. Very early blastomeres must contain ovisac elements; as the ovum produces its own envelopment, the cells of its earliest division must be capable of producing the fetal membranes.

2. Embryomata, even though no chorion elements are found therein, may have originally contained them or may contain them at the time of examination, because

(*a*) Unless the entire tumor is cut serially (and this is nearly impossible in many cases) portions of chorion elements may be overlooked.

(*b*) Although the primarily displaced cells may have contained elements of all three layers of the blastoderm and also elements of the ovisac, in their development these elements may not grow equally, so that there is a preponderance of certain tissues over others. This, as Bonnet says, depends upon the changing outer relations of environment, pressure, metabolism, chemistry, blood supply, and function of the organ in which they are found. The faulty, arrested development of some of the elements is shown in the embryomata of the testicle, where the epiderm, in contrast to the analogous growths of the ovary, is extremely little in evidence, and also in actual embryomata of the ovary that are represented by a single tooth or glial tissue or thyroid gland structure, or even by a chorio-epithelioma itself, as shown by Lubarsch in such a case affecting a girl aged thirteen years. The author concludes that up to this time there are no grounds upon which the question of the blastomeric or polar body origin of embryomata can be determined. It is more important to distinguish between teratomata which contain all three layers of the blastoderm and

come from very early displaced elements, and those teratomata which occur later at the position of folds and furrows of the fœtus by invagination and snaring off of epiderm and mesoderm or even, perhaps, also entoderm. Wilms believes that in the growth of embryomata some of the original cells are differentiated and form adult tissues and organs, while others remain quiescent. The presence in these tumors of the undifferentiated elements of the three blastodermic layers would explain why, in the metastases of embryomata, all of the structures found in the primary tumor are present.

Besides the usual ectodermal and mesodermal structures that predominate in embryomata of the ovary there have been described central nervous tissue, formations that resemble the eye, trachea, thyroid gland, lung, bowel, pelvic bone and ribs, bone-marrow, nose, mammæ, submaxillary gland, fetal genital gland, extremities, voluntary muscle fibre, chorion villi, and chorion epithelium. It seems likely, therefore, that it needs but time and minute histological examination to find in these tumors any and all organic formations of the body.

Attention has recently been turned to the presence of thyroid gland tissue in embryomata. Gottschalk reported an ovarian tumor which he believes originated from the primordial follicle. Kretschmar described a similar formation, but considered it an endothelioma. Pick first pointed out the fact that both of these cases were nothing more than teratomata of the ovary in which there was a predominance of thyroid gland tissue. At present his opinion is supported by Carl Ruge and Robert Meyer. Meyer and Katsudura have had similar cases, and in both painstaking examination showed the tumors to be teratomatous. From what has been said before it is not surprising that in some teratomata but one sort of tissue is found. Such a case does not refute the blastodermic origin of these growths, for we have seen how the development of the displaced blastomere may be confined to one set of cells. Saxer has described a teratoma of the ovary consisting of a single tooth enveloped in the ovarian stroma. In this instance but one set of cells of the original blastomere had developed.

It is probable that but for Gottschalk's case teratomata con-

taining thyroid gland tissue would never have received particular attention. Its presence is by no means unusual. Where it exists in predominating amount, however, the tumor might be confounded with Gottschalk's "folliculoma malignum," and this form has been given prominence. Pick has proposed to call such a growth either struma thyreoidea ovarii aberatta or teratoma strumosum thyreoideale ovarii. It seems better to use the last of these terms than the first. Struma thyreoidea ovarii aberatta certainly does not convey the definite impression that we are dealing with an ovarian teratoma in which there is a large proportion of thyroid gland tissue.

There is no doubt that the significance of a teratoma is the same whether it contains a large or a small amount of thyroid gland or any other sort of tissue. If the term "dermoid" as applied to the usual teratomata of the ovary is misleading and scientifically inaccurate, then the term "struma thyreoidea ovarii aberatta" is also faulty.

The specimen of teratoma that I wish to report was removed by Dr. J. G. Clark from a woman aged thirty-six years. Her history is entirely negative.

The pathological description of the tumor, somewhat abbreviated, is as follows: Pathological No. 525. Specimen consists of a cystic tumor about the size of a goose-egg. Upon section the contents are found to be hair and sebaceous matter. The cyst lining resembles skin. The so-called "dermoid prominence" contains a spicule of bone and a circumscribed, translucent, brownish-yellow tissue which forms the largest part of the entire thickness of the prominence.

Histologically: All the elements and structures of the skin are present in the cyst lining. Chief interest centres about the translucent brownish-yellow tissue in the dermoid prominence. This consists of an area of closely packed cystic glands containing a homogeneous translucent material that has an affinity for acid stains. The stroma is made up of fibrous tissue upon which the epithelium of the gland acini rests. This epithelial lining looks like a ribbon of protoplasm enclosing here and there small, dark nuclei. The whole picture is identical with that of the thyroid gland.

There is perhaps no more clinical significance to teratoma strumosum thyreoideale ovarii than to any of the teratomata. Gottschalk's and Kretschmar's cases were malignant. Wilms calls embryomata clinically malignant because by their size and growth they may lead to the death of the individual. If, therefore, it is understood that there is no sharply defined anatomical characteristics of malignancy he would join Pfannenstiel in calling teratomata malignant. It is possible that a metastatic ovarian struma thyreoidea might occur; but it is not probable, as metastases from a hyperplastic thyroid gland, or from the adrenals, usually occur in the osseous system.

In none of the cases reported has any abnormality of the thyroid gland been noted. It is well to bear in mind that struma colloides may be malignant even though it presents but the histological picture of the normal gland.

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PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX, AND THE REPORT OF A CASE.

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The history of carcinoma of the vermiform appendix is of extremely recent date, fully three-fourths of the cases now on record having been reported within the last six years. The condition may be studied from two aspects, the clinical and the pathological. Unfortunately, the clinical side is not very satisfactory, the diagnosis of carcinoma of the vermiform appendix usually being impossible before operation, and in a large percentage of cases can only be made by the microscope. The similarity of the symptoms to those of appendicitis makes the diagnosis very difficult. Fortunately, the treatment is the same in both conditions.

Etiology. In nearly 60 per cent. of the cases of carcinoma of the vermiform appendix in the literature there has been a definite history of previous attacks of appendicitis. The microscope more than bears out this statement. Letulle and Weinberg believe that their cases developed on top of an obliterating appendicitis. Ribbert claims that there is a primary inflammation in all cases.

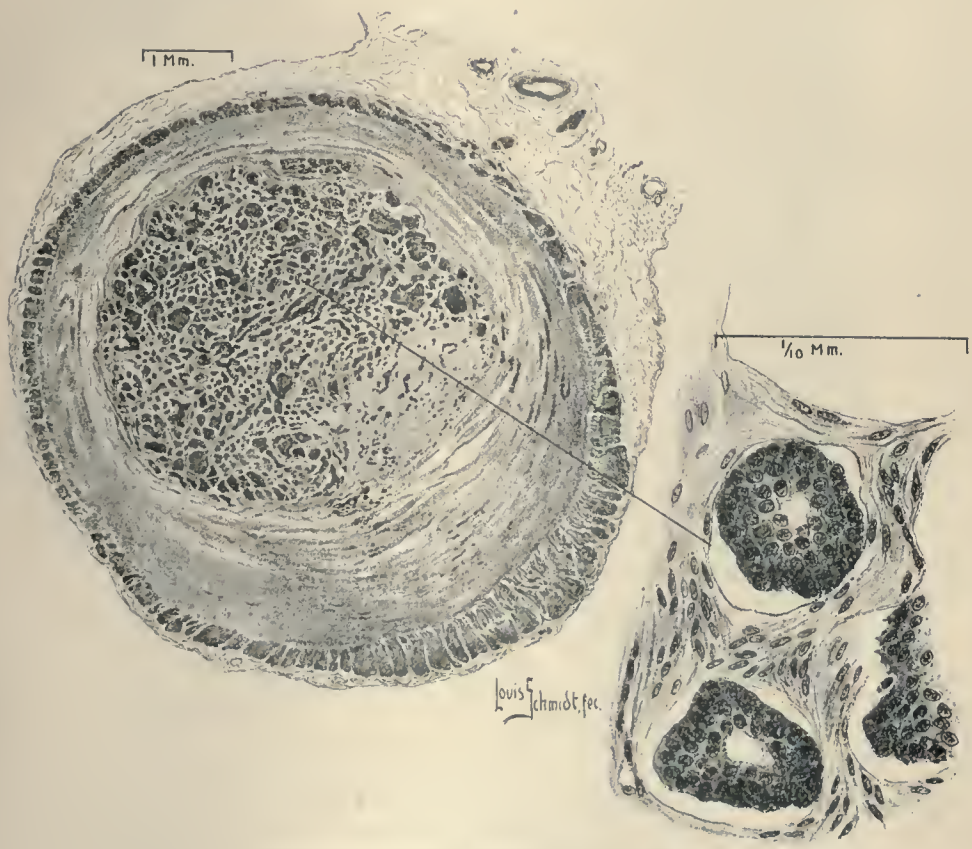
Age. The age at which carcinoma of the vermiform appendix occurs is of interest, mainly from the fact that about 65 per cent. of cases occur before thirty. This seems to concur with the

theory that the disease follows appendicitis, as the latter is chiefly a disease of early and middle life. Cases of carcinoma of the vermiform appendix have been reported occurring in patients varying in age from fifteen to fifty years. About 75 per cent. of cases reported have occurred in females. As the disease is frequently discovered accidentally, the greater number of abdominal and pelvic operations performed on women may account for this seeming disparity of the sex.

Symptoms. *Pain.* According to Hurden, this is the chief symptom, and in moderately early cases it is usually of a dull, aching character, occurring in the right iliac fossa. The sharp, cutting, or lancinating pain so common in carcinoma of other parts of the body is rare in this disease. In Moscheowitz's careful study of fourteen cases pain was present in 78.5 per cent. of cases. *Tenderness* was present in 71.4 per cent. of the cases and *rigidity* in 28.5 per cent. Temperature varies considerably, but when present to a marked degree is probably due more to an accompanying appendicitis than the carcinoma. *Pulse* usually rises with the temperature, and from the same causes. The tumor is rarely, if ever, palpable as such, although a mass is not infrequently present. Loss of weight, cachexia, hæmatochezia, and low hæmoglobin are usually found late in the disease, and after the growth has involved surrounding structures. The usual symptoms are those of relapsing appendicitis.

Rarity of the Disease. Nothnagel and Maydl found two cases in 40,000 autopsies. Deaver found three cases in 706 appendices removed for disease of that organ, and one of his was probably secondary to disease elsewhere in the body.

Pathology. *Macroscopically.* The length of the vermiform appendix varies greatly. In one of Harte and Willson's cases the organ was the unusual length of 15 cm., while others report appendices as short as 4 cm. Adhesions are frequently present. Fecal concretions and strictures are not uncommon. The carcinoma has been described as a tumor the size of a walnut, in other cases the size of a pea or bean, while in many cases no new-growth was present macroscopically. The location of the carcinoma is usually near the tip; in only about 15 per cent. of cases is it



Section of vermiform appendix 1 cm. from tip.

found near the base. In some cases the organ is the seat of acute suppuration and necrosis, in others it is the seat of catarrhal inflammation, while in still others little or no gross change can be seen.

Microscopically. The most frequent varieties are the adenocarcinoma, the alveolar carcinoma, the colloid, and the scirrhous types.

History of Case. This case occurred in the gynecological service of Dr. John G. Clark, at the University of Pennsylvania Hospital.

Mrs. L. F., aged twenty-seven years. Hospital No. 860; gynecological No. 986.

The previous history of the case is unimportant. For the last two years the patient had been suffering from pelvic inflammatory disease of the right side. There were no symptoms pointing directly toward the appendix, nor was there any history of previous attacks of appendicitis, although these symptoms might have been easily masked by the pelvic condition.

The symptoms at the time of operation were: pain in the lower abdomen, more especially on the right side; dysmenorrhœa, leucorrhœa, and backache.

Abdominal examination shows slight tenderness and rigidity over the entire lower abdomen. No special tenderness over the vermiform appendix and no mass in this region. A small, reducible, inguinal hernia present on the right side.

Vaginal examination showed the uterus retroflexed and adherent. A sausage-shaped tumor on the right side. Left adnexa apparently normal.

Diagnosis. Retroflexion of the uterus, adherent; right pyosalpinx; right inguinal hernia, reducible.

At operation the above diagnosis was confirmed and the following operations performed: Dilatation and curettage; Clark-Mann operation for shortening the round ligaments; right salpingo-oöphorectomy; radical cure of inguinal hernia. At the completion of every abdominal section Dr. Clark makes a routine of examining the vermiform appendix if the patient is in good condition. This was done in this case, and the appendix was found

slightly reddened and adherent toward its tip; it was therefore removed. The patient made an uneventful recovery, primary union having occurred, and since then has been free from symptoms. The operation was performed eight months ago.

Pathological Report. *Macroscopic Description.* The vermiform appendix is 7.5 cm. long; its surface shows a few adhesions toward the tip. Diameter at base, 7 mm.; at middle, 6 mm.; at point three-quarters of a centimetre from tip, 7 mm. The organ looks as if it were the seat of a mild chronic inflammation, especially toward the tip; on opening the appendix this appearance is confirmed except toward the tip, where it is apparently the seat of an old, obliterating appendicitis. The mucosa at the base and middle is reddened and somewhat swollen. At a point beginning 1.5 cm. from and extending to the tip the lumen is occluded by a solid, yellowish-white mass, which is firm to the touch and gives the impression described above; no strictures or concretions are present. Walls seem normal in thickness.

Microscopically. Section through the base of the appendix. The serous coat is free of adhesions. The muscularis appears normal. In the submucosa the lymphoid tissue appears to be increased, and in the central part of some of the solitary lymph follicles there is free blood. The surface epithelium of the mucosa shows proliferation, irregularity, and some desquamation. The glands are normal in number and configuration; their epithelium is regular; there is a moderate round-cell infiltration of the stroma. This picture continues throughout the serial sections until the tip of the appendix is approached; here, about 1.5 cm. from the tip, the picture changes and the well-defined lumen of the appendix is considerably narrowed; here, under the surface epithelium, there are several dilated glands. The arrangement of the intestinal glands at this area is normal for four-fifths of the circumference of the mucosa. Toward the mesoappendix the glands lie deeper and encroach upon the submucosa. The collection of glands here appears almost separated from the superficial mucosa by a condensation of the stroma; some of the glands in question are dilated, but show no well-marked epithelium changes. In two places, one immediately overlying the sub-

mucosa and the other between the submucosa and the muscularis, there are nests of epithelium cells. The cells are small, closely packed together, and somewhat irregular in size and staining properties, and show no intercellular substance, although the nests are almost solid plugs; vacant areas appear, around which the cells are arranged with some regularity. Section farther on toward the tip shows an increase in the number of epithelium nests in the same relative area as those previously described; one of them lies directly under the surface epithelium of the mucosa, and in the periphery of this one a small strip of high, columnar epithelium can be observed. No direct transformation of this epithelium into the epithelium of the new-growth is found in this section. The lumen of the canal at this area is well preserved. Proceeding toward the tip the epithelial nests gradually encroach upon the mucosa, so that, finally, it is represented merely by portions of glands that show the original high, columnar epithelium. In several areas direct transformation of these cells into those of the epithelial nests may be observed; in other places isolated, well-preserved glands are found. At a point about 1 cm. from the tip of the appendix the lumen has entirely disappeared, its place being taken by the new-growth. This appearance is well shown in the drawing. In the muscularis at this area are found strings of isolated epithelial cells which show great variation in size and staining properties. About three-fourths of a centimetre from the tip the epithelial nests penetrate the wall of the appendix and enter the mesoappendix. The tube and ovary removed from this patient showed the usual microscopic changes found in inflammatory disease of these organs.

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THE HEART AND CIRCULATION IN PREGNANCY AND THE PUERPERIUM.[1]

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It was asserted by Larcher that the heart becomes hypertrophied during pregnancy. This view has generally been adopted by French writers and opposed by most German authors following Gerhardt. A study of the matter seemed to us of interest on its own account, as well as for the light it might throw on the conditions that may determine hypertrophy.

1. The Vascular System in Woman. There are certain differences in the circulatory system of women as compared to that of man that require consideration before the effects of pregnancy can be properly estimated. In general the statement may be truthfully made that the heart is smaller, its walls somewhat thinner, and its power less in the adult woman than in the adult man. The bloodvessels are probably of less calibre, even allowing for the differences in size and weight; so that the vessels in a man would be on the average of greater calibre than those of a woman of equal weight. This assertion cannot be positively proved, but is at least likely when the greater frequency in women of positive

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hypoplasia of the heart and vessels is kept in mind. The comparative narrowness of the vessels is, perhaps, in keeping with the higher proportion of adipose and lower proportion of muscular tissue in woman. Further, it is probable that the elasticity of the vessels is greater. The effects of these differences on the circulation are of opposite character. The smaller size and lesser power of the heart would in themselves tend to lower pressure, while the narrower channels of circulation would act in the opposite direction, and the greater elasticity of the vessels would, on the contrary, dispose to lower blood pressure. The resulting degree of pressure must depend upon the value of the conflicting influences. This can be determined by actual measurement with some form of apparatus by which peripheral blood pressure can be estimated. Reference will be made to the scanty observations that have been published, and our own determinations in pregnant and parturient women will be detailed. It may be said here that the pressure is uniformly lower in woman, and clinical observation sustains the view that from every aspect the circulation of woman may be regarded as less active than that of man.

2. The Effect of Work on the Heart and Circulation. This question requires preliminary consideration, because it has very frequently entered into discussions of the effects of pregnancy on the heart. Laborious occupations have long been recognized as causes of hypertrophy of the heart and of arteriosclerosis. The effect of less protracted muscular exertion is not so uniform or certain. The normal heart is possessed of a considerable degree of reserve power, which enables it to maintain the circulation during physical strains of considerable magnitude without suffering change. When, however, the heart is subjected to excessive strain it is liable to dilatation, in proportion to the degree of the labor imposed and the inefficiency of the heart muscles to meet the demand. In athletic exercises or any temporary occupation involving similar exertion the right heart suffers to a greater degree than the left, doubtless as a result of its relative weakness and of the comparatively greater labor imposed upon it by the acute emphysema of the lungs and consequent compression of the terminals of the pulmonary artery. Soon, however, the heart regains its equilibrium of action, if the exertion is not excessive, but in certain cases

such recovery does not follow, and the phenomena of acute dilatation of the heart are observed, as in mountain climbers, athletes, or the like.

Between these extremes of chronic muscular overexertion (laborious occupations) and acute excess of labor (mountain climbing, etc.) are various grades of strain that may or may not affect the heart in accordance with the strength of that organ and the degree of work imposed. Without entering into details about any other of such conditions, we may proceed to a consideration of pregnancy as one that has been supposed to increase the work of the heart sufficiently to cause hypertrophy of its walls. Among the factors supposed to contribute to increased work of the heart in pregnancy are the following : Increase in the number and size of the vascular channels (uterine, placental, etc.), increased quantity of blood (plethora of pregnancy), increased intra-abdominal pressure due to the growing uterus, insufficient expansion of the thorax, and compression of the lungs. Opinions vary as to the existence and significance of these factors of supposed increase of cardiac work. There is undoubtedly an increase in the size and the number of vascular channels in the uterus, the effect of which, independent of other conditions, must be an increased area of internal friction and consequently increased work. Fellner, quoting Lahs, states that there is a decrease of work involved in increased channels when the influx and outlet are unaltered, even when there is a considerable numerical increase in channels. The truth of this statement must depend upon the relation of increased width of the channels and the increased number. A great increase in number with but slight increase in width of each would increase pressure, while a slight increase in number with considerable increase in calibre would have the opposite effect. What the exact conditions and result may be in the uterus and placenta cannot be readily ascertained, though it seems likely that some increase in friction must occur. The increased quantity of blood (plethora) assumed to occur in pregnancy is wholly suppositious. Pathologists and physicians have long since ceased to regard plethora as of the importance once ascribed to this condition, and, indeed, there are very good grounds for believing with Cohnheim and others that plethora does not exist otherwise than as a very temporary condition after ingestion of fluids. The

plethora of beer drinkers to which Oertel and Bollinger called attention is probably a frequently repeated and not a stationary condition, and that supposed to exist in "full-blooded" individuals and in pregnant women is very doubtful. If, however, plethora does exist, this fact would give little ground for assuming that the heart's work is increased. Mere increase in the amount of the blood would not directly increase the work of the heart. Whether or not the tissues of the body contain more fluid is aside from the present question; as far as the circulatory blood is concerned, there is much reason to believe that this is but little altered from the normal. If the amount of blood were sufficient to keep the vascular channels in a state of considerable tension, then the work of the heart would be increased, because the expulsive force required of the ventricle rises quickly with the increased distention of the arteries and their corresponding inability to distend farther. Known facts regarding the compensatory mechanisms by which much vascular overloading is preventable, and the direct clinical observations of the peripheral blood pressure in pregnancy, show that such overdistention could not and does not maintain itself. It might be profitable to inquire into the condition of the blood itself to determine whether there is an increase in viscosity of this fluid, for it is the friction of the concentric layers of blood within the vessel upon each other, rather than friction of the blood on the vessel wall, that determines increased resistance to the flow of blood. The evidence regarding viscosity is rather in the direction of a decrease, and therefore of decreased blood pressure, than the reverse.

The direct effect of a growing uterus on the circulation is probably in the direction of increasing the pressure by offering a mechanical impediment to the circulation through the large abdominal vessels. In part the injurious effects of such pressure are obviated by diastasis of the abdominal muscles and general relaxation of the walls, but the resultant is probably in the direction of increased resistance.

The intrathoracic conditions of pregnancy seem to be of such a character as to increase the work of the right ventricle. These conditions are the upward displacement of the diaphragm, the compression of the lungs, and the restricted movements of the thorax. In a measure the comparatively inadequate expansion of the lungs

(through insufficient thoracic expansion) neutralizes the other conditions by allowing a dilatation of the pulmonary arterioles, but it is probable that this factor is of slight significance.

Taking into consideration all of the condition named, it seems doubtful that the work of the heart is increased during pregnancy. If there is an increase it is probably not great, and the fact that women with poorly compensated valvular disease may pass through pregnancy without any loss of compensation almost establishes the contention that whatever increase of work is imposed on the heart falls well within the reserve power of that organ, for even in well-compensated valvular disease there is but little reserve power. When this reserve power is exhausted symptoms of cardiac weakness present themselves; the absence of such symptoms is significant that any additional labor imposed on the heart must be comparatively slight.

There have been a few direct observations of the blood pressure during pregnancy, which would indicate that there is no great variation from the normal. This, of course, is not an absolute measure of the work of the heart, and can, therefore, have only a limited value in determining the question in hand. In addition, it is to be observed that most of the estimations of the blood pressure have been made by means of instruments none too accurate in their results.

3. The Weight of the Heart. Observations of the weight of the heart are usually unreliable, because of the lack of system in removing the great vessels, the pericardium, and other appendages. In consequence the figures given by different authors vary widely, and no certain conclusions can be drawn regarding pathological conditions, except in cases in which the increase of weight is very considerable. Kerkring, in 1670, stated that the average weight of the heart in women is 210 grams. Cruveilhier (1724) found the weight to vary from 180 to 210 grams. Tabor (1793) estimated the average weight at 283 grams. Bouillaud, in 14 cases, determined an average of 262 grams, and a variation from 200 grams to 350 grams. Lobstein (1835) assumes 255 grams as the medium weight, and Gluge (1846) found the average in 4 cases 288 grams, the maximum being 320 and the minimum 250. Wulff (1856) weighed the hearts of 3 women and found the average 288.4

grams. Clendenning (1838) determined the weight of the heart in 44 women between the ages of twenty and sixty years, and found the average 240 grams, the proportion to the total weight of the body being 1 : 187. Reid (1843) found an average weight in 53 cases of 256 grams, and a proportion to total body weight of 1 : 176. Peacock (1854) found the average weight for women between twenty and fifty years to be 250.1 grams. Blot (1869) regards as the normal weight 220 to 230 grams. Recently Arnold (1899) weighed the heart in 82 women, and found an average of 260 grams, the limits being 225 to 300 grams; and Hamilton found the weight in 4 cases from 283 to 312 grams. Blosfeld (1864), in 8 cases, found an average of 310 grams. Gocke (1883) found an average of 340 grams.

The average of the figures given by the fifteen authors quoted is 263 grams. These figures, however, are certainly high when a comparison is made with the weights obtained by a more accurate method like that of Müller.

H. Vierordt (1890), in a review of the weights of the organs in 2707 cases, found the weights of the heart in women as follows: At twenty-one years (22 cases), 250.6 grams; twenty-two years (19 cases), 251.6 grams; twenty-three years (22 cases), 258.5 grams; twenty-four years (22 cases), 284.1 grams; twenty-five years (26 cases), 260.7 grams.

Müller found average weights in women: twenty to thirty years, 220.6 grams; thirty to forty years, 234.7 grams; forty to fifty years, 264.1 grams; fifty to sixty years, 256.9 grams.[1]

A comparison of the weights obtained in normal women with those of the pregnant or parturient shows no certain increase of

[1] The following is a description by Hirsch of the method of Müller for weighing the separate parts of the heart:

The large vessels are first separated close to the valves and the total weight is determined. Then the adipose tissues are carefully separated with forceps and curved scissors. With a certain amount of care this may be done with a residue of not over 8 per cent. (Müller). The ventricles are separated from the septum on a level with the septum, the auricles having been separated exactly in the auriculoventricular groove. The several parts are then weighed separately, and from the comparison of the relation of the total weight of the heart and the total weight of the body the proportional weight is obtained.

It was possible to determine by this method whether the whole organ or any one of its parts was enlarged or decreased in size.

weight in the latter. Indeed, the evidence is in favor of the conclusion that the weight of the heart is diminished when compared with the total body weight.

Blot (1869) found an average weight of 291.9 grams in 20 puerperal cases; while Loehlein (1876) estimated the average in 9 cases, in which death was due to rupture of the uterus, at 247.2 grams (minimum 202, maximum 312), and in 6 parturient nephritic women at 300.8 grams (minimum 250, maximum 348). When the average of the two series is compared it will be found to correspond closely with that given by Ducrest, one of the early advocates of the hypertrophy theory; and Loehlein's conclusion, that the high average obtained by Ducrest was due to inclusion of nephritic cases, is justified. MacDonald (1878) weighed the heart in 2 cases of eclampsia and found the figures 269.2 and 255.1 grams.

Letulle found the increased weight of the heart of pregnancy 3 grams at the most.

The most important contribution toward the determination of the comparative weight of the heart in the pregnant and non-pregnant woman is that of Müller. His figures are based upon a study of a series of cases at different periods after labor, some being complicated, while others were uncomplicated. The average weight in the non-complicated cases was 227.7 grams.. According to the figures cited from various authors, this would indicate a distinct reduction in the size, and, according to Müller's own figures, obtained by the more accurate method which he employed, the weight given does not indicate any particular variation from the normal. In all of his cases there was a tendency for the heart index (relation of heart to the total body weight) to fall below the normal; a fact which may, perhaps, be explained upon the ground that the increase in weight at this time is mostly due to deposit of fat. He concludes that the heart, at most, enlarges in proportion to the increase in body weight, but his observations give no support to the claim of Larcher, that there is a distinct hypertrophy during pregnancy. Müller estimated the different portions of the heart separately and found that the relation between the weight of the auricles and the ventricles is slightly altered in favor of an increase in weight of the ventricles, especially the left; but all of the alterations in weight discovered by him were practically within physiological variations.

Hirsch, in reviewing the subject, alludes to the previous observations of Müller, and adds a case of his own, making in all 22 cases, of which 2 died from ruptured uterus, 1 from placenta prævia, and 18 from sepsis. While the average weight was as stated before, not increased and even proportionately diminished, there was one case in which the heart was somewhat increased in size. As all of the patients were ill for some time before death, some proportionate increase by wasting of the muscles of the body might have been expected, but the results showed a reduced heart index.

As far, then, as may be judged by estimations of the weight of the heart, the evidence disproves the assumed hypertrophy, and if the comparative weight or heart index is determined, there seems to be a reduction rather than an increase.

Dreysel, however, claimed that the increase in weight of the heart during pregnancy was 0.44 grams per kilo of increased body weight, which indicates an increase at the rate of 1 : 230, or a slight excess, though not beyond physiological limits. The result, it will be seen, is somewhat at variance with that given by Müller.

4. The Thickness of the Heart Muscle. Another method of determining whether or not hypertrophy occurs in pregnancy is the estimation of the comparative thickness of the ventricular walls. Larcher claimed to have found an increase of one-quarter to one-third in thickness of the left ventricle, the auricle and the right ventricle remaining normal ; and it was upon this conclusion that he based the claim that the heart is hypertrophied during pregnancy. His figures were obtained from a study of 130 pregnant and puerperal women, and these results were compared with the normal figures of Laennec. Ducrest also published observations of the same sort. In 97 puerperal cases he found the thickness of the left ventricle to average 15 mm. (maximum 22 mm., minimum 11 mm.). Assuming that Bizot's figures (10 mm.) correctly stated the thickness of the left ventricle in the female, he concluded that the statement of Larcher was confirmed by his own observations. Buhl, however, found the average normal thickness of the left ventricle to be from 16 mm. to 17 mm. and of the right ventricle 6 mm. Gerhardt measured the heart in 2 cases, from which, as well as from his own clinical investigation, he came to the conclusion that there was no hypertrophy or any change in the relationship of the right

and left ventricles. MacDonald found the left ventricle 19 mm. thick in 2 cases of eclampsia. It must be taken into account, however, that these were complicated cases. Engel found the right ventricle disproportionately large in 4 of 5 cases, while, on the other hand, Ducastel found the ventricles normal in 3 of 5 cases.

As far as the determinations of the thickness of the ventricles and other parts of the heart are concerned, it must be confessed that this method seems even less trustworthy than that of determining the total weight of the heart or the weight of different parts. Whatever importance attaches to the method, however, is in disproof of hypertrophy.

A third method, based upon anatomical and post-mortem investigation, is that of studying the histological features with reference to the occurrence of fatty degeneration in the muscle, as it was assumed that if hypertrophy occurred the restitution to the normal after the conclusion of parturition would be by a fatty degeneration. This is a method that was employed by Fritsch. Handfield-Jones also alludes to the fatty degeneration of cardiac involution, but gives no data that may be utilized to determine the occurrence or non-occurrence of hypertrophy during pregnancy.

Physical Examination. If a large number of post-mortem examinations could be made in uncomplicated cases and accurate weights and measurements obtained, the question of the probable occurrence of hypertrophy during pregnancy could be settled. Unfortunately, the cases that come to autopsy are usually complicated in such ways that the data are untrustworthy, and, in addition, the methods generally employed in the past have been liable to considerable error, especially in the direction of overestimating the weight and size.

Under these circumstances the results of physical examination, appealed to by some authorities following Gerhardt's example, are the best evidence that can be obtained, though it must be confessed that percussion is somewhat unreliable, on account of the fulness of the mammary gland, the abdominal distention, and the upward displacement of the diaphragm. Our own studies were arranged so as to exclude, as far as possible, the errors that these conditions might introduce, and, in particular, we invariably repeated the physical examination after labor so as to eliminate, as far as possible, the effects of mere displacement, while, at the same time, esti-

mating the blood pressure at different times. Before entering upon our own results, it may be well to review the literature of this aspect of the problem.

Percussion. The principal support of Larcher's view that has been derived from physical examination is that of Duroziez, whose observations were confined to percussion. He regards the greatest vertical and horizontal diameters of the cardiac dulness as 9 cm. and 12 cm., respectively. His studies, made in 135 cases of pregnancy, gave an excess in the vertical diameter in 95 out of 175 separate determinations made at different periods in the latter part of pregnancy, while the horizontal diameter was excessive in 85 out of 95 examinations. The average measurements were 10 cm. for the ventricle and 15 cm. for the transverse diameter. After parturition he found a rapid subsidence of the hypertrophy in women who did not nurse their children, while a persistent enlargement was sometimes observed in nursing-mothers. In multiparæ permanent hypertrophy was found. Duroziez admits the difficulty experienced in the percussion of the heart in pregnant women, but, notwithstanding this fact, does not hesitate (as Loehlein points out) to state with confidence that there is a return to the normal in the area of dulness on the first day after labor, a recurrence of enlargement on the second day, and greater enlargement on the third day in nursing-women.

Lwoff and Fellner also claim to have detected enlargement on percussion with a gradual return to the normal during the puerperium. Lwoff found the vertical diameter especially increased. The results of Gerhardt are in direct opposition to those of Duroziez, Lwoff, and Fellner. While admitting that the lower part of the precordial area is broader than normal, he concluded that the cause of this increase is not any enlargement of the heart, but the upward and anterior displacement of the organ by the increased arching of the cupola of the diaphragm. As a result of this the heart is crowded against the anterior wall of the thorax, the edge of the left lung is displaced, and the heart is seemingly hypertrophied. The rapid subsidence of the apparent enlargement after labor and the absence of any indications of increased work of the heart in the sphygmograms, confirmed him in his opinion, while the figures of Larcher and Ducrest seemed to him within physiological limits.

Auscultation. Frequent references have been made by systematic writers to the occurrence of a systolic murmur or *bruit de souffle* over the heart during pregnancy. Larcher himself refers to this in his paper, published in 1859, and alludes to the thesis of Jacquemier (1837), in which particular attention is given to this point. Moreau is quoted by Jacquemier as having observed the same fact. Fritch quite frequently noted a complete replacement of the first heart sound by a murmur in puerperal women, and believed this due to the reduced quantity of blood in the heart. He could make the murmur disappear by causing the patient to sit up and by compressing the aorta or iliac vessels.

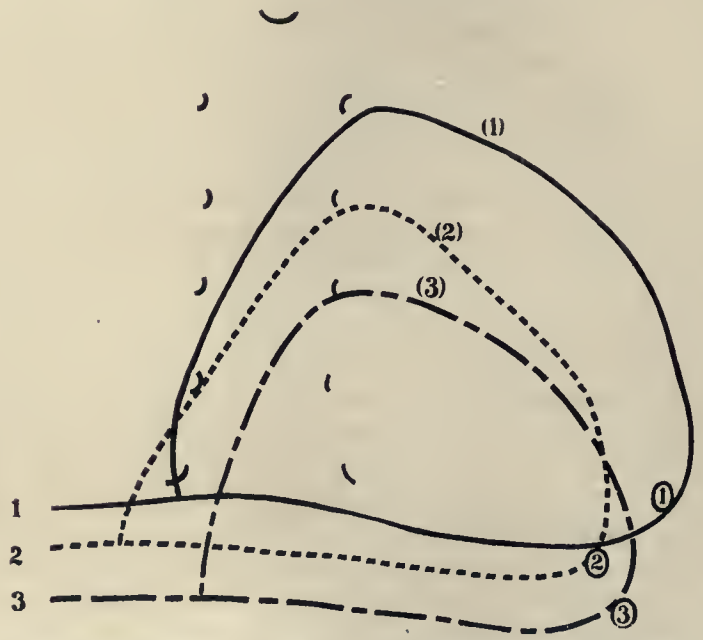
Loehlein examined the heart in 375 puerperal cases, finding a murmur in 99, of which 44 had had normal labors and 55 labors attended with considerable hemorrhage. His observations led to the conclusion that heart murmurs are more common after than before childbirth, are best heard from the third to the fifth days, and frequently disappear when the patient rises. They are usually heard at the base of the heart, are systolic and blowing in character, and rarely replace the first heart sound completely. In a subsequent series of 156 cases the cardiac conditions in 98 healthy puerperal women were noted. No murmur was heard in 31 (though some alteration of the first sound was recorded in 11 of these); a feeble and inconstant murmur was heard in 36 cases, and a distinct murmur was found in 31 cases (six times during or immediately after labor, ten times during labor and more distinctly after labor, fifteen times after labor only); altogether, a murmur was audible in 68.3 per cent. of the cases.

Handfield-Jones found a heart murmur in only 5 or 6 of 50 non-anæmic multiparæ at the seventh or eighth months of pregnancy.

Marx found a murmur in 27 of 60 healthy pregnant or parturient women. Among the 27 the murmur was found both before and after labor in 14, while it was found in 13 only subsequent to childbirth, from the second to the sixth days; 9 of the 14 cases constituting the first group were distinctly chlorotic. The murmur was best heard in the pulmonary area.

Fellner frequently heard an accidental murmur at the apex, or less commonly at the base of the heart. He believes this murmur is due to relative insufficiency of the mitral valve. He also refers to the occurrence of a systolic basal bruit. In 95 per cent. of his

cases he claims to have detected a distinct and rather rough diastolic murmur to the left of and often under the sternum. This was heard during the last period of pregnancy, but more distinctly in the early days of the puerperium, sometimes even as late as the tenth day. When heard during labor it seemed to grow louder during the pains, suggesting that increased pressure aggravated the conditions causing the murmur. He does not attempt to decide



Outline of heart dulness before labor (1), immediately after labor (2), and two weeks later (3). The position of the suprasternal notch, intercostal spaces at the sternal end, and the xiphoid junction are indicated as landmarks.

whether the murmur is a venous one or the result of relative valvular insufficiency.

The character of the first heart sound has been referred to by some writers, and is, of course, a matter of importance. Fellner found it strikingly soft during the early days of pregnancy, but states that he never observed complete disappearance of this sound among 900 cases. Fritch, on the other hand, refers to cases in which a systolic murmur completely replaced the first heart sound.

The character of the second heart sound is also referred to, though less attention has been given to it than to the first sound. Fellner speaks of the occasional occurrence of a reduplication of the second sound.

Pulse Rate in the Puerperium. Slowing of the pulse has been frequently alluded to by obstetricians. Loehlein investigated the question with particular care, and found a reduction to 50 in 31 (6.5 per cent.) of 477 cases. Of these, 10 were primiparæ, 18 II-para and 3. III-para. The significance of a slow pulse, and particularly its bearing on the condition of the heart, cannot be stated dogmatically. Undoubtedly a number of influences play a part in the alteration of the rate. Among other influences, exhaustion in particular seems to be important.

Our own studies of the heart and circulation in and after pregnancy were entirely clinical, and embraced physical examinations before and after labor, with determinations of blood pressure and sphygmograms.

We have before alluded to the difficulties encountered in percussion of the outlines of the heart, on account of the fulness of the mammary gland. With care, however, fairly satisfactory results could be obtained, and at all events the comparative outlines before and after labor showed the altered conditions represented in the accompanying illustration, and are also shown in the tables giving details regarding the physical examination. The outlines of the heart were obtained by first carefully marking its borders with oil, using a fine camel's-hair brush, and then pressing tissue paper against the skin so as to transfer the markings to the paper. Copies of these outlines were then made on heavier paper. A typical outline is selected for reproduction.

Our cases are separated into three groups: (1) primiparæ, of which there were 39; (2) multiparæ, of which there were 21, and (3) complicated cases, of which there were 10. We have excluded these complicated cases from the tabulations because there was either cardiac or renal disease antedating pregnancy. These cases, however, are instructive in showing that the effect of pregnancy upon the heart is comparatively slight, since the conditions present were such that any considerable strain must have produced a decided effect on the heart, which, however, was not observed.

Table I.

No.	Before labor.			After labor.			Before.	After.	Before.	After.	Remarks.
	Right border.	Upper border.	Left border.	Right border.	Upper border.	Left border.	Apex	Apex	Murmur	Murmur	
1	—R. sternum	2d rib	—M.-cl.	No change	3d rib	No change	3d	4th	Yes	No	Age 19. Pulsation seen and felt in 1st and 2d interspaces before labor; in 2d, after labor murmur heard at base; recti separated.
2	+R. "	2d "	M.-cl.	R. sternum	3d "	No change	4th	4th & 5th	"	Yes	Age 18. In labor when first seen; murmur not heard 10 days after labor; recti not separated.
3	Mid. "	2d "	—M.-cl.	No change	3d "	No change	4th	5th	"	"	Age 20. Murmur not present on tenth day; always basal; recti slightly separated.
4	+R. "	2d "	+M.-cl.	—R. sternum	3d "	M.-cl.	3d	4th	"	"	Age 25. Pulsation seen in 2d interspace; murmur basal; 2d pulmonic rather loud before delivery; split after.
5	L. "	3d "	—M.-cl.	Mid. "	No change	No change	4th	5th	No	"	Age 17. Examination before delivery uncertain; patient in pain; forceps delivery; recti separated.
6	R. "	2d "	M.-cl.	Mid. "	3d rib	—M.-cl.	4th	4th	Yes	"	Age 22. Pulsation in 2d interspace before and after labor; recti separated; murmur basal.
7	—R. "	3d "	—M.-cl.	No change	No change	No change	4th	5th	"	"	Age 21. Murmur at base only before labor; over body of heart after labor.
8	+R. "	1st interspace	+M.-cl.	—R. sternum	3d rib	—M.-cl.	3d	5th	No	"	Age 25. Apex in third interspace anterior axillary line, moved down after rupture of membranes and still more after delivery; murmur eight days after delivery.
9	+R. "	2d rib	M.-cl.	Mid. "	3d "	No change	4th	5th	"	"	Age 22. Murmur heard second day after labor; second pulmonic reduplicate after delivery.
10	+R. "	2d "	M.-cl.	No change	No change	No change	4th	4th	"	No	Age 19. Second examination eight hours after labor; no subsequent examinations on account of sore breasts; recti separated.
11	L. "	2d "	+M.-cl.	Mid. sternum	3d rib.	M.-cl.	4th	5th	Yes	Yes	Age 20. Entire heart was apparently pushed upward and to the left.
12	L. "	2d "	+M.-cl.	No change	No change	No change	5th	5th	No	No	Age 19. Case of twins; abdomen very large; only one examination made after delivery; thirteen hours.
13	R. "	2d "	—M.-cl.	Mid. sternum	No change	No change	3d	4th	"	Yes	Age 20. Murmur noted on tenth day; shape of ribs peculiar, curve great, 2d rib low in position; recti separated.
14	Mid. "	2d "	M.-cl.	No change	2d rib	No change	4th	3d	Yes	"	Age 26. Has had two miscarriages; pulsation visible in second interspace after labor; recti not separated.
15	R. "	2d "	+M.-cl.	" "	No change	No change	4th	5th	"	"	Age 27. Has had one abortion; only examined once after delivery.
16	+R. "	2d "	M.-cl.	R. sternum	3d rib	No change	4th	5th	?	"	Age 19. Repeated observations were made of this patient; she did not nurse child; murmur absent two weeks after delivery.
17	R. "	2d "	—M.-cl.	No change	No change	No change	4th	4th	Yes	No	Age 20. The note under left clavicle is impaired and breathing is harsh; for three weeks after delivery she had an irregular fever for which no cause could be found.

18	+R.	"	2d	"	+M.-cl.	R. sternum	No change	No change	3d	4th	"	?	Age 28. Has had several abortions; first child carried to term; heart dulness large; only two examinations made.
19	R.	"	2d	"	M.-cl.	R. "	3d rib	—M.-cl.	4th	5th	"	Yes	Age 19. Forceps delivery.
20	R.	"	2d	"	M.-cl.	—R. "	3d "	—M.-cl.	3d and 4th	5th	"	No	Age 18. The change in outline not noted until some days after delivery; delivery by forceps.
21	R.	"	2d	"	M.-cl.	No change	3d "	—M.-cl.	4th	4th	No	"	Age 20. This girl developed typhoid fever almost immediately after delivery.
22	R.	"	2d	"	M.-cl.	Mid. sternum	3d "	M.-cl.	4th	5th	"	Yes	Age 19. Very little change noted in outline until the tenth day; murmur appeared on third day.
23	R.	"	2d	"	M.-cl.	No change	2d interspace	—M.-cl.	3d	5th	Yes	"	Age 21. The diminution in dulness was most marked above and to the left.
24	R.	"	2d	"	+M.-cl.	" "	No ch'ge	No ch'ge	3d and 4th		No	"	Age 25. Second pulmonic split after labor.
25	R.	"	2d	"	+M.-cl.	" "	No change	No change	4th and 5th		Yes	"	Age 23. Murmur always basal; only two examinations.
26	R.	"	2d	"	M.-cl.	Mid. sternum	3d rib	—M.-cl.	3d	4th	"	"	Age 18. Second pulmonic reduplicated after labor; murmur only apical before labor, afterward heard over entire heart.
27	R.	"	2d	"	—M.-cl.	Mid. "	3d "	No change	4th	5th	"	No	Age 29. murmur disappeared after "dropping," the effect of which was to lessen area of dulness.
28	—R.	"	2d	"	+M.-cl.	Mid. "	3d "	M.-cl.	4th	5th	"	Yes	Age 29. Pulse-rate very slow; murmur transmitted to axilla before and just after labor; later disappeared.
29	L.	"	3d	"	M.-cl.	No change	No ch'ge	No ch'ge	4th	5th	"	"	Age 35. Heart area unusually small.
30	R.	"	2d	"	M.-cl.	" "	No change	No change	4th & 5th	4th & 5th	No	"	Age 23. Only two examinations made, the second 8½ hours after delivery; no change noted except murmur.
31	R.	"	3d	"	M.-cl.	" "	No change	No change	4th	5th	"	No	Age 18. Second examination made seven days after delivery; the apex was found lower down; no other change.
32	R.	"	2d	"	+M.-cl.	" "	No change	No change	4th	5th	Yes	Yes	Age 22. Great distention at second examination eight hours after delivery; subsequent examination impossible; inflamed breast.
33	+R.	"	2d	"	M.-cl.	R. sternum	3d rib	No ch'ge	4th	5th	?	No	Age 26.
34	—R.	"	2d	"	M.-cl.	No change	No change	No change	4th	4th	Yes	"	Age 16. Pulsation visible in second interspace before labor, not after; at second examination, ten hours after delivery, abdomen was very tympanitic.
35	+R.	"	2d	"	M.-cl.	—R. sternum	2d interspace	No change	3d & 4th		4th	No	"	Age 20. Pulsation visible and palpable in second and third interspaces; second examination four hours after labor.
36	R.	"	2d	"	+M.-cl.	No change	No change	No change	4th & 5th		5th	"	"	Age 25. Dulness appears large on account of peculiar bulging of chest; second examination twenty-four hours after forceps delivery.
37	R.	"	2d	"	M.-cl.	—R. sternum	3d rib	—M.-cl.	4th	5th	Yes	"	Age. 24.
38	+R.	"	2d	"	M.-cl.	Mid. sternum	3d "	No change	5th	5th	No	"	Age 26. Forceps delivery; several examinations show well the diminution of dulness to the right and above after labor.
39	R.	"	2d	"	M.-cl	" "	3d "	—M.-cl.	4th	5th	Yes	"	Age 16. Shows well change of dulness above and to the left after labor; recti slightly separated.

SYNOPSIS OF PRIMIPARÆ.

Number of cases	39
Ages	from 16 to 35 years.
Upper border before labor, at second rib	in 35 cases.
Upper border before labor, at third rib	in 4 cases.
Upper border after labor, at third rib	in 22 cases.

(In all of these cases it had been at the second rib.)
Upper border after labor, unchanged, in 17 cases.

Apex before Labor.

In third interspace	8
In fourth interspace	28
In fifth interspace	3

Apex after Labor.

In fourth interspace (moved down)	5
In fifth interspace "	22
Unchanged	12

Murmurs.

Only before labor	7
Only after labor	7
Doubtful before and negative after labor	1
Doubtful before and positive after labor	1
Positive before and doubtful after labor	1
Murmur both before and after labor.	15
No murmurs at any time	7

The murmurs were purely systolic in time, with one exception. In this the murmur was heard midway between the first and second sound.

Table II.

No.	Before labor.			After labor.			Before.	After.	Before.	After.	Remarks.
	Right border.	Upper border.	Left border.	Right border.	Upper border.	Left border.	Apex	Apex	Murmur	Murmur	
1	R. sternum	3d rib	—M.-cl.	Mid. sternum	No change	No change	3d	3d & 4th	No	No	Age 18. Para II. Pulsation felt in 2d interspace after labor; recti separated after labor; not demonstrable before.
2	R. "	2d interspace	M.-cl.	Mid. "	No change	No change	4th	5th	"	Yes	Age 30. Para V. Murmur heard only at 2d left interspace; recti not separated.
3	+Mid. "	3d rib	—M.-cl.	No change	No change	No change	4th	5th	Yes	No	Para II. In pain for 36 hours when first examined; labor very long; uterine inertia; recti split.
4	R. "	2d "	M.-cl.	Mid. sternum	3d rib	No change	3d & 4th	4th & 5th	No	Yes	Age 32. Para III. The murmur is peculiar in that it is just between 1st and 2d sounds at apex; no murmur at base; 2d pulmonic split.
5	R. "	2d interspace	M.-cl.	Mid. "	3d interspace	No change	5th	5th	Yes	"	Age 29. Para III.
6	R. "	3d rib	M.-cl.	No change	No change	No change	3d & 4th	3d & 4th	"	"	Age 27. Para III. Second examination four hours after delivery; beat less forcible and murmur less loud after delivery.
7	R. "	2d "	M.-cl.	" "	No change	No change	5th	5th	"	"	Age 21. Para II. Second examination 2½ hours after delivery; murmur basal.
8	R. "	2d "	M.-cl.	" "	No change	No change	4th	4th	"	"	Age 30. Para IV. Second examination two hours after delivery; pulsation in 2d left interspace before and after labor.
9	—R. "	2d "	M.-cl.	Mid. sternum	2d rib	No change	4th	5th	"	"	Age 24. Para IV. Murmur present after being out of bed; pulsation in 2d luterspace to left before labor.
10	+R. "	2d "	M.-cl.	R. sternum	3d rib	No change	4th	5th	"	"	Age 25. Para II. 2d pulmonic split after labor.
11	Mid. "	2d interspace	M.-cl.	No change	No change	No change	4th	5th	?	No	Age 22. Para II In labor and membrane ruptured when first seen; recti split after labor.
12	R. "	2d interspace	—M.-cl.	" "	3d rib	—M.-cl.	4th	5th	Yes	Yes	Age 20. Para II. Before labor area small, great tympany, no liver dulness; after labor heart area much larger below.
13	+Mid. "	3d rib	M.-cl.	Mid. sternum	No change	—M.-cl.	4th & 5th	4th & 5th	"	"	Age 33. Para II. Forceps delivery; much hemorrhage; recti not split.
14	Mid. "	3d "	M.-cl.	No change	No change	No change	4th	4th	"	No	Age 26. Para III. Membranes ruptured and patient in pain when examined first; recti separated.
15	Mid. "	2d "	M.-cl.	" "	No change	No change	4th & 5th	4th & 5th	"	"	Age 20. Para II. The area of dulness is very large; no other evidences of organic disease.
16	+Mid. "	2d "	M.-cl.	" "	3d rib	No change	4th	5th	"	Yes	Age 25. Para II.
17	+R. "	2d "	—M.-cl.	Mid. sternum	3d "	No change	4th	5th	No	"	Age 20. Para II. After labor there was a pulsation in 2d left interspace where murmur was heard; recti split.
18	Mid. "	2d "	M.-cl.	No change	No change	No change	4th	5th	Yes	"	Age 37. Para VI. Second examination 23 hours after delivery.
19	+R. "	2d "	M.-cl.	R. sternum	No change	No change	4th	5th	No	No	Age 30. Para II. Patient of Dr. Norris, Preston Retreat.
20	R. "	3d "	—M.-cl.	No change	No change	No change	4th	4th	Yes	Yes	Age 22. Para II.
21	L. "	2d "	+M.-cl.	Mid. sternum	3d rib	—M.-cl.	3d	4th	"	"	Age 22. Para II. Pulsation in 2d left interspace before and after labor.

SYNOPSIS OF MULTIPARÆ.

Before.

Number of cases	21
Upper border at second rib	in 12
Upper border at third rib	in 9

After.

Upper unchanged	in 14
Upper moved down	in 7

Apex Beat before Labor.

In third interspace	in 2
In fourth interspace	in 16
In fifth interspace	in 3

Apex Beat after Labor.

Moved down	in 13
Unchanged	in 8

Murmurs.

Only before labor	3
Only after labor	3
Doubtful before and none after	1
Murmur both before and after	12
No murmurs at any time	2

In many of these cases a pulsation was noted to the left of the sternum in the second and third interspaces, and a split second sound was audible in the same area. The murmur was usually heard best at the base, though it was often audible over the entire cardiac area.

The most notable change in the cardiac dulness after labor was a diminution in the breadth of the upper portion, causing the extension to the left in the second and third interspace to decrease decidedly. This would correspond with a subsidence of distention of the conus arteriosus and root of the pulmonary artery.

In practically every case the costal angle was greatly increased before delivery, and the liver dulness was diminished so that in many instances only a slight change of note indicated the passage from pulmonary resonance to abdominal tympany.

SUMMARIES OF BLOOD-PRESSURE ESTIMATIONS.

1. *Primiparæ.*

Before labor (average of 18 cases; Riva-Rocci, narrow cuff)	$123\frac{5}{18}$ mm.
After labor (average of 18 cases; Riva-Rocci, narrow cuff)	$122\frac{8}{18}$ mm.
Before labor, highest pressure observed	140 mm.
Before labor, lowest pressure observed	96 mm.
After labor, highest pressure observed	140 mm.
After labor, lowest pressure observed	103 mm.

The lowest pressure, 96 mm., occurred in Case 36, in which the pressure was 130 twenty-four hours after delivery, falling to 103 two days later, subsequently rising to 113, when the patient left her bed. Ergot was administered during labor.

ESTIMATIONS OF PRESSURE DURING AND AFTER LABOR.

		Pulse.
Case 2. Before labor, between pains	121 to 131 mm.	68 to 96
Immediately after labor	141 mm.	56

The estimations were as follows:

	Before Labor.	Pulse.
July 6, 1903, 11 A.M.	121 to 131 mm.	68 to 96
	After Labor.	Pulse.
July 6, 1903, 4.30 P.M.	141 mm.	56
" 7, " 10.30 A.M.	122 mm.	
" 8, " —— P.M.	128 mm.	
" 9, "	120 mm.	
" 17, "	130 mm.	
" 27, "	140 mm.	

Case 5. During labor	120 to 140 mm.	84 to 90
Forty-eight hours later	127 mm.	72
Two weeks later	140 mm.	84

SUMMARIES OF BLOOD-PRESSURE ESTIMATIONS.

	Pressure.	Pulse.
Case 8. During labor (membranes ruptured)	105 to 122	88
Twenty-four hours after	$103\frac{1}{2}$	92

Breech wedged in; labor, 48 hours; ether; much blood lost.

	Pressure.	Pulse.
Case 13. Week before labor	130	
In labor four hours	175 to 185	56
Four and one-half hours after forceps operation	160 to 165	52
Twenty-four hours later	135	60
Ten days later; out of bed	142	100

This patient had no binder or ergot, but was given f ℥ iss sherry during labor.

		Pressure.	Pulse.
Case 20.	Three weeks before labor . . .	139	80
	In labor twelve hours, pains slight . .	118	96 to 102
	Ten hours after forceps	130	
Case 19.	Four days before labor	112	
	In labor	110 to 126	
	Three hours after forceps . . .	112	
Case 29.	Week before labor	$119\frac{3}{5}$	100
	In labor, between pains	142	80
	After labor twenty-one hours . . .	118	60
	After labor, ten days	125	64
	After labor, thirteen days . . .	132	72

This patient was in bed a long time. She had a repair of perineum and an abscess in the thigh as a result of ergot injection.

2. *Multiparæ.*

Fifteen cases before labor by Riva-Rocci; narrow cuff averaged .	$122\frac{4}{5}$
Fifteen cases after labor by Riva-Rocci; narrow cuff averaged .	$121\frac{2}{5}$
Highest pressure before (same case)	163
Highest pressure after (same case)	140
Lowest pressure before	91
Lowest pressure after	100

Blood Pressure in Pregnancy. Unfortunately these observations were made before it was known that the width of the rubber cuff used in compressing the arm influences the determination. It is proper also to state that, as the figures here given are only those representing systolic pressure, the absolute condition of blood pressure is not accurately indicated. At the time that these studies were made we lacked satisfactory apparatus for determining diastolic pressure. The figures given below to show the comparative determinations of Riva-Rocci, Gärtner, and Hill and Barnard roughly indicate the diastolic pressure in the Hill and Barnard figures, but the narrow cuff and other imperfections made these figures too high. Measurements were made with the apparatus of Riva-Rocci (with the usual one and one-quarter inch cuff), the Gärtner tonometer, the Oliver instrument, and in some instances the greatest pulsation was noted according to the plan of Hill and Barnard. In practically all instances (except where the Oliver instrument was used) the measurements were made with the Gärtner mercury manometer.

The normal blood pressure in adult women has been estimated by a number of observers. Gumprecht (*Zeit. f. klin. Med.*, Bd.

xxxix., Heft 5 and 6) found the average with the Riva-Rocci apparatus to be 120 mm. Hensen (*Deutsches Archiv f. klin. Med.*, Bd. lxvii., Heft 5 und 6), using the same apparatus, found the average pressure in 30 healthy working women to be 132 mm. Doleschal (*Inaug. Dissert.*, 1900), using Gärtner's tonometer, found the average pressure in 100 persons to be 120 mm.; while Weiss (*Münch. med. Woch.*, 1900, Nos. 3 and 4) found the average pressure in women to be 100 mm. with the tonometer.

Taking Gumprecht's and Hensen's figures as a basis, the results obtained in our cases would show the average to be within normal limits, though great variations occurred in the individual. Thus, in 18 primiparæ the Riva-Rocci instrument showed an average pressure of $123\frac{5}{18}$ in the week preceding delivery, while in 17 multiparæ the average was $122\frac{3}{17}$.

In primiparæ the variations were between 96 mm. as the lowest and 140 mm. as the highest. In multiparæ the lowest reading was 91 mm. and the highest 163 mm.

These pressures were all taken under the same conditions as to position, etc., and on women who were apparently healthy. The patients, however, varied in weight from 100 to 150 pounds, and presented all degrees of physical vigor from the very robust to very delicate. The influence of physique on blood pressure is uncertain, but it seems evident that a delicate girl of eighteen would not show the same degree of blood pressure as a vigorous woman of thirty who had worked hard until the time of admission.

There seemed to be very little reason, either from physical examination, blood-pressure estimations, or from the numerous pulse tracings which were made, to believe that pregnancy, *per se*, is a cause of heightened pressure.

In two instances, where the pressure was at the upper bounds of the normal, the abdominal muscles were found to be unusually tight after delivery, suggesting the possibility of an influence on the pressure due to a heightened intra-abdominal tension. This is borne out by the fact that the upper border of heart dulness was higher in primiparæ. The rule was to find a more or less well-marked separation of the recti muscles which persisted for a considerable time after delivery. Also, as the high pressures were found in women with good-sized arms, it is probable that the

disproportion between the size of the arm and the width of the cuff had a certain effect.

Concerning the use of the Gärtner instrument, it may be stated that it was, on the whole, unsatisfactory. In almost all cases its results were higher than those obtained by the Riva-Rocci apparatus, and for this difference no satisfactory explanation could be found.

It may be of interest to show the comparison of estimations obtained with different instruments.

COMPARISON OF THE GÄRTNER AND RIVA–ROCCI INSTRUMENTS.

CASE 8. May 2, 1903.

Gärtner,	Riva-Rocci,
100	105
" 105	" 110
" 104	" 108

May 16, 1903. In labor; membranes ruptured four hours. Pulse, 88.

Gärtner,	Riva-Rocci,
115	110
" 116	" 122
" 130	" 120
" 117	" 110
" 135	" 105
" 110	
" 130	
" 130	
" 120	

May 19, 1903, 12 noon. Pulse, 92.

Gärtner,	Riva-Rocci,
100	106
" 95	" 105
" 110	" 101
" 98	" 103
" 105	

CASE 9. Flush slow.

Gärtner,	Riva-Rocci,
112	102
" 112	" 100
" 125	" 103
" 117	" 105
" 124	" 100
" 90	

CASE 15. Skin of finger thick; slow flush.

Before Labor.

Gärtner,	Riva-Rocci,
100	125
" 105	" 126
" 105	" 120
" 110	" 122

Skin of finger now soft. Second series of examinations two weeks after first and eight hours after labor. Temperature, 99°.

After Labor.

Gärtner, 145	Riva-Rocci, 135
" 135	" 136
" 142	" 135
" 135	

CASE 16.

Gärtner, 108	Riva-Rocci, 112
" 115	" 115
" 120	" 113
" 135	" 115
" 130	" 112
" 135	
" 123	

CASE 24. Pulse, 56. Perhaps the slow pulse accounts for great difference between pressures.

Gärtner, 126	Riva-Rocci, 110
" 140	" 112
" 150	" 115
" 126	" 112
" 125	
" 140	
" 128	
" 132	
" 140	
" 132	

CASE 26. Absolutely no reason for difference was discovered.

Gärtner, 135	Riva-Rocci, 112
" 136	" 107
" 136	" 111
" 140	" 113
" 137	

Comparisons similar to this might be given in any desired number, but these are purposely selected because in each instance there were present the most favorable conditions for use of the tonometer: thin skin; well-fitting ring; quiet patient accustomed to use of these instruments; recumbent position, and the same manometer with both forms of instrument. In many instances the figures agree almost perfectly. More often we found the variations so great on repeated trials with the Gärtner instrument that as many as ten observations were taken to obtain an average. The first pressures of a series were sometimes high, at other times low, no constant behavior being found. The flush seemed to be affected in a measure by the degree of primary pressure established before

removing the rubber band. When this was excessive the results were lower than when the primary pressure was only slightly greater than that at which flush appeared. On one occasion (not a case of pregnancy) there was difficulty in getting any flush; this was a case of shock and excessive hemorrhage, due to a crush of thigh. There is but little difference in the time required to make the examination with the two instruments.

COMPARISON OF GÄRTNER, RIVA-ROCCI, HILL AND BARNARD, AND OLIVER.

Julia C., aged twenty-five years. Pregnant second time. Soft systolic murmur over base, with slight accentuation of pulmonic second sound.

Gärtner.	Riva-Rocci.	Hill and Barnard.	Oliver.
130	130	120	125
128	130	115	(Average from
110	130	110	several observa-
125	125	110	tions.)
123	125		
	Same Patient, Forty-eight Hours after Delivery		
120	122	100	100
115	124	100	(Average.)
125	126	105	
111			
121			
120			

COMPLICATED CASES.

The following summaries are given to show the state of the circulation in cases in which serious weakening of the heart would have occurred were the conditions such as has been asserted to exist during pregnancy. The normal course of events, however, indicates the falsity of that assumption, and supports our belief that there is no special strain upon the heart during pregnancy; and hypertrophy, if it exists, must be due to other causes.

CASE 1. *Nephritis complicated with hydramnios.*—Mrs. Martha K., aged thirty-four years, white; second pregnancy. Examined May 14, 1902. She gives a history of eclampsia in her former labor. Two weeks previous to admission she began to have swelling of the hands and feet, and albumin, one-fifth by bulk, in the urine. The patient is small and thin, with peculiarly shaped ribs, so curved that the interspaces seem displaced. The abdomen is

tense, and the irregularity suggests twins. The heart is not enlarged. The apex is in the third interspace (which, owing to the extreme curve of the ribs, is about equal to the fourth interspace at the edge of the sternum) and inside the midclavicular line. No murmurs are heard. The second aortic sound is accentuated. Blood pressure by the Riva-Rocci on April 13th varies between 160 and 165. On April 14th, one hour after a vapor bath, it varies between 138 and 160 (patient is having slight pains).

15*th*. Second examination twelve hours after delivery. Patient has on a firm binder and pad. The condition proved to be hydramnios, with a large placenta. No murmurs are heard. The aortic second sound is still loud. Blood pressure by the Riva-Rocci, between 178 and 180. Pulse, 56. She is having slight after-pains. The heart has moved down slightly.

26*th*. Heart dulness still farther down, the apex being in the fourth interspace (equivalent to the fifth at the margin of the sternum). A short systolic murmur is now heard just inside the apex. This is not transmitted. Second sound is not so loud. Blood pressure by the Riva-Rocci, 125 to 130; pulse, 68. The patient made an uninterrupted recovery. The most notable feature, as far as the circulation is concerned, was the high blood pressure.

Case 2. *Nephritis, uræmia.*—Mrs. H., aged twenty-six years, white; second pregnancy. Examined April 29, 1902. The patient is very œdematous, and has the appearance of a nephritic. The previous labor showed only a slight œdema. There is no history of cardiac symptoms before pregnancy. Cardiac dulness begins above at the upper border of the second rib and extends to the right border of the sternum and to the midclavicular line on the left, where the apex is found in the fourth interspace. Over the dulness to the left of the sternum, best marked at the apex, there is heard a systolic murmur transmitted toward the axilla. Both second sounds are loud. The urine coagulates almost entirely on boiling. Blood pressure by the Gärtner, 190 to 195; by the Riva-Rocci, 185 to 190.

11*th*. Second examination made eight hours after delivery. There is practically no change in the heart outlines or sounds. Murmur is perhaps more distinctly heard. She is even more œdematous, is uræmic, and has a bronchitis. The blood pressure was taken

frequently, but the presence of the œdema and the frequent cough made the results unreliable. Though on treatment by vapor baths, enemata of salt solutions, cathartics, etc., there has been no improvement. This patient, after a long illness, left the hospital in good condition. Very high blood pressure was notable.

Case 3. *Nephritis (?), albuminuria.*—Mrs. Lizzie R., aged thirty-seven years, white; eighth pregnancy. Examined April 30, 1902. Former labors were uneventful, and the present pregnancy showed no abnormality until five weeks before admission, since which time she has been in bed on account of albuminuria. The patient is thin, but the abdomen is of the usual size and tension. There is some œdema and some enlargement of the veins of the leg, which, she says, has been present during earlier pregnancies. Heart dulness begins above at the lower border of the second rib, on the right to the right border of the sternum, on the left to just inside the midclavicular line, where the apex is felt in the fourth and fifth interspaces. Over the apical region there is heard a short systolic murmur, which is not transmitted. The second sounds are not especially loud. Blood pressure by the Riva-Rocci varies between 128 and 130, by the Gärtner between 110 and 125. The pulse is 118.

Second examination made fifteen hours after labor, which was not unusually long or hard, and during which nothing abnormal occurred. The heart dulness is somewhat lower. The breadth of the dulness is not changed. The short systolic murmur is as before. Blood pressure: Gärtner, 98 to 110; Riva-Rocci, 118 to 120. Pulse, 108.

May 2*d*. Area of dulness unchanged. Murmur at apex still present. Just to the right of the apex the first sound seems to be split. Blood pressure: Gärtner, 90 to 105; Riva-Rocci, 110 to 120. Pulse, 108.

4*th*. Blood pressure: Gärtner, 132 to 141; Riva-Rocci, 130 to 137. Pulse, 96 to 100.

21*st*. To-day no murmur can be heard. The patient feels very well. Blood pressure: Gärtner, 105 to 112; Riva-Rocci, 102 to 110. The patient's recovery was apparently perfect.

Case 4. *Mitral regurgitation.*—Allen P., aged eighteen years, colored, primipara. Examined March 25, 1902. She gives a

rather doubtful history of shortness of breath and swelling of the feet, even before pregnancy. The chest is small, but well formed, and the abdominal distention is about normal. Cardiac dulness begins above at the top of the first rib and extends on the right to a full finger's breadth beyond the right sternal border, on the left to the anterior axillary line, and below to the fifth rib. On palpation the apex is felt in the fourth interspace, but almost as strong a pulsation is felt in the third interspace, and in the second interspace, close to the sternum, there is a visible systolic pulsation. All these pulsations are more evident on sitting. No murmurs are heard, but the second pulmonic sound is somewhat accentuated.

26*th*. The blood pressure by the Riva-Rocci varies between 115 and 120; by the Gärtner, between 125 and 140.

27*th*. Second examination made six hours after labor. The area of heart dulness has moved down about an interspace, and extends less to the right. The apex is now most strongly felt in the fifth interspace, though pulsations in the upper interspaces are still apparent. Over practically the entire area of dulness a distinct systolic murmur can be heard, with, perhaps, most intensity at the apex. The second pulmonic sound is as before.

April 8th. Third examination shows no change in the outlines. The systolic murmur is now heard only when the patient sits up, and is not transmitted. The second sounds are both loud. In the sitting posture the pulsation in the second interspace is still visible. Blood pressure: Riva-Rocci averages 112; Gärtner averages 130.

Case 5. *Mitral regurgitation.*—Florence G., aged seventeen years, colored, primipara. Examined September 2, 1902. Girl is of medium size and well nourished. The abdomen is normal in size and tension. No separation of the recti muscles demonstrable. She states that she has never had dyspnœa, palpitation, or œdema. Heart dulness above extends to the lower border of the second rib; on the right to midsternum; on the left to the midclavicular line, where the apex is in the fourth interspace. Distinct pulsation is felt to the outer side of the left line of dulness and over practically the entire area to the left of the sternum, especially in the second interspace. Over the area of dulness, and most marked at

the apex, can be heard a blowing systolic murmur, which is transmitted to and plainly heard in the axilla. The second pulmonic sound is accentuated. Blood pressure by the Riva-Rocci varies between 120 and 125; pulse 80.

5*th*. Second examination made one hour after delivery, which presented nothing unusual. There is but little change. The apex is now in the fifth interspace, and the pulsation in the second left interspace is no longer visible. The murmur is as above described. Blood pressure by the Riva-Rocci varies between 145 and 150. No ergot or binder used in this case.

Case 6. *Mitral regurgitation*.—Esther B., aged twenty-four years, colored; third pregnancy. Examined April 10, 1902. Patient is short and stout, with a thick chest wall. Says that she is naturally "short-winded," but no more now than is usual. The abdomen is rather larger than normal. Cardiac dulness begins above on the upper border of the first rib, on the right it extends to a finger's breadth beyond the right sternal margin, on the left about one-half inch beyond the midclavicular line. Apex is in the fourth interspace, and above in the third can be felt a distinct pulsation. In the second left interspace close to the sternum can be heard a short systolic murmur, which seems very close to the ear. The second pulmonic sound is accentuated. Blood pressure varies between 122 and 135 by the Gärtner; between 122 and 125 by the Riva-Rocci.

17*th*. Second examination made thirty hours after labor, at the end of which a repair under ether was made. The shortness of breath is no longer present, and the patient lies more comfortably. The heart dulness extends less far to the left, and the apex beat is lower down in the fifth interspace. The murmur so close to the ear before noted in the second left interspace can no longer be heard, but over the entire area of dulness to the left of the sternum can be heard a systolic murmur, which is, perhaps, best marked at the apex. The second pulmonic sound is accentuated, and the closure of the valve can be distinctly felt. Blood pressure: Gärtner averages between 105 and 115; Riva-Rocci between 110 and 113.

27*th*. Third examination shows the same area of dulness as the second. In the recumbent position there is heard a soft systolic

murmur just inside the apex, and the second pulmonic sound is accentuated and split. In the erect position the murmur is indistinct, but the split second is unchanged. Patient still complains of some shortness of breath, but there is no œdema or palpitation. Evidently there was an organic lesion with some dilatation before labor, but no sign of failure of compensation during delivery.

Case 7. *Mitral regurgitation; uterine hemorrhage.*—Martha L., aged twenty-four years, colored; fifth pregnancy. Examined August 4, 1902. Former labors were easy, but she has always had some swelling of the feet and shortness of breath while carrying the child. Patient is tall and well built; abdomen normal in size; says that "dropping" has occurred. During the present pregnancy many varicose veins have developed on the lower extremities and genitals, and she has been short of breath. Heart dulness begins above at the lower border of the second rib, extends on the right to a little beyond the right sternal border, on the left to a finger's breadth beyond the midclavicular line. Apex is seen and felt in this line in the fifth interspace. A systolic pulsation is also noted in the second left interspace close to the sternum and over the left border of the heart. At the apex there is heard a systolic murmur which is transmitted to the axilla, and is also heard over the body of the heart, especially at the pulmonic area, where the second sound is markedly accentuated. Blood pressure: Riva-Rocci, 120 to 123; greatest pulsation at 90.

9*th*. Second examination made twenty-two hours after labor, which was unusually easy, lasting only four or five hours. There was no evidence of circulatory failure. During the night a rather severe uterine hemorrhage occurred. Area of heart dulness unchanged. Pulsation still seen in the second left interspace. Murmur as before—long, blowing, and transmitted to the axilla. Blood pressure: Riva-Rocci, 125 to 130.

20*th*. Blood pressure by Riva-Rocci 130. No change in heart.

21*st*. Blood pressure, Riva-Rocci, 128 to 130; heart as before. This is a typical case of mitral regurgitation, yet the labor was perfectly normal, except for the hemorrhage following it, which, perhaps, may have eased the circulation.

Case 8. *Mitral regurgitation.*—Sydney S., aged twenty-five years, colored; second pregnancy. Examined February 24, 1902.

The patient is short and fat. The tension of the abdominal wall and the size of the fœtus are normal, but the quantity of liquor amnii is plus. She has had dyspnœa and swelling of the feet for some time, even before pregnancy.

The area of cardiac dulness is greatly increased, beginning above at the top of the second rib, on the right at right margin of the sternum, on the left almost at the anterior axillary line. Apex is in the fifth interspace. Over the entire præcordia, most marked at the apex, there is a systolic murmur which is transmitted to the axilla. The second pulmonic sound is accentuated. Blood pressure varies between 115 and 120 by the Riva-Rocci ; greatest pulsation occurs between 90 and 100.

March 17th. Second examination made eight hours after delivery, which was easy, lasting only seven hours. There is but little change in the total area of heart dulness. The second tracing gives the impression that the entire heart had been pushed slightly upward and to the left. The systolic murmur presents the same characteristics as before. Blood pressure 125 to 130 by the Riva-Rocci. This is also a case of mitral regurgitation in which labor apparently produced no bad results.

Case 9. *Mitral regurgitation.*—Mary B., aged twenty-five years, white ; second pregnancy. Examined March 4, 1902. The patient is very small, weighing only 112 pounds, and has had cardiac symptoms for some time. The area of heart dulness is markedly increased, beginning above at the upper border of the second rib, extending to a full finger's breadth beyond the right sternal margin, and on the left to the anterior axillary line. Over the entire area of dulness to the left of the sternum there is visible and palpable pulsation. Apex in third and fourth, diffuse. Over same extent can be heard a systolic murmur, which is, perhaps, best marked at the third left chondrosternal junction. At this point the murmur has a peculiar whistling quality, and is apparently very close to the ear. At other points the murmur is dull. Blood pressure by the Gärtner between 105 and 120 ; by the Riva-Rocci between 90 and 97.

28th. Second examination several hours after labor, which was easy, though artificially induced. The cardiac dulness extends less far above, but is otherwise unchanged. Below the lower line of

dulness a pulsation is distinctly felt. Apex now found in fourth and fifth interspaces. Outer border is still in the anterior axillary line. Murmurs are unchanged. Blood pressure: Gärtner between 110 and 127; Riva-Rocci between 96 and 97. In this case, also, the mitral regurgitant lesion caused no symptoms during the progress of the labor.

Case 10. *Cardiac dilatation.*—Olivia E., aged twenty-five years, colored; third pregnancy. First examination April 30, 1902. The patient is rather fat. She states that her former labors were easy. She has had no swelling of the feet or other symptoms, except some shortness of breath on exertion. The abdomen is of usual size; tension normal. Cardiac dulness begins above at the upper border of the second rib, extends on the right to the right border of the sternum. Apex felt in the fifth interspace in the anterior axillary line. At the apex a rather faint systolic murmur covers the first sound, and this murmur is audible over the body of the heart to the left of the sternum. The second sounds are loud. Pulse, 84. Blood pressure: Riva-Rocci, 115 to 120; greatest pulsation occurs at 100. Patient was delivered 10.30 P.M. of April 30, 1902, the labor being uneventful. Examination made twenty hours later showed no change in the cardiac condition. Blood pressure by the Riva-Rocci averaged 132; greatest pulsation averaged 118. Pulse, 76.

May 2d. Murmur is indistinct. Apex position unchanged. Blood pressure by Riva-Rocci averaged 130; greatest pulsation 110. Pulse, 76.

4th. Blood pressure: Riva-Rocci, 124; greatest pulsation 110. Pulse, 100.

19th. The cardiac area remains as large as on former examinations. The apex is in fifth interspace in the anterior axillary line. No murmurs can now be heard. The second pulmonic sound is accentuated. Blood pressure: Riva-Rocci averages 122; greatest pulsation 102. Pulse 76.

Case 11. *Cardiac dilatation.*—Mrs. B., aged twenty-four years, white; first pregnancy. Examined April 14, 1902. The patient had two chills within the previous twenty-four hours, and at the time of examination she had a temperature of 101°, with a pulse of 136. The abdomen is greatly distended and tympanitic, and the

stomach tympany is especially high, so that no superficial dulness is obtainable. The outer border of heart is made by palpation to be in the anterior axillary line, and the apex apparently in the third interspace; at least in this place the pulsation is most strongly felt. Over the base of the heart is heard a systolic murmur and an accentuation of the pulmonic second sound. Blood pressure averages by the Riva-Rocci 106, and by the Gärtner 108.

15*th*. Second examination made twelve hours after delivery. The cardiac area is larger than before. Pulsation is visible over most of the area to the left of the sternum as high as the second interspace. The murmur is still audible, but the accentuation of the pulmonic second sound is much less marked. The pulse is 140 and of poor quality, and the patient looks very ill. The blood pressure by the Riva-Rocci averages 96; by the Gärtner, 102. This is probably a case of dilatation due to the toxæmia associated with the fever, as no history of previous heart trouble was obtainable.

Conclusions. The conclusions arrived at by us were that there is not, during pregnancy, any hypertrophy of the left ventricle, nor any special increase in its work. The increase of dulness toward the left is due to the upward displacement of the diaphragm and the consequent displacement of the heart in an upward and outward direction.

The comparative outlines before and after labor show a rapid return to the normal position.

We were struck by the frequency of an increase in the extension of dulness toward the left in the second and third interspaces and by the frequency of distinct pulsation in the same area. In the absence of any evidence of retraction of the lung, and in view of the fact that the pulsation discovered in this region was distinctly marked, it is evident that this condition of things is ascribable to distention of the conus arteriosus and root of the pulmonary artery. The frequent presence of a systolic murmur most clearly audible in the same area further substantiates this opinion. Moreover, the position of the right border of the heart seemed on the average somewhat too far toward the right, which, with the conditions present at the root of the pulmonary artery, convinced us that

there is probably during the later months of pregnancy some continuous dilatation of the right ventricle, though this is apparently of very moderate degree. Such a state of affairs can scarcely be regarded as surprising when we reflect that the upward displacement of the diaphragm and pressure upon the lungs must necessarily increase the difficulties of the pulmonary circulation. Our belief in the existence of a dilatation of the right ventricle is, however, based upon observed facts rather than upon theoretical deductions.

The condition of the abdominal recti is important from the point of view of the circulation. In multiparæ separation of the recti materially lessens the tendency to displacement of the diaphragm, and diminishes in a corresponding degree the displacement of the heart during pregnancy. After delivery this diastasis of the recti, however, may occasion a downward displacement of the apex of the heart, and the contrast before and after labor may be quite as pronounced as in primipara, though the first position occupied may not have been far from the normal. Later, if the separation of the muscles is not considerable, and the normal tone of the abdominal walls is regained, a restitution to the normal of the heart and its apex occurs.

The investigations of the blood pressure made by us show conclusively that there is no material increase of this pressure before or after labor. During labor we sometimes found notable increase in the blood pressure, such as has also been observed by others.

When a comparison of the figures is attempted, the difficulties due to the imperfections of apparatus and the personal equation of the observer become apparent. Fellner, using the Gärtner tonometer, found the pressure during pregnancy from 80 mm. to 100 mm. These figures, it will be seen, are materially lower than those frequently observed by us. During labor there was an increase during pains of 10 mm. in the earlier period, and later a more decided increase. After labor the pressure fell to a point lower than it had been before. Lebedeff and Porochjakow (*Centralbl. f. Gynäkol.*, January 5, 1884), using the sphygmomanometer of von Basch, found a difference of 18 mm. during the pains of labor. Of course, such increase may be explained by the holding of breath, the expulsive efforts, etc. MacDonald, with Mahomed's instrument, before labor obtained the best pulse tracings when the

pressure was 5.6 ounces, and recorded as an average obliterating pressure 16.9 ounces ; after labor the figures were 5 ounces and 16 ounces, respectively ; while in healthy non-pregnant women 4 ounces and 13.5 ounces are stated as being normal. These results are in no way substantiated by more recent methods of observation.

In conclusion, we wish to express our thanks to Dr. B. C. Hirst for his kind permission to study the patients under his care in the maternity department of the University Hospital.

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A FATAL CASE OF STOKES-ADAMS DISEASE WITH AUTOPSY, SHOWING INVOLVEMENT OF THE AURICULOVENTRICULAR BUNDLE OF HIS.

A PRELIMINARY COMMUNICATION.

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The symptom-group known as Stokes-Adams' disease was first recognized by Adams in 1827, but more accurately described by Stokes in 1846. In recent years the subject has been discussed by Huchard in France, His, Hoffmann, and Jacquet in Germany, and by Prentis, Edes, Osler, and Babcock in America.

The symptoms that characterize the affection are: 1. *Slow pulse,* the rate falling temporarily or permanently to 30, 20, or even less. 2. *Cerebral attacks,* such as vertigo, syncopal or epileptiform seizures, unconsciousness. 3. *Pulsation of the veins in the neck* exceeding in rate the pulsation of the arteries twofold, threefold, fourfold or more. The disease was first recognized in old persons and in such as presented clinical or postmortem evidences of cardiac and vascular disease. Later instances were met with in younger persons and in some cases no lesion of any sort was found at autopsy. In Edes' series reference was made to the condition of the heart and vessels in 31 of the 35 cases that came to autopsy. In 26 of these sclerotic and myocardial changes were observed. In some cases lesions of the nervous system, such as compression of the medulla or changes in the vagus and cardiac plexus, have been described.

Recently, the resemblance of the clinical symptoms to the phenomena of "*heart block,*" as produced by physiologists, has been pointed out. Gaskell first showed that constriction of the circular layer of muscle at the auriculoventricular junction of the heart of tortoises causes a cessation of the rhythmic action of the heart so that the auricles and ventricles become independent in their contractions, the former beating more rapidly than the latter. Various physiologists have confirmed this discovery and have discussed the nature of the mechanism which controls the rhythmic contractions. The prevailing opinion of physiologists at the present time is that the impulse to contraction originates at the large venous openings into the auricles and is propagated downward through

the auricle into the ventricle within the muscle tissue itself. In a review of the evidence bearing on the transmission through the muscle of the impulse to contraction, His[1] states that there are grave difficulties in the way of those who believe that nerve centres are the basis of cardiac activity. Rhythmic contractions certainly occur in the severed apex of a frog's heart after the contractions have been set in motion by some excitation. "Automatism," or *power of automatic contraction*, is therefore wanting, but there is present a *capacity for rhythmic contractility* after a stimulus has been given. Automatism in the frog's heart is found only in parts adjoining the auriculoventricular zone and the sinus region where there are ganglion cells. It does, however, also exist in embryonal hearts before ganglion cells are developed, though the experiments of Fano showed that even in such embryonal hearts the automatism is greatest near the sinuses and decreases progressively toward the apex of the ventricle. Physiologists agree that the ganglion cells at the venous sinuses are the principal source of the impulses for cardiac contraction, but Gaskell and Wooldridge proved that the nervous connections between auricles and ventricles may be severed without cessation of the ventricular contraction, and Krehl and Romberg have shown that in the adult heart the ganglia may be wholly separated without influencing cardiac contraction. The effect of the operation in the experiments of the latter authors was so slight that the heart maintained a blood pressure of practically normal degree. It would seem, therefore, that the impulse for contraction is transmitted from the sinus region to the auricle and ventricle through the muscle cells rather than through any nervous path. As a further evidence suggestive of this view Gaskell found that by stimulating the aortic bulb contractions could be made to run from ventricle to auricle; that is, in a direction the reverse of the normal. These experiments His regards as strongly antagonistic to the assumption that the impulse flows through a nervous mechanism.

If then the impulse travels through the muscle cells, it is necessary that a muscular connection be shown to exist between auricle and ventricle. Wm. His, Jr., first accurately described this connection in the mammalian heart in the form of a bundle of muscular tissue extending from the right side of the interauricular septum to the interventricular septum immediately below the *pars membranacea*. The "auriculoventricular bundle of His" is approximately 18 mm. long, 2.5 mm. broad, 1.5 mm. thick (Retzer). His' observation has been confirmed by Retzer, Bräunig, Humblet, and others. Though this bundle is an insignificant structure, physiological and anatomical evidence points to it as the pathway of the stimulus to contraction. In his experiments with Graufner, His found that

[1] Wien. med. Blätter, November, 1894.

by introducing a delicate knife through the auricle and dividing the auriculoventricular bundle in the septum (in rabbits) the auricles and ventricles ceased beating at the same rate. When the experiment was accurately performed the resulting condition was that of complete heart block, the auricles and ventricles beating independently of each other. A similar result has been obtained by Tigerstedt, who succeeded with a special appliance in compressing the auriculoventricular connections without hemorrhage and in producing the condition of heart block.

The most convincing experiments in this direction are those of Erlanger, who operated on the intact heart of dogs and other animals. With the aid of a specially devised curved needle, acting as a clamp, he was able to reach the auriculoventricular bundle of His by introducing the needle behind the posterior aortic leaflet and pushing the point through the interventricular septum. When the clamp was adjusted it was found that the muscle bundle of His alone was involved in the compression if the experiment was accurately performed. The amount of pressure could be regulated by means of a thumb-screw and complete or partial constriction could thus be established. The result of such compression was to produce first occasional failure of ventricular contraction; next, a ratio of the auricular to the ventricular beats of 2 to 1, 3 to 1, 4 to 1, and finally complete heart block in which the ventricles contracted independently of the auricular rhythm. Sometimes at the moment when complete block was established the ventricle ceased beating for periods varying from a few seconds up to fifty-five seconds. This phenomenon Erlanger explains as probably resulting from the fact that a certain time is necessary after complete severance of the connection between auricles and ventricles for the development in the ventricle of its inherent rhythmicity.

The experiments of Gaskell, His, Tigerstedt, Erlanger and others practically establish the fact that experimental heart block and the phenomena of Stokes-Adams' disease are identical. Up to the present communication, however, no case has been observed pathologically in which a lesion has been found involving the bundle of His. Dr. Erlanger tells me that when presenting his experimental work he suggested the possibility of involvement of His' bundle by a patch of sclerotic endocarditis beginning on the anterior mitral leaflet at its base and aortic border and extending to the interventricular septum where the bundle of His passes upward toward the auricle. The case about to be reported confirms the accuracy of his prediction.

J. B., aged fifty-seven years, a native of Germany, a wheelwright, was referred to the Out-patient Department of the University Hospital by Dr. B. F. Wentz, and to the medical ward by Dr. H. D. Jump. The patient was a married man, the father of five children, two of whom died in infancy: one of pneumonia, the other

of measles. He had been a healthy man, the only illnesses remembered by him being slight attacks of influenza, malaria, and lumbago. He denied venereal history, and there was no evidence of any such infection. He had never had any severe injury to the head or other parts of the body. He used tobacco in moderation, but had drunk beer to excess until two years ago, after which time he was very moderate in its use. The fatal illness began without warning while at his work about two and a half years ago. He suddenly fell backward and became unconscious for a few moments. There were no convulsive movements and he did not bite his tongue. The bladder was not emptied. He very speedily recovered from this attack and went back to work. Three months later he had another exactly similar attack and then the attacks came on in more rapid succession, about every two or three weeks. Except in the first attack he said he always fell forward. Two years ago he sometimes had spasmodic movements in the legs during the attacks, but the seizures were of varying severity, sometimes being extremely mild, when the patient did not fall nor lose consciousness but merely became slightly giddy for a few moments. In such mild attacks he was able by holding to some object to steady himself and prevent his falling. He found that stooping was more likely to provoke the attacks than any other movement or exercise. He has been troubled with flatulence after eating and has had obstinate constipation. Sometimes the attacks came on while eating, and occasionally belching would prevent their occurrence. At times there was pain in the head before the attack was fully developed and less severe headache was almost constantly present. He noticed that his face became cyanosed before the attacks and his friends observed that the cyanosis was intense during the attacks. After the seizure there was always violent palpitation.

The patient stopped working in May, 1905, and went to bed. During June there was a series of attacks, one following another every few minutes. Later they were less frequent, but he continued to suffer with the attacks until his admission to the hospital. He has lost sixty pounds in weight and has grown steadily weaker. He never had œdema nor dyspnœa.

Condition on Admission. The patient was admitted to the University Hospital on September 19, 1905, when the following notes were recorded:

The patient is a fairly well-nourished man; no cyanosis nor jaundice. There is marked pulsation in the epigastrium and in the veins of the neck. There is also visible pulsation of the brachial arteries. Radial pulses equal and synchronous; rate 36 and the character of the pulse "slow" (pulsus tardus). The radial and brachial arteries are somewhat hard. The pulse tension is moderately increased.

No enlargement of superficial lymphatic glands.

Eyes, nose, mouth, and ears normal; tongue slightly coated; teeth in fair condition.

Chest somewhat increased in the anteroposterior diameter; intercostal angle wide. Moderate depressions above and below the clavicles. Decided pulsation in the supraclavicular fossæ. Chest expansion fair and equal on both sides.

Apex beat visible in the fifth space just outside the midclavicular line. The impulse is moderately strong and there is a systolic thrill accompanying the beat.

Vocal fremitus is slightly diminished over the entire chest.

Percussion. The pulmonary note is everywhere slightly hyperresonant. Heart outlines: from the third space above to the sixth rib below and from the midsternum on the right to a point just outside the midclavicular line on the left.

Auscultation. The breath sounds are moderately weak, the expiratory sound slightly prolonged. There are no rales.

A somewhat harsh systolic murmur is heard at the apex of the heart and transmitted to the axilla. It is also heard toward the base of the heart. The second pulmonary sound is not accentuated, but is hollow and distant in character.

Abdomen. Epigastric pulsation is marked. Liver dulness begins at the sixth space and extends to the costal margin. Splenic dulness is normal in extent and the spleen cannot be felt.

The extremities are normal in appearance; reflexes normal. Station, gait, and muscular co-ordination normal.

Examination of the Urine. Specific gravity 1018, straw color, clear; reaction acid; no albumin; no sugar. Microscopically, a few hyaline and granular casts and scattered leukocytes were found.

September 22, 1905. The patient's condition has remained the same as on admission. There have not been any attacks and he feels quite comfortable.

Blood Examination. Red blood corpuscles, 5,260,000; white blood corpuscles, 14,000; hæmoglobin, 85 per cent.

23*d*. The patient began to have attacks this morning, a number occurring during the day. They have been mild in character, beginning with a momentary pallor, then a flushing or cyanosis and slight tremor of the arms. After the attack the face is pale and gradually the color returns. During several of the attacks it was noticed that the pulse stopped beating for a few seconds, and during one attack the interval was fifteen seconds. After the attack the pulse rate increased for a short time, then subsided to a steady rate of from 16 to 18 per minute. The pulsation of the veins in the neck continued during as well as between the attacks at from 80 to 100.

No change has occurred in the physical signs since the attacks have begun.

24*th*. The attacks are continuing at about one-half hour intervals. The pulse during the day has been from 18 to 26 and the volume has been good. The character of the attacks has not changed. During the seizures there seems to be only partial unconsciousness lasting a few seconds. The tremor attending the attacks is very slight. The eyes sometimes roll or move rapidly from side to side or upward in the earlier part of the attack and become fixed in a staring position when the attacks subside. The patient is quite weak and very nervous.

25*th*. The patient's strength has improved, as the attacks have been much less frequent.

26*th*. The paroxysms have grown more frequent and more marked. The development of the seizures to-day has been in the following order: The face first becomes yellow or pallid and the lips cyanosed; the eyes become fixed and staring, then move upward and to the left; the pupils change from a moderately contracted to a somewhat dilated condition, then the arms become a little rigid and tremble. The legs move very slightly in the same fashion. The pulsation at the wrist stops a few minutes before or during the attacks, and during one of the seizures the interval was thirty seconds. The venous pulsations in the neck continue through the attack. After the paroxysm the face becomes moderately flushed; the pulse begins to beat strongly, the respirations become deeper and more rapid than during the attacks. Unconsciousness is to-day somewhat more complete and of longer duration than previously.

During the afternoon the patient began to vomit, the first vomiting occurring just before an attack. Before and during the beginning of every seizure in the afternoon the pulse at the wrist stopped for from fifteen to twenty-five seconds.

27*th*. The patient is weaker and is becoming slightly drowsy. He slept poorly during the night and vomited repeatedly. After midnight the attacks followed each other in rapid succession. The seizures this morning are very severe. During one the pulse stopped for *two minutes and ten seconds*. The convulsive movements always follow the cessation of the radial pulse, and it is noticed that the face always becomes flushed before the patient recovers consciousness. The following table shows the duration of the cessation of the radial pulse, the number of venous pulsations in the neck per minute, and the rate of the radial pulse immediately after the attacks and some time later:

10.22 A. M. Ventricular beat for five minutes between attacks 147 per minute.

	Cessation of pulse.	*Venous pulse in neck.*	*Radial pulse.*
10.27	45 sec.	144	122
			1 min. later 24
11.20	80 sec.	140	132
			30 sec. later 84
			1 min. later 50
			2 " " 22
12.03	50 sec.	118	100
			1 min. later 80
			1½ " " 24
12.10	2 min. 10 sec.	120	90
			1 min. later 40
			1½ " " 38
12.20	Several attacks in rapid succession.		
1.00 P. M.	50 sec.	.....	96
			1½ min. later 20
1.30	1 min. 20 sec.	.....	100
			1 min. later 40

27*th*. The patient continued having repeated attacks of the same general character at short intervals. In the afternoon Cheyne-Stokes respiration began and shortly afterward the attacks ceased. Three hours later the patient died very quietly. The ventricular pulse remained low (18 to 26) to the last and the venous pulse in the neck continued rapid.

During the continuance of the severe paroxysms repeated examinations were made and confirmed the previous physical examinations. The systolic murmur heard at the apex was constantly present and the heart sounds corresponded accurately with the pulse felt at the wrist. Occasionally feeble heart sounds were heard and sometimes these coincided with slight evidence in the pulse tracing of weak systolic efforts. No suggestion of sounds corresponding to the venous pulsation could be heard over any part of the heart.

The accompanying pulse tracings were made with a tambour applied to the pulsating vein and a Jaquet's sphygmochronograph applied to the radial pulse (Fig. 1). In order to have the record of venous pulsation and arterial pulse on the same paper, the lever recording venous pulsations was of necessity a little behind that marking the arterial beats. The two records do not, therefore, present synchronous pulsations at any given point.

During the last few days of life a condition of complete heart block was seemingly present. The auricular (venous) and ventricular pulsations were entirely independent. Between the paroxysms the pulse rate was from 18 to 26 and the venous rate from 80 to 140. The latter rate was sustained during and between the seizures, while the pulse beats ceased for periods varying from twenty seconds to two minutes and ten seconds just before attacks and rose to from 90 to 140 immediately after the seizure. In the intervals the radial pulse was regular and fairly strong, the rate being from 18 to 20 or 30 (Fig. 2). The blood pressure was estimated on one or two occasions between attacks and was found

CHRONIC ACETANILID POISONING.

REPORT OF TWO ADDITIONAL CASES.*

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Chronic acetanilid poisoning is probably very much more frequent than the medical profession appreciates, for the reason that the symptoms may be comparatively inconspicuous. The drug in its pure form or in various proprietary combinations is so easily obtained that its indiscriminate use has naturally resulted. A very striking case came under my observation three years ago and was reported by myself and Dr. C. Y. White. Since that time two additional cases have been under my care: one, a private patient, was sent to me by a medical friend on account of obscure symptoms, which proved to be the result of chronic acetanilid poisoning; the other, a hospital patient with rather more marked symptoms, was referred to me on account of other conditions.

CASE 1.—Mr. W. C. H., aged 38, a merchant, consulted me in July, 1902, on account of increasing weakness, nervousness and slight shortness of breath. There were occasional palpitations of the heart and frequently a sense of throbbing in the neck. He had noticed a blue color of the lips and finger nails. For several years he had suffered from facial neuralgia and later from severe headaches. With these exceptions he had always been in good health.

Examination.—The patient is a strongly built, well-nourished man. The face, lips and finger nails were deeply cyanosed, but the surface was not specially cold. There was marked pulsation of the vessels of the neck; pulse rate 85, and on slight exertion reached 105 or 110.

Physical examination: The heart was found to be enlarged to the left and to the right, the left border extending beyond the midclavicular line and the right border a little beyond

* From the William Pepper Laboratory of Clinical Medicine; Phoebe A. Hearst Foundation.

the right edge of the sternum. The heart action was irregular and the apex impulse rather diffuse. On auscultation the sounds were found to be somewhat indistinct and vibrating in quality, but there was no murmur. Lungs were negative.

Abdominal organs were apparently normal. The spleen was not palpable.

The station was good, the knee jerks and other reflexes normal. The eyes were a little prominent, but otherwise normal. There was a slight tremor of the hands. No enlargement of the thyroid gland.

Urine: The urine on the patient's first visit was found very dark and showed a considerable amount of indican, but was otherwise negative. Subsequently repeated examinations showed no abnormalities in color or in other appearances.

Blood: Repeated examinations of the blood were made, but unfortunately the records have been mislaid. A constant result of these examinations was the discovery of marked polycythemia, the number of red corpuscles being 6,000,000 or greater. There was no excess of leucocytes. Histologic examinations showed no abnormalities in the erythrocytes except an apparent enlargement. Nucleated red cells were never found, and basic granulations and polychromatophilia were absent.

History.—Later I obtained the information that the patient had for some time taken a proprietary remedy known as cephalgin on account of his facial neuralgia and headaches. The amount could not be determined, as he carried it about and took doses at irregular intervals and without any care to avoid excess. I learned that the blueness of the skin was of about a year's duration, which agreed quite accurately with the time during which he had been taking the remedy mentioned. It was difficult to obtain an accurate history from the patient, as he either could not recall the taking of the drug, or wished to conceal the fact from me. From his wife, however, I learned that he had taken a great deal of the preparation, that he had grown steadily more nervous and irritable, that he slept almost constantly from the time of his return from business to the next morning, and that he was quite altered in his general character and disposition.

Treatment.—The patient returned at intervals from July, 1902, until January, 1903. At first we had reason to believe that he continued to take some of the antineuralgic remedy, though he denied it to us. Subsequently, under tonic treatment, together with the administration of iron, arsenic and cardiac stimulants, his condition improved and by the end of 1902 he was practically well, and has so remained up to the present time.

Remarks.—Recently I saw him on the occasion of the illness of another member of his family, and he told me that he thought he had taken much more of the cephalgin than he

had told me in the beginning, and expressed himself as quite certain that his condition was directly and entirely due to the drug taken.

CASE 2.—Miss M. E., aged 27, was admitted to the University Hospital, June 30, 1903, with the following history:

History.—The patient had had the usual diseases of childhood, but subsequently was in excellent health until eight or nine years ago, when she began to suffer from sick headaches. The attacks grew more and more frequent up to four or five years ago, when she began to use "tablets" to relieve the pain, and continued them steadily up to March, 1903, when she discontinued their use. Her stomach had become increasingly irritable, and about nine months ago she noted a change in the color of her skin. At first this was of a grayish or light purplish hue. Later it became a deeper blue. During five or six weeks before admission she had also suffered from dyspnea and palpitation of the heart. This discoloration of the skin improved somewhat after discontinuance of the tablets.

Examination.—Temperature normal; pulse and respiration a little rapid. The patient complained of disturbance of the stomach and of some headache. The skin of the face was of a light steel blue color; at times it had a dusky hue; at other times a clear blue. The finger nails and lips were more deeply cyanosed. The surface temperature felt normal.

Physical Examination: There was found slight enlargement of the heart, mainly to the left. The first sound at the apex was distinctly murmurish; the second pulmonic sound was slightly exaggerated. The lungs, abdominal organs and nervous system were practically normal.

Blood: R.B.C., 3,460,000; W.B.C., 6,900; hemoglobin, 72 per cent. (Accurate determination of the hemoglobin was almost impossible on account of the peculiar dark discoloration of the blood.) Histologic examination showed no abnormalities in the character of the blood corpuscles.

Urine: Color dark brown, distinctly smoky, reaction acid, specific gravity, 1038; no albumin, no sugar, no bile. Microscopic examination showed some leucocytes and a few red blood corpuscles with calcium oxalate crystals and scattered epithelial cells.

The patient improved gradually, and was discharged from the hospital on August 7, 1903.

Subsequent History.—April 19, 1904: The patient was readmitted, giving the following history:

For three months after her discharge she was in excellent health, but about Dec. 1, 1903, the headaches recurred and soon became severe. She now presents a peculiar pallor of the skin, together with some cyanosis. There is extreme prostration of strength.

Physical Examination.—The area of cardiac dullness is increased decidedly on both sides, and on auscultation a well-marked systolic murmur is audible at the apex, practically replacing the first sound. The second pulmonic sound is accentuated. The spleen is much enlarged, being easily palpated two inches below the costal margin. The liver also extends below the edge of the ribs. Lungs, negative.

Blood:[1] R.B.C., 3,170,000; W.B.C., 9,680; hemoglobin, 64 per cent. Histologic examination shows moderate anisocytosis and poikilocytosis. No nuclear red cells.

Urine: Mahogany brown in color, alkaline, sp. gr. 1024; no albumin, no sugar. There was a whitish sediment. Microscopically, triple phosphate crystals with epithelial cells and leucocytes were discovered. Uro-erythrin was present in moderate amount; indican was present in excessive quantity. No reaction with Rosenbach's test. No hematin, hemoglobin, methemoglobin, hematoporphyrin, bile pigment, pathologic urobilin, nor melanin could be found. No phenol nor acetone. No color reaction with iron chlorid. The high color was probably due to humin substances derived from indican.

April 25, 1904: The patient complained of pains in the region of the heart, as well as continued facial, frontal and orbital pain. The color of the skin improved progressively from the day of her admission to the hospital.

Blood: R.B.C., 3,680,000; W.B.C., 9,200; hemoglobin, 68 per cent. Microscopic examination showed a few nucleated red cells, poikilocytosis, and variability in the staining affinity of the erythrocytes.

April 28, 1904: The patient has continued to improve. Dr. Fife reports the following results of the examination of the urine:

Amount (total for twenty-four hours), 680 c.c.; sp. gr., 1022; acid, volatile fatty acids equal 51.6 c.c. of 0.1 normal acid solution. No acetone, no phenol. Tests for blood and bile pigments negative. Heller's test for urophein positive; Harley's test for urohematin negative. No urobilin. Indican excessive in amount. Both the indoxyl sulphates and indoxyl glycuronate present to Strauss' test.

May 6, 1904: At this time, some doubt having been cast on our conclusion that acetanilid had alone caused the symptoms, and the patient having denied the taking of any acetanilid between her first and second visit to the hospital, we administered the drug in doses increasing from 20 to 45 grains daily, with the result that from April 30 to the present time there has been a progressive increase in cyanosis and a return of the dark color of the urine. The chemical examination, however, again showed the absence of blood pigments.

The following examination was reported by Dr. Fife,

1. Dr. C. A. Fife made the various chemical examinations of the blood and urine.

May 16: Amount of urine 600 c.c. dark reddish brown color, acid reaction, color becoming brown wine-red on addition of an alkali. This had been noted at previous examinations, but was not recorded in the reports, probably due to paramidophenol, a derivative of acetanilid. Excessive amount of both indoxyl sulphate and glycuronate (Strauss). Total sulphates, 1.4212 H_2SO_4, ethereal sulphates, .3769 H_2SO_4; preformed sulphates, 1.044 H_2SO_4; total nitrogen, 9.4 grms. The indophenol reaction of paramidophenol present in ethereal extract (Jaffé method). Oxycarbamid not demonstrated. No blood pigments present. The high color is probably due to paramidophenol and possibly in part to substances derived from the indican.

Blood: Blood serum obtained by puncture of a vein with a hollow needle was distinctly colored, but on spectroscopic examination showed only the absorption bands of oxyhemoglobin. When treated with ammonium sulphid and with Stokes ferrous tartrate solution, it exhibited the band of reduced hemoglobin. Examination of the blood showed some nucleated red corpuscles, poikilocytes and irregularity in the affinity for stains.

June 10, 1903: Acetanilid was discontinued on May 24. After this time the patient steadily improved. On June 5 the following notes were recorded: The patient's condition is much improved. There is now only a dull feeling in the head and slight pains in the extremities. The dusky or ashy color of the skin has practically cleared up.

Remarks.—In attempting to determine the quantity of acetanilid which the patient had taken before her admission to the hospital, I found it difficult to reach a reliable conclusion. Her physician wrote that she had first consulted him on account of severe headaches, and that after various attempts at relief had failed, and even morphia hypodermically was unsuccessful, he gave her some three-grain tablets of acetanilid, instructing her to use them with care. As there were two physicians in the same office, she obtained the tablets from one or the other of them, so that neither knew the amount which she was receiving. I quote the following from her physician's letter:

"For a period of one year she used these tablets, sometimes as many as six in one day and at times two or three days in succession; then there would be a period during which she would not use them. The taking of this drug in the dose mentioned was so irregular that it is impossible to determine the exact amount. She denied having obtained it elsewhere. During the past eight months, since her return from the hospital, she has had none of the drug nor any coal-tar product. In summing it up I should say that Miss E. took the drug for a period of two years, that she

never took more than 20 grains in any one day, and there were whole weeks in which she did not take any of it. I am inclined to think that there were times when she took as high as 20 grains every day for a week."

This letter was written shortly after her second admission to the hospital, when we thought that she must have taken acetanilid in the interval between her previous discharge from the hospital and her re-admission on account of the return of cyanosis. She, however, denied this, and, as the letter indicates, her physician believes she took none. The prompt return of the cyanosis, however, when acetanilid was administered, assured me that our suspicions were correct and that she had in the interval obtained the drug elsewhere than from her physician.

These cases were of special interest from the point of view of diagnosis. The first had been regarded as an obscure vascular disorder, and even after the true cause was suspected offered some difficulties on account of the lack of morphologic changes in the blood. In some experimental work now under way, Dr. C. Y. White has found that morphologic changes are not readily producible. The blood of dogs may be rendered thick and chocolate colored without presenting any evidence of alterations in the character of the red corpuscles.

Another matter of interest in these cases was the denial by the patients of the use of the drug. In this respect they agreed entirely with the case previously under my observation. I felt convinced that the deception by the patient was not merely the result of a fear that we would discontinue the drug, but was somehow the consequence of a moral disturbance. In the first case here reported the patient afterward spoke quite frankly of his use of the drug, though at the time of the active symptoms he could not be induced to confess that he was taking it, even when it was certain that he was doing so.

The polycythemia in the first case was of interest to me and was the occasion of the comment which I made in discussing Osler's paper on "Chronic Polycythemia, with Cyanosis, and Enlargement of the Spleen"; that some of the cases reported as instances of this unusual condition might be cases of acetanilid poisoning. In the case of the patient referred to there was polycythemia and cyanosis but no splenic enlargement. The last, however, is a frequent symptom of chronic acetanilid poisoning, and the whole picture might, therefore, be

readily that of chronic polycythemia. It was not supposed by me that all cases of this condition could be so explained, and at the present writing a very pronounced case with 9,000,000 red corpuscles per c.mm., extreme cyanosis, and considerable splenic enlargement is under my care, in whom no suspicion of acetanilid poisoning can be entertained, nor is any other hemolytic agent of external origin operative in this case.

Finally, a point of interest in these cases, as well as in the previous case reported by me, was the readiness with which neuralgic symptoms were controlled after the acetanilid was withdrawn. It would seem that the continued use of the drug so lowers the patient's resistance that instead of having a normal controlling effect on the neuralgic manifestations it acts as a general depressant and that the neuralgic symptoms occur with even more frequency while it is being used than would otherwise be the case. Discontinuance of the drug and the adoption of general tonic treatment soon proved successful in the two cases here recorded.

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VARIETIES OF SPLENIC ANÆMIA.

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

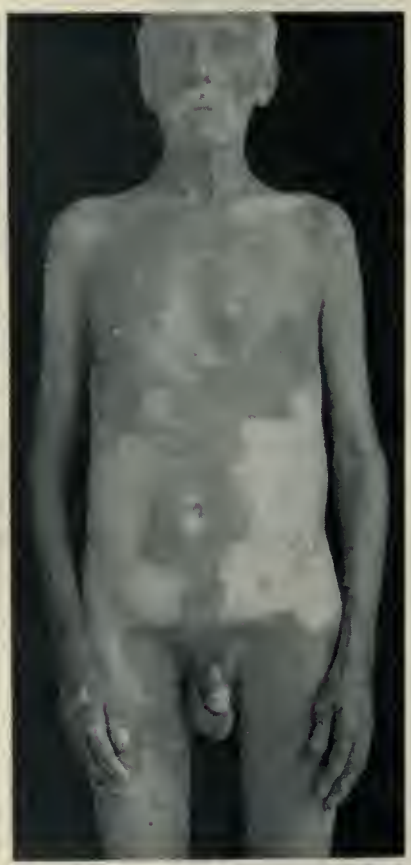
This report of five cases, with pathological studies in three of of them, is presented as a contribution to the knowledge of the condition generally designated as splenic anæmia. I have elsewhere expressed doubt regarding the individuality of such a condition, and the conviction that many different sorts of diseases have been classed under this name. For convenience of clinical terminology the name may, however, be retained, and perhaps some order may be established before long.

Case I. *Male, aged fifty-nine years, history of dysentery(?), duration over two years, probably six years or more; stunted growth, pigmented skin, clubbed fingers, osteoarthritis, enlarged spleen; chloroanæmia with leukopenia, hemorrhages, diarrhœa; early enlargement followed by diminution in the size of the liver; numerous intercurrent infections; death in stupor; autopsy.*—L. C., a cigarmaker, aged fifty-nine years, native of Belgium, was admitted April 18, 1900. The history recorded at that time is as follows: His father died of phthisis, his mother of jaundice, one brother of rheumatism. He had jaundice twenty-two years before and gonorrhœa sixteen years before. He denied syphilis and malaria, but had been in Mexico and Africa with the French army and may have had malaria. He gave an uncertain account of some sort of diarrhœal disease in Africa, perhaps dysentery. He was married at thirty-two; his wife and two children died of phthisis.

Four and a half years ago noticed a beginning alteration in the skin in the form of patches of pigmentation, alternating with light areas. Six or seven months ago had a chill and fever, and this has been repeated at intervals of a few weeks. He complains of a buzzing in his ears and of a scaly, itchy eruption on his legs. During the last two months has grown weak and dyspnœic.

Status Præsens. The patient is a somewhat undersized man. There is a bronze discoloration of legs and arms, and to a less extent of abdomen and chest, with areas of lighter color between. In places on the abdomen the skin in the bronzed areas is desquamating, leaving normal-colored skin beneath. The fingers are markedly

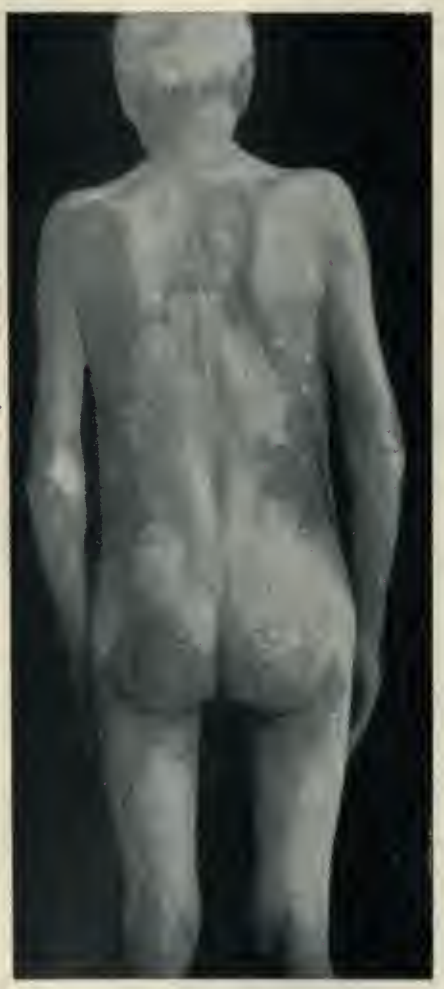
FIG. 1.



clubbed. Patches of dermatitis are found on both ankles, and there is slight œdema. The liver extends from the fifth rib to within an inch of the umbilical level. The spleen extends from the eighth rib to an inch below the anterior superior spine of the ilium. Two marked notches can be felt in the anterior border. Scattered rales

are heard in the lungs; a systolic murmur and an accentuated second sound at the aortic interspace. Otherwise normal physical signs are obtained (Figs. 1 and 2).

FIG. 2.



April 18, 1900. Blood examination: Red blood corpuscles, 3,520,000; hæmoglobin, 51 per cent.; white blood corpuscles, 5280.

May 1*st* Blood examination: Red blood corpuscles, 3,630,000; hæmoglobin, 76 per cent.; white blood corpuscles, 2600. (The

first hæmoglobin estimate was thought erroneous at the time.) Differential count: Polymorphonuclear, 68.9 per cent.; mononuclear, 1.9 per cent.; transitional, 4.9 per cent.; lymphocytes, 22.6 per cent.; eosinophiles, 1.4 per cent.

Urine Examination. Specific gravity, 1010; acid; no albumin; no sugar; microscopically negative.

6*th.* The patient had a chill, followed by fever, delirium, and cellulitis of right leg, which finally required incision for the removal of a small amount of pus. The leukocytes numbered 6120; the blood was examined for malarial organisms at the time of this chill, and repeatedly later, but none were found. The cellulitis seemed the result of scratching one of the eczematous patches on the ankle.

June 5*th.* Slight jaundice, no change in liver, no fever.

13*th.* Right-sided orchitis; œdema of right leg.

14*th.* Chill; temperature, $104\frac{3}{5}°$; impairment and rales at right base.

21*st.* Still impairment at right base.

24*th.* Blood: Red blood corpuscles, 3,560,000; hæmoglobin, 46 per cent.; white blood corpuscles, 2760.

July 3*d.* Considerable hemorrhage for several days, due to extraction of a tooth.

August 9*th.* Continuance of slight jaundice; also occasional elevations of temperature. No bile in urine.

September 11*th.* Marked pharyngitis.

October 17*th.* Periodic neuralgia in various parts of the body of late.

November 2*d.* Spleen seems a little smaller; liver certainly smaller.

9*th.* Definite neuritis. Arsenical treatment suspended. Improvement on discontinuing the drug. Pigmentation more marked of late.

26*th.* Another attack of lymphangitis of right leg. Inguinal glands at saphenous opening enlarged. The attack began with chill and fever. Blood examination: Red blood corpuscles, 3,710,000; hæmoglobin, 74 per cent.; white blood corpuscles, 4160.

December 17*th.* Another attack of right-sided orchitis.

January 7, 1901. Diarrhœa.

17*th.* Considerable hemorrhage after extraction of a tooth.

February 17*th.* Chill; temperature, 101°; facial erysipelas.

March 4*th.* Pain in right elbow.

19*th.* Marked pharyngitis and laryngitis. Some impairment of resonance in right chest. Mucopurulent blood-streaked sputa. No tubercle bacilli. Daily fever in afternoon. Blood: Red blood cor-

puscles, 4,670,000; hæmoglobin, 60 per cent.; white blood corpuscles, 1920.

May 8*th.* Another attack of right orchitis.

June 10*th.* Recently complains of pain in region of spleen.

16*th.* Much pain in right arm.

July 8*th.* Marked diarrhœa. Blood: Red blood corpuscles, 2,950,000; hæmoglobin, 45 per cent.; white blood corpuscles, 2720.

October 15*th.* Liver smaller, lower border only two fingers' breadth below costal margin. Hair growing very white. Pain in right arm continues.

22*d.* Blood: Red blood corpuscles, 4,060,000; hæmoglobin, 61 per cent.; white blood corpuscles, 2460. Differential count: Polymorphonuclear, 78 per cent.; mononuclear, 6.52 per cent.; transitional, 6.5 per cent.; lymphocytes, 6.5 per cent.; eosinophiles, 2.5 per cent.

November 11*th.* Thickening about right elbow-joint.

February 5, 1902. Blood and mucus from bowel. Fistula discovered.

March 4*th.* Increased diarrhœa. Patient's strength failing greatly. Blood: Red blood corpuscles, 3,160,000; hæmoglobin, 64 per cent.; white blood corpuscles, 10,600.

8*th.* Blood: Red blood corpuscles, 3,890,000; hæmoglobin, 68 per cent.; white blood corpuscles, 11,040. Unconscious and restless during night; died in stupor.

Autopsy. (Dr. Hendrickson, pathologist.)

Pathological Diagnosis. Pigmentation of skin and jaundice; chronic splenic tumor; atrophic cirrhosis of liver; acute lobar pneumonia; chronic interstitial orchitis; arteriosclerosis of aorta; chronic arthritis of right radiohumeral joint.

Detailed Description of the Organs. External Appearance. Body that of an extremely emaciated and poorly developed white male. Mucous membrane pale; rigor mortis absent; no œdema; considerable post-mortem lividity of dependent portions. Over sacrum is discovered a small bed-sore about 3 cm. in diameter and superficial in character. There is marked jaundice with a brownish pigmentation of the skin. The distribution of the pigment is confined entirely to the extremities. It is found over lower extremities below the knees in large, irregular patches, which are more or less confluent; the intervening areas of skin are of normal appearance. The same pigmentation is found over the hands and forearms. Fingers show marked clubbing. Superficial lymph nodes not enlarged.

Abdominal Cavity. Spleen is found enlarged and projects about 6 cm. below the costal margin. Upper border firmly adherent to the under surface of diaphragm. Liver does not extend below the costal margin except in the epigastric spaces, where it projects 3 or 4 cm. below the xiphoid process. Otherwise cavity negative. Mesenteric lymph nodes not enlarged.

Pleural Cavities. Negative.

Pericardial Cavity. Negative.

Heart. Weight, 270 grams; normal except myocardium, which is paler than it should be.

Lungs. Left: Surface dark red in color, but everywhere smooth. On section cut surface dark red and from the cut vessels considerable blood flows. Consistency considerably increased, and on pressure a marked amount of dark, bloody fluid and air escapes. The condition is uniform from apex to base. Bronchial lymph nodes deeply pigmented, but not enlarged. Right: Surface dark-red and smooth. No evidence of pleurisy. On section the lower lobe and small portion of the upper lobe are found consolidated. This part of lung is grayish-red in color, and on pressure a small amount of puriform fluid can be expressed. Middle lobe and upper portion of upper lobe are not so firm in consistency, but show marked congestion. Bronchial lymph nodes also pigmented, but not enlarged.

Spleen. Weight, 950 grams; considerably increased in size. Except where adherent to diaphragm, surface smooth. On section, capsule slightly thickened; trabeculæ prominent; pulp increased in amount and dark red in color. Malpighian bodies not visible. Consistency of the organ decreased.

Gastrointestinal Tract. Normal except at lower portion of rectum, where the mucous membrane shows marked swelling and congestion of the bloodvessels.

Pancreas. Normal.

Liver. Considerably decreased in size; surface roughly lobulated, giving rise to a typical hobnail surface. Over the anterior surface of the right lobe is found an irregular-shaped area of depression about 4 cm. in diameter, which, however, shows no thickening of Glisson's capsule. Also along the free border near the gall-bladder there is an area of depression. Section through these areas shows no scars in the depth. General appearance of cut surface is dark brownish-red, but liver tissue is divided into large areas of varying size by connective tissue. Consistency of liver distinctly increased. Gall-bladder normal.

Adrenals. Normal.

Kidneys. Of normal size; capsule strips readily; surface grayish-red in color. Weight of kidneys, 300 grams. No injection of stellate veins. Cut surface shows moderate congestion of bloodvessels, but otherwise no visible change.

Bladder and Ureter. Normal.

Prostate. Normal.

Testicle. Left, normal; right, slightly decreased in size. Slight increase in thickness of its surrounding coats. Throughout the gland proper is discovered a marked increase in grayish, firm connective tissue. Tubules do not pull out as readily from this gland as from the left.

Aorta. Shows a few scattered patches of sclerosis. None of the lymphatic glands show increase in size.

Bone-marrow. From shaft of femur is dark grayish-red in color, and of firm consistency.

Organs of Neck. Marked congestion of bloodvessels of mucous membrane over larynx and trachea. Considerable mucus in trachea. Right thyroid lobe slightly increased in size. On section, however, nothing abnormal can be discovered.

Spinal Cord. Examination without sectioning shows nothing abnormal.

Right radiohumeral joint removed *in toto.* Examination of the interior of this joint shows a superficial erosion of cartilage and bone over a small portion of the prominence separating the radial articular surface from adjacent bone. Also a more marked erosion of the articular surface in the greater sigmoid cavity of the ulna.

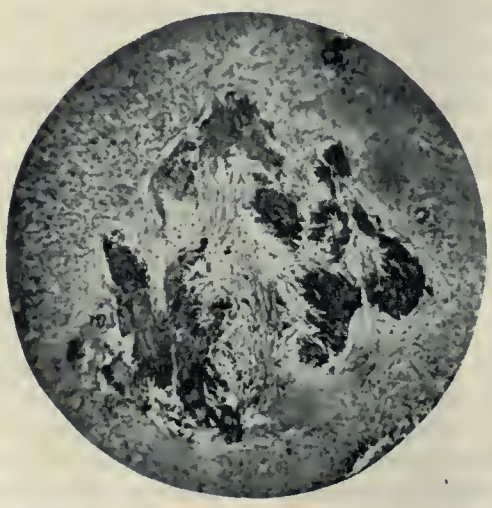
Microscopic Features. (Examination by Dr. Stengel.) *The Spleen.* There was throughout this organ a diffuse connective-tissue hyperplasia, involving the walls of bloodvessels, the trabeculæ of the organ, the splenic pulp, and the Malpighian bodies. Throughout the pulp this process was diffuse and cellular, but in and around the Malpighian bodies and elsewhere in circumscribed foci it was of a denser nature with a marked tendency to hyaline change. In a number of places a peculiar form of pigmentary deposit was observed within areas of dense fibroid tissue. In such areas brownish pigment masses of a hyaline or almost crystalline appearance were found within a focus of dense connective tissue. Stained with ferrocyanide of potash and muriatic acid these formations gave a distinct iron reaction, which, with the general appearances, showed the pigmentation to be of hemorrhagic origin. The coarse character of these lesions and the marked connective-tissue change around them gave a peculiar appearance that

I have not seen in any other spleen, exeepting from one other case of similar clinical character (Fig. 3).

The connective-tissue growth in the walls of bloodvessels and surrounding them was very pronounced, and many of the smaller vessels were entirely obliterated.

In the splenic pulp many pigment cells containing rather coarse, brownish pigment were found, quite apart from the areas of marked pigmentation before referred to. Everywhere throughout the spleen there were foci of recent hemorrhage, sometimes side by side with older hemorrhagic pigmentation, and sometimes independent of such. Altogether there were decided evidences of congestion and

FIG. 3.



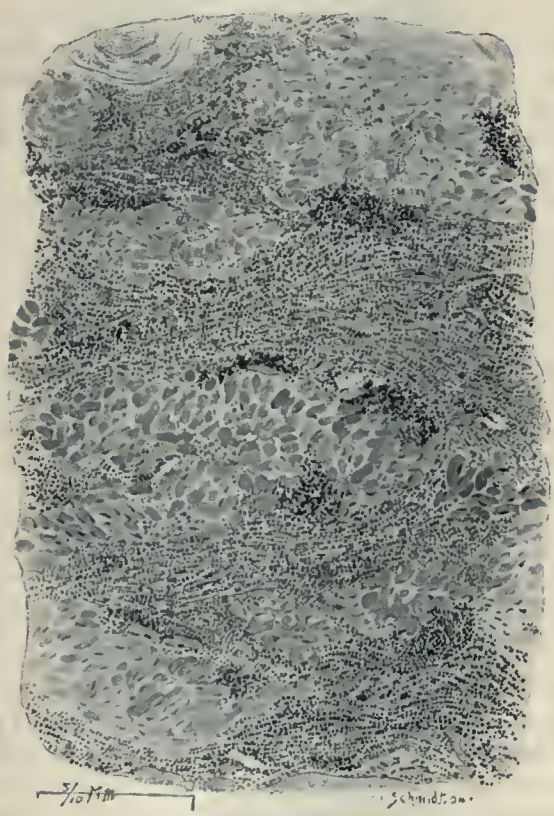
Coarse hæmatogenous pigment masses surrounded by fibrous tissue.

hemorrhagic processes of old and recent origin with secondary fibroid and pigmentary changes. Independent of these the substance of the organ presented a diffuse fibroid change of seemingly irritative character. Under higher powers swollen and proliferated endothelial cells were moderately conspicuous in the sinuses, but nowhere were these aggregated to form distinct masses.

The Malpighian bodies were extensively altered. Many had become converted into fibrous and hyaline masses; others were partially affected by fibrous change beginning around the central vessel; only a few were found without some alteration of structure.

The Liver. There was a very pronounced grade of connective-tissue infiltration of interlobular and intralobular character. In many places the hepatic lobules were surrounded by a dense cellular connective-tissue growth which was most markedly interlobular, but also invaded the atrophied lobules. The liver cells

FIG. 4.



Section of liver. × 41.6.

themselves were moderately pigmented, but were quite generally distorted and atrophied. The portal veins were widely distended, but the central vessels of the lobules were narrowly contracted and nearly free of blood (Fig. 4).

The Lymphatic Glands. All of the lymphatic glands showed diffuse, fibrous change of moderate character, and intense congestion

with widely dilated blood spaces. The glands from various portions were not examined with reference to the distinctive changes in the different groups.

The Bone-marrow. The marrow from the shaft of the femur showed distinct lymphoid characters. The majority of the cells were large and small neutrophile myelocytes, with pale, eccentric nuclei. Eosinophile myelocytes were present in small numbers, and rather more eosinophile cells of the ordinary type. Some pale hæmoglobin-containing cells of doubtful nature were observed, but no distinct nucleated red corpuscles. Polymorphonuclear cells and fat cells were not numerous.

Other Organs. The sections of the lung showed decided fibroid and cellular pneumonia. There was undoubtedly an old fibroid process with more recent bronchopneumonia. The pancreas and kidney showed moderate sclerotic change. The right testicle was markedly altered, being practically converted into fibrous tissue. Several areas of hemorrhagic pigmentation, similar to the coarse pigmentation in the spleen, were found in the testicle.

Case II. *Female, aged two years and eight months. Enterocolitis at one year; little evidence of rickets; pallor, enlarged spleen, palpable superficial lymph glands; severe anæmia, at first without, later with leukocytosis; diarrhœa, terminal tuberculosis, and endocarditis; duration one and a half years; autopsy.* Elsie S., aged two years and three months; admitted October 13, 1899.

Family History. Both parents and two sisters are living and in good health.

Previous History. One year before had a severe attack of enterocolitis. The child was healthy with this exception until the present illness. Began to walk when twelve months old (Fig. 5).

Present illness began when she was twenty months old. The parents first noticed increasing size of the abdomen and pallor.

Status Præsens. Ashy pallor; slight osseous signs of rickets; abdomen large and globose, quite tense. Enlarged spleen, with notches easily palpable. Liver enlarged to percussion, but edge cannot be felt. No fluid in abdomen.

All superficial lymph glands enlarged and easily palpable. Heart is found under sternum, extending an equal distance to right and left. A short systolic, puffing murmur is heard at the left side of cardiac dulness. Breath sounds harsh, but resonance good.

Blood Examination. Red blood corpuscles, 2,920,000; hæmoglobin, 30 per cent.; white blood corpuscles, 7600. Differential count: Polymorphonuclear, 50 per cent.; mononuclear, 17 per cent.;

lymphocytes, 31 per cent.; eosinophiles, 1.6 per cent.; myelocytes, 0.4 per cent.

There was constant diarrhœa, the movements numbering from three to five daily.

FIG. 5.

October 25, 1899. The condition continues without much change. The skin has become somewhat yellowish. At this date the spleen extends a finger's breadth below the anterior superior spine of the ilium, and the anterior edge is within one-half inch of the middle line. The liver is still enlarged to percussion, but the edge cannot be felt.

The heart is now in a more normal position, extending from the third rib above to the sixth below and from left nipple line to right border of sternum. The same soft, systolic murmur is heard, but it is not transmitted beyond the cardiac borders. The point of maximum intensity is at the pulmonary region. The second pulmonary sound is not accented.

The left kidney can be plainly felt in the back, being seemingly pushed backward; the right is less plainly felt.

26*th*. Several small masses can be felt in the abdomen. They seem to disappear after a movement of scybalous masses.

November 4*th*. The submaxillary, submental, and cervical glands are distinctly enlarged.

15*th*. Moderate fever and continued diarrhœa.

December 8*th*. General urticaria followed by swelling of eyelids, face, legs, and arms.

10*th*. The swelling has disappeared.

11*th*. Blood: Red blood corpuscles, 3,920,000; hæmoglobin, 40 per cent.; white blood corpuscles, 14,720. Differential count: Polymorphonuclear, 49.2 per cent.; mononuclear, 2.4 per cent.; transitional, 12.8 per cent.; lymphocytes, 34 per cent.; eosinophiles, 1.6 per cent. Polychromatophilia; a considerable number of normoblasts.

16*th*. Physical signs the same, but liver seemingly larger. Edge can be felt. Kidneys still easily palpable in flanks.

January 27, 1900. Has been better of late. Now a greenish-yellow pallor is noted.

February 15*th*. Sudden fever, with scarlet flush of face and neck; later, papules which were bright red at first, but soon faded.

The later notes have been unfortunately mislaid, but the final phase was one apparently of disseminated pneumonia with continued fever of about 103° to 104°; respirations varying from 50 to 68, and corresponding pulse rate.

(The autopsy was made by Dr. Flexner.)

Pathological Diagnosis. General lymphatic enlargement, with congestion and hemorrhage of the glands; splenic tumor, with infarctions; anæmia of the organs; subacute, vegetative, mitral endocarditis; necrosis of the mucous membrane of the œsophagus; tuberculosis of the lymphatic glands and tuberculosis of the lungs; infarction of kidneys.

Bacteriological Diagnosis. Staphylococcus aureus from heart's blood; aortic valves; œsophagus; lungs.

External Appearance. Body of an emaciated, very pale child. Length 82½ cm. The abdomen is much distended. No evidence

of fluid. The spleen can easily be felt in the left hypochondriac region. Its lowest border is 21 cm. in the midaxillary line below the ribs. The circumference of the abdomen below the ribs is 47½ cm., and just above the umbilicus 43½ cm. There is a very small amount of subcutaneous fat; indeed, it is in most places absent. There is very slight œdema of the lower borders of the ribs. Over the extremities, particularly the lower extremities, are minute, petechial hemorrhages. Over the abdomen are several pigmented depressions, which are probably the remains of small furuncles. No rigor mortis.

Abdominal Cavity and Peritoneum. Upon opening the abdominal cavity the omentum is seen to be adherent to the greatly enlarged spleen. Upon being stripped back, which can be done in part only on account of the old adhesions, it is found that there is a fresh exudate of yellow fibrin over the upper part of the enlarged organ. In the lower border there is an infarction about 2 cm. in width. The surface of the spleen is mottled, the predominating color being brown, and lighter areas corresponding to other infarctions can be seen on its superficial surface. There are no adhesions, excepting to the diaphragm on the upper edge, with the exception of those to the omentum as already described. The spleen weighs 465 grams. Its measurements are 17 x 9 x 5 cm. Its consistence is firm and even very hard. On section the infarctions described are found to be on the anterior surface; they are three or four in number, varying from 1½ to 3 cm. in their widest portion. They are either anæmic or mixed in character. The mixed ones show a cortical anæmic layer and a deep brownish-red, rather soft, central portion. They extend about 2 cm. into the substance of the organ. In other portions the spleen is of a reddish-brown color, and there is no distinction of Malpighian corpuscles. Here and there on the cut surface are whitish points about the size of pinheads, which are taken to be small, dense thrombi.

Liver. With the exception of an adhesion on the anterior surface of the right lobe to the abdominal wall, measuring 1½ cm. in diameter, and very old in nature, it is free from adhesions. Its weight is 690 grams. Its cut section is cloudy. Its consistence is not increased.

Kidneys are alike. The capsule strips off easily, showing in each organ a recent infarction about 4 mm. in diameter in the cortex, about which the tissues are greatly congested or hemorrhagic. On section the cortex is pale, pyramids somewhat more injected. Beneath the mucous membrane of the pelvis there is a reddish accumulation which looks like tissue, or may be hemorrhage. Adrenal glands appear normal.

Heart and Pericardium. Pericardial cavity contains about 30 c.c. of clear, yellow fluid. The layers of the serosa are smooth. The right ventricle is dilated. The left ventricle is contracted. The heart's flesh is pale. The tricuspid, pulmonary, and aortic valve segments are delicate. The mitral segments are covered with vegetations, quite adherent, which average in size about a bird-shot, some being larger, and as large as a hemp-seed. The two edges of the valve are rather difficult to separate, but this union is due probably to a small clot formed post-mortem over the edge. In the diaphragm there are scattered whitish points, probably tubercles.

Lungs. The right lung is bound over the upper portion of the upper lobe to the chest wall. The left lung is bound over the apex to the chest wall. There is no fluid in the pleural cavities. The lungs are insufflated. On section the upper lobes contain disseminated, gray tubercles; fewer in the lower lobes. There are no definite foci of consolidation, although in the pleura over each upper lobe are small hemorrhages. Beneath the parietal pleura on the left side, and following the intercostal muscles, are found white or caseous areas of tuberculosis. In the bifurcation of the trachea there is a large gland, the size of a pigeon's egg, which upon section is completely caseous.

Stomach and Intestines. The stomach shows nothing of special interest. Post-mortem digestion. The duodenum contains a number of elevated, swollen, solitary follicles, after which there is no swelling of any of the follicles throughout the length of this intestine. In the lower part Peyer's patches are visible, but nothing more. The mucous membrane of the large intestine is attenuated. In general, the intestine is thin and apparently atrophic.

Tonsils. Enlarged, and there are irregular depressions. No definite foci can be made out. In the upper part of the œsophagus, on a line with the upper part of the thyroid cartilage, there are two foci of necrosis, each about 4 mm. in width, over which there is a dirty-white exudate.

Lymphatic Glands. The inguinal, axillary, and cervical glands can easily be made out by palpation. The glands of the neck cause the tissue on each side to project. All the lymphatic glands of the body, upon examination, are found to be enlarged and to be very red in color. The greatest enlargement is found in the cervical and in the inguinal regions, in both of which places the superficial as well as the deep sets are swollen. The swelling affects the individual glands and not the invading tissue. In the cervical region the largest gland is about the size of a pigeon's egg. Most of them vary

from a pea to a cherry in size. In the inguinal region the largest is about the size of an almond. The retroperitoneal glands form chains and large, red bodies. The mesenteric glands and the glands in the mesocolon and the omentum are all enlarged and congested or hemorrhagic. The glands about the pancreas are especially enlarged. Some of them contain whitish nodules, evidently tubercles. The largest of the mesenteric glands contain also a white area, suggesting tuberculous caseation.

Bone-marrow. The bone-marrow of the femur is abundant and red in color. Its consistence is soft.

Microscopic Features. (Dr. Stengel.) The sections of the spleen varied considerably in their appearances according to the part of the organ from which they were taken. Those from the areas of infarction showed only the usual features of dense hemorrhagic infiltration and pigmentation. In other parts the splenic tissue was markedly sclerotic, and sections stained with Biondi's or Van Gieson's stain presented a uniform, rather dense, fibrous reticulum. Hyperplasia of the endothelial cells of the sinus was evident in some places, and large (swollen) endothelial cells of rounded or irregular shape, with one or a few pale nuclei, were found scattered through the spaces. In a few areas groups of such cells were seen lying together. The proper splenic pulp and the Malpighian bodies had undergone an evident atrophy, and many of the latter were converted into hyaline material. A few doubtful miliary tubercles were seen in the sections. These consisted of a small giant cell surrounded by a group of round (lymphoid) cells. There was no evidence of necrosis.

Lymphatic Glands. The sections of mesenteric lymph glands showed marked thickening of the capsules and of the trabeculæ, the latter separating the lymph follicles in an unusually marked manner. The medullary part of the glands was occupied by numerous widely distended blood spaces or vessels. The lymphoid tissues proper showed no special alteration, but decided proliferation of endothelial cells of the sinuses was seen in places, and numerous macrophages containing one, two, three, or more erythrocytes or fragments of such were found. The red corpuscles within the lymph sinuses were much broken, and everywhere fragments of irregular or more commonly rounded shape, and with distinct basic staining reaction, were found among the degenerated erythrocytes. These fragments were of precisely the appearance of blood plaques, and from their situation and general character could be plainly recognized as derivatives of degenerated red corpuscles.

The Liver. Marked lymphoidal and leukocytic infiltration between the columns of liver cells was the most striking feature of the

sections as seen under a low form. In areas there was distinct interlobular fibrosis surrounding the portal vessels. The latter were considerably dilated and, besides containing fragmented and degenerated red corpuscles as well as normal erythrocytes and leukocytes, in many places also contained numerous plaque-like formations such as have been described for the lymphatic glands. Here and there in the dilated portal vessels could be found large endothelial cells of the same appearance as those of the spleen and lymphatic glands. These were distinguishable from the lining endothelium of the bloodvessels of the liver, and if derived from this source had manifestly undergone secondary change. No such cells could be found outside of the bloodvessels. They were too numerous and widespread to be attributed to accident or artefact.

The Lung. The lung tissue in general showed no marked alterations in the sections examined, but a few peribronchial miliary tubercles were seen in portions especially selected to determine the nature of the gray bodies observed at the autopsy.

The Bone-marrow. Unfortunately the material was lost and microscopic examination could not be made.

Case III. *Female, aged twenty-one years, married, two stillborn children; probable onset years before; enlarged spleen, palpable superficial lymph glands, pain in left side, slight anæmia, splenectomy; postoperative pneumonia; recovery; histological examination of spleen.*—Annie D., aged twenty-one years, negro; lived in North Carolina until a year ago, when she came to Philadelphia. Had two stillborn children about a year ago. Her father died of malaria, her mother of an accident. No brothers or sisters. The patient has always been in good health; menses always regular and normal. She says that for many years there has been more or less pain in the left side of the abdomen. She cannot tell exactly how long this has been. Until three months ago the pain was not, however, severe enough to keep her from attending to her usual duties, but during the last three months it has been so severe at times as to compel her to take to bed. During the same length of time she has noticed a lump in the left upper abdominal quadrant. The pain is dull and aching in character, but becomes more severe when the patient moves about. There has been some loss of weight during the last three months.

Status Præsens. The patient is fairly well nourished, looking somewhat older than her years. There is nothing striking on external examination excepting a projection in the left upper half of the abdomen. The superficial lymphatic glands, cervical, axillary, inguinal, and epitrochlear, are all palpable. Heart and lungs nor-

mal. Occasionally a short systolic murmur was heard over the root of the pulmonary artery.

Abdomen. There is marked prominence of the left side above. This moves downward on full inspiration. On palpation a greatly enlarged spleen could be palpated and was distinguishable by the notches in front. At first palpation was somewhat difficult on account of tenderness, but later the patient seemed to be suffering less pain. The mass extended downward and forward to within an inch and a half of the linea alba at the level of the umbilicus, and to about the level of the crest of the ilium below. The posterior border is felt as a thick, rounded surface, while the anterior border has a fairly sharp edge with a distinct notch. No nodules or irregularities can be felt along the edge above the ribs. The mass extended to the sixth rib. The liver extended from the sixth rib to the edge of the ribs. It was not palpable. The stomach was crowded upward and forward, as could be determined by inflation, and the colon was pushed downward.

Blood. Red blood corpuscles, 4,440,000; white blood corpuscles, 5600; hæmoglobin, 70 per cent. The stained specimens show a slight reduction in the color of the red blood corpuscles, but no other peculiarities were discovered. Degenerative changes, such as polychromatophilia and basic degeneration, were wanting. The differential count of the leukocytes at this time showed no marked peculiarities, though the count has been lost.

Urine. Specific gravity, 1020; amber color, acid, no albumin, no sugar. Microscopically granular precipitate, epithelial cells, and a few leukocytes were found.

The patient was kept under observation for some weeks, during which the condition remained practically unchanged. There was apparently no increase in the size of the spleen and no change in the patient's general condition excepting perhaps a decrease in the amount of pain. Her weight remained exactly the same. It was decided that the case was one of splenomegaly and that, on account of the pain and incapacity of the patient, operation was desirable. For this purpose she was returned to the service of Dr. John G. Clark, who originally had referred her to me, and who has kindly permitted me to report the case.

On the day preceding the operation the differential count showed the following figures: Lymphocytes, 29 per cent.; mononuclear, 7.4 per cent.; transitional, 5.4 per cent.; polymorphonuclear, 50 per cent.; eosinophiles, 7.8 per cent.; basophiles, 0.4 per cent. The subsequent leukocytic counts following the operation will be seen in the table on the following page.

The operation of splenectomy was performed by Dr. Clark on January 28, 1904. The following notes were recorded at the time: The spleen was rather dense in consistency and the surface showed numerous nodules about 1 to 2 cm. in diameter, with depressed centres. The relations of the organ were found as described in the physical examination. There were a few adhesions posteriorly and some in front, between the lower border of the tumor and the great omentum. These were tied off; the others gave no trouble. The splenic vessels were ligated with some difficulty on account of the very narrow space between the tail of the pancreas, the cardiac end of the stomach, and the spleen. The liver was slightly enlarged and showed a number of scar-like depressions on the surface of both lobes.

Date.	Red blood corpuscles.	Hæmoglobin.	Leukocytes. Total count.	Lymphocytes.		Mononuclear.		Transitional.		Polymorphonuclear.		Eosinophile.		Basophile.	
				%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Jan. 1, 1904	.....	.....	5,600												
" 27, "	.....	.....	.....	29.0	.....	7.4	.....	5.4	.....	50.0	.....	7.8	.....	0.4	
" 29, "	.....	.....	.....	5.0	.....	4.2	.....	4.0	.....	86.5	.....	0.2			
" 30, "	3,750,000	55 %	35,000	3.0	1050	4.4	1540	7.6	2660	84.8	29,680	.....	.....	0.2	70
" 31, "	.....	62 %	16,640	5.0	832	2.5	416	10.2	1697	74.4	12,380	3.6	599	0.5	83
Feb. 1, "	3,350,000	.....	12,720	3.4	432	2.4	305	8.2	1043	74.8	9,514	10.5	1335	0.3	38
" 2, "	.....	.....	21,120												
" 3, "	.....	.....	21,760												
" 4, "	4,190,000	55 %	17,680												
" 6, "	.....	.....	21,120												
" 10, "	.....	.....	20,000	6.6	1320	2.2	440	7.8	1560	81.0	16,200	2.4	480		
" 14, "	3,840,000	.....	21,520												
" 16, "	.....	.....	23,860												
" 18, "	.....	.....	9,600	9.0	864	2.6	250	9.6	921	70.7	6,787	7.9	758	0.2	19
" 24, "	.....	.....	9,000												
Mar.14, "	4,030,000	55 %	9,120												
May 5, "	4,900,000	55 %	7,280	18.6	1354	2.8	204	5.7	415	61.9	4,506	11.0	800		

Almost immediately after the operation the patient complained of pain at the base of the left chest and in the left upper part of the abdomen. The temperature rose to 102° and subsequently kept constantly above normal. At first physical examination was difficult because of the impossibility of turning the patient, but indefinite rales or friction sounds were heard. Later decided signs of a lobar pneumonia were detected. Before this time, however, the upper angle of the incision was opened in the effort to discover the cause of the pyrexia, and a small area of induration, but no suppuration, was discovered. On February 17th, twenty days after the operation, and after the first elevation of temperature, the fever subsided

by crisis, going from 103° to the normal in the course of a few hours, and remaining normal continuously thereafter. At the same time the leukocytes declined from over 20,000 to 9600, and subsequently remained normal or subnormal.

After the full recovery from the operation the patient showed no change in appearance or physical signs, excepting those referred to the left upper part of the abdomen. She complained of some dragging and other unpleasant sensations in this region, but as compared with her condition before the operation was certainly much relieved.

Three months after the operation I found her in comparatively good health, able to attend to her work as a chambermaid, and with practically no local symptoms. The lymphatic glands seemed to have increased somewhat in size, but the difference was not very marked.

Among the interesting features in the blood count of the case was the behavior of the lymphocytes and eosinophile cells. It has been found by experiment, as well as after operative removal of the spleen in man, that there is an increase in the number of lymphocytes and later an increase in the eosinophile cells. The proportion of the latter was at the time of the operation decidedly increased (7.8 per cent.). The lymphocytes were not specially increased (29 per cent.), but the polymorphonuclear cells were actually and relatively reduced in number. This reduction was, however, in favor of the mononuclear and transitional cells, which at this time and subsequently showed conspicuous increase.

Unfortunately the intervention of an acute pneumonia altered the figures that probably would have been obtained. The result of the postoperative pneumonia are the same as is usually seen in normal persons—a marked polymorphonuclear leukocytosis and a reduction of eosinophiles. After the subsidence of the pneumonia there was a return to practically the same conditions as were observed before operation, viz., a marked eosinophilia and reduction of polymorphonuclear in favor of the mononuclear and transitional cells.

Macroscopic Appearance of the Spleen. The organ measured 22 x 13 x 7 cm., and after hardening weighed 1230 grams. The striking features when seen in the fresh state were numerous nodular projections on the surface, which presented the appearance of secondary tumors. These varied in size from small masses a half to 1 cm. in diameter up to large nodes fully 2½ or 3 cm. in diameter. The larger nodes were distinctly umbilicated, the depression being quite marked and of a whitish, cicatricial appearance at the

bottom. Elsewhere the surface of the organ was red in color, somewhat modified by a more or less thickened capsule. The projecting nodules were numerous anteriorly and on the convex surface of the organ; they were fewer posteriorly and in the hilum. The consistence of the organ as a whole was distinctly increased and was uniform in all portions. On section through its substance

FIG. 6.

Spleen. × ½.

practically the entire organ was seen to have been invaded by a growth of a dense consistence and pinkish-red color. This extended inward and toward the hilum, leaving only small parts of the substance of the spleen, which could readily be distinguished by their darker color, uninvolved. Posteriorly and at the hilum the spleen substance was comparatively free. As seen in the cross-sec-

tion the nodular masses on the surface were manifestly not separate new-growths like secondary tumors, but projecting parts of a large invading mass which occupied the greater part of the organ. The appearance was not unlike such a one as might result from separate pyramidal growths, with the apices projecting from the surface of the organ and extending deeply into the substance, the bases being completely fused or at most leaving small areas of normal splenic tissue here and there between them (Figs. 6 and 7).

FIG. 7.

Macroscopic appearance of section (photograph). The lighter areas represent new-growth; the darker areas are uninvolved splenic tissue.

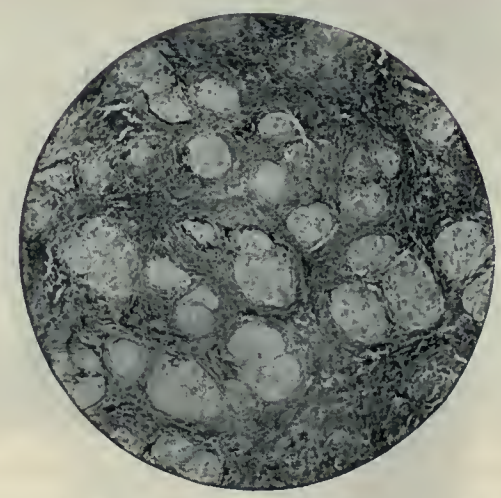
Careful examination of the umbilications of the nodules presented no evidence that these had resulted from secondary softening of the centres of the growths, but suggested rather that the elevation surrounding the depressions was the result of an infiltrating process that had not affected the centre so that the fibrous tissue of trabeculæ had prevented the elevation at the point of umbilication. Cross-sections showed some excess of fibrous tissue in this central zone, and the cicatricial appearance on the surface was due to thickening of the capsule of the spleen at the point noted, quite as much as to actual fibrous tissue formation in the centre of the nodes. Nowhere in the substance of the new-growth could any evidence of necrosis be discovered by the naked eye, no areas of softening, of caseation, or the like. The tissue was uniform in char-

acter, somewhat glistening on section and, as before stated, pinkish-red in color.

Microscopic Appearances. Portions of various parts of the organ were placed in Zenker's fluid, Müller-formol, and absolute alcohol, and sections were stained with eosin-hæmatoxylin, Van Gieson's stain, Biondi's mixture, carbol-fuchsin, methylene blue, and by Gram's method.

The sections showed a marked new growth of connective tissue forming alveoli of various sizes (from 0.13 to 0.26 mm. in diameter), and containing large, clear cells, with pale nuclei, and often cells

FIG. 8.



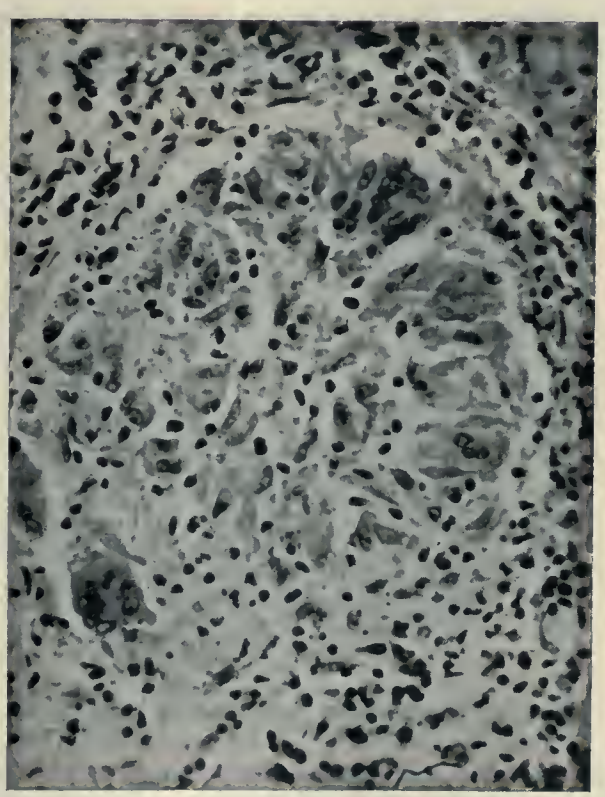
Microphotograph of section of spleen under low magnification, showing the alveoli containing endothelial cells surrounded by fibrous walls. The photograph exaggerates the density of the fibrous tissue.

containing several nuclei of the same character. In certain areas giant cells with centrally or eccentrically clustered nuclei were abundant, and everywhere such cells were present, at least in small numbers. The lymphoid elements of the splenic pulp were an inconspicuous feature in all the sections, being crowded into mere zones surrounding the alveolar formations where these were well developed, and being displaced by more diffuse connective-tissue growth in other places.

The alveolar spaces referred to were generally rounded in outline and surrounded by a wall of well-developed connective tissue of considerable thickness. For the most part this wall was compact

and separated from the surrounding alveolar or splenic tissue by a sharp line of separation, but elsewhere the transition was more gradual and formed by connective tissue of a less dense character intermixed with lymphoid elements (Figs. 8, 9, 10 and 11).

FIG. 9.

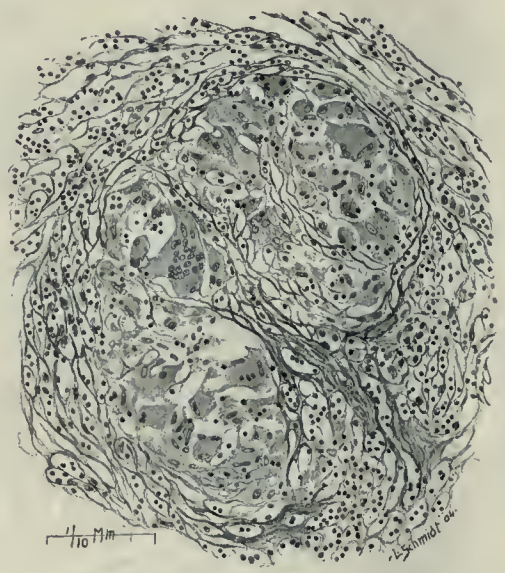


Microphotograph (high power), showing one of the alveoli containing endothelial cells, giant cells, and leukocytes.

Within the alveoli were found the large endothelial cells before deseribed. In sections through favorable parts of the growth the cells were separate and clearly marked, but more commonly there was an apparent or real confluence making large protoplasmic structures containing large vesicular nuclei. These almost invariably showed nucleoli. Many of the cells contained two or three nuclei.

In the peripheral parts of the alveoli, and to a less extent in the centre, giant cells with clusters of nuclei were common. The protoplasm of the cells was clear and rather glistening. It did not present any appearance of degeneration, though in some places it was possibly somewhat hyaline. In some of the alveoli, especially those with less well-developed walls, the endothelial cells were separated by or intermixed with erythrocytes or lymphoid cells, but there were no macrophages. Pigmentation was practically absent in this part of the tissue, but was present to a small extent in the reticular connective tissue.

FIG. 10.



Section of spleen. Biondi's stain. × 142.5.

The size of the endothelial cells containing one or two nuclei varied from about 10μ to 20μ in diameter, the average being about 15μ; the size of the giant cells was from 30μ to 72μ, the average of a number being 51μ. The large masses of fused character were even larger, in some places nearly filling the alveolus.

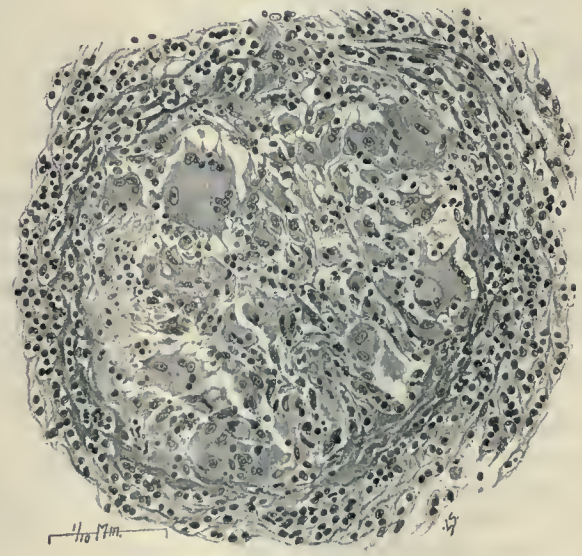
In the portions of the spleen comparatively free from the uniformly infiltrating growth there was still evidence of an active endothelial proliferation, but as the organ was practically entirely involved it cannot be determined if this process were simply an extension from the growth proper or an evidence of prior involve-

ment in lesser intensity of a condition that caused complete transformation in the parts that have been designated the growth proper.

The Malpighian bodies were retained in some places, though atrophied. Elsewhere they were converted into connective tissue or had become hyaline. This, however, was an inconspicuous feature. In general the endothelial and fibrotic process had simply caused a disappearance of normal splenic features.

In sections from one part of the spleen the Malpighian bodies were conspicuously involved, being occupied by a rounded, acinus-like area of endothelial proliferations, lying adjacent to the blood-

FIG. 11.



Section of spleen. Mallory's stain. × 157.

vessel of the Malpighian body and sometimes pushing the vessel to one side, but never involving it. In some parts the area of endothelial character was minute; elsewhere almost the whole Malpighian body was transformed. There was no evidence of fibrous-tissue formation in these areas.

Sections stained with carbol-fuchsin and Gabbett's solution showed *no tubercle bacilli*, and those stained by Gram's method likewise showed no bacteria of any kind.

CASE IV. *Man, aged fifty-one-years; history of malaria, stunted growth, pigmented skin, clubbed fingers and toes, enlarged abdomen*

(tympany), enlarged spleen, slightly enlarged liver, moderate anæmia, leukopenia, diarrhœa, hemorrhages from bowel, rectal ulceration, tendency to chills, no malarial organisms; duration at least three years, probably longer.—C. T., aged fifty-one years, laborer on railroad, a native of Italy, had come to America six years before. Admitted to Pennsylvania Hospital September 30, 1901.

Family history negative. He himself had had some operation for a mass in the right inguinal region forty years before. During ten years after he was twenty years old he had mild attacks of chills and fever every summer. At thirty-three had some kind of bloody diarrhœa for six weeks. Six weeks ago first had pain in the left side of abdomen and distention of the abdomen and diarrhœa. The stools were free of blood, but the patient had much rectal pain.

On physical examination the patient was found a small-sized man with darker skin than the average Italian and distinct pigmentation in places. The fingers and toes showed clubbed extremities. The abdomen was enlarged and tense, but did not contain free fluid. The spleen could be felt extending far down into the abdomen. The liver dulness was small in vertical extent. Later the abdominal distention subsided and the spleen was then found extending to within an inch of the anterior superior spine of the ilium. Rectal examination showed an ulceration in the anterior wall of the rectum (Fig. 12).

Blood Examination. Red blood corpuscles, 4,190,000; hæmoglobin, 60 per cent.; white blood corpuscles, 4000.

Urine. Specific gravity, 1012; acid; some albumin present; granular and epithelial casts.

The sputum contains no tubercle bacilli. The feces contain no amœbæ; the blood serum does not agglutinate Shiga's bacilli.

March 5, 1902. Chill, temperature of $104\frac{1}{5}°$; tongue greatly swollen. Later, ulceration under tongue. Leukocytes 11,400. No malarial organisms.

April 1*st.* Admitted to University Hospital. Same conditions noted; also enlargement of practically all superficial lymph glands. Liver extends from sixth rib to two inches below ribs. Edge easily felt. Spleen as before. A small ventral hernia.

4*th.* Blood: Red blood corpuscles, 3,980,000; hæmoglobin, 70 per cent.; white blood corpuscles, 4400.

10*th.* Hemorrhage from bowel; diarrhœa.

June 6*th.* Hemorrhage from bowel, about eight ounces; diarrhœa.

7*th.* Considerable hemorrhage from bowel; chills, but no fever.

August 12*th.* Slight hemorrhage, followed by temperature of $102\frac{2}{5}°$, soon normal.

From this date no notable changes. The patient frequently complained of abdominal pain near the umbilicus (ventral hernia), in the left side (spleen), and in the rectum (ulcers). Repeated examinations showed persistence of the ulcers. At

FIG. 12.

intervals he had accessions of cough, with rough breathing and rales. The blood was examined repeatedly and was found in about the same condition as above recorded. Constant diarrhœa and frequent hemorrhages were the marked symptoms. The patient was transferred to the Philadelphia Hospital.

This case in its general appearance and in the tendency to repeated infections resembled Case I. very closely. Studies of the blood serum were made to determine if any explanation of the tendency to infection might be found. Dr. J. S. Evans, who conducted these examinations, reported an increase rather than reduction in both immune bodies and complements. The mechanism of the infections must therefore be sought in some other direction.

Case V. *Woman, aged forty-four years; doubtful history of malaria, enlargement of spleen, succeeded by evidences of hepatic cirrhosis (ascites); no anæmia, hydrothorax; duration two and a half years or more.*—Ellen D., aged forty-four years, white, married. Was admitted to the University Hospital November 24, 1903. The following history was recorded:

The patient is a widow and has five children, all of whom are well. She has worked hard all her life.

The family history is negative excepting that one brother died of consumption. No history of new-growths.

Menses began at thirteen years, always normal. Labors normal. The last one eighteen years ago. There was some uterine trouble six years ago and she was confined to bed for six weeks. She had malaria two years ago, but her description of the symptoms is not very convincing.

About two years ago the patient first noticed some enlargement on the left side of the abdomen. This continued without any local symptoms excepting a slight feeling of fulness and occasionally moderate pain. There has been no loss of weight, but she has become weaker. Her color has at times been a trifle sallow. A little swelling of the feet has recently developed. This comes on during the day and disappears at night. Physical examination showed slight pallor and a subicteric hue of the skin, but no distinct jaundice. Very slight œdema of the legs and feet. No cyanosis. Lungs normal, excepting that the breath sounds appear a little harsh. Heart normal in size; the first sound at the apex is a little lacking in muscular quality, but there are no murmurs. The abdomen is enlarged, especially on the left. The spleen can be easily felt, and on the anterior surface are several distinct notches. The lower border extends below the umbilicus.

The liver extends from the sixth rib to below the costal margin. As the abdomen is generally distended it cannot be plainly felt beneath the ribs, but in the epigastric spaces the edge is distinctly palpable and the substance of the organ is evidently hard and rough. There is decided movable dulness and fluctuation in the peritoneum.

Examination of Blood. Red blood corpuscles, 5,500,000; white blood corpuscles, 8800; hæmoglobin, 81 per cent.

Urine. Clear, brownish-red; specific gravity, 1025; no albumin, no sugar; urates, a few leukocytes, and epithelial cells.

November 28, 1903. Paracentesis of the peritoneum was performed and eleven pints and three ounces of clear fluid, yellowish-green in color, were removed. The liver could then be plainly felt and was decidedly hard.

30*th.* Some pain at the right base and a pleural friction sound. Blood: Red blood corpuscles, 5,300,000; white blood corpuscles, 7200; hæmoglobin, 80 per cent.

December 1*st.* Considerable reaccumulation of abdominal effusion. Right-sided hydrothorax.

5*th.* Increase in effusion in right chest; white blood corpuscles, 7400. Urine: Specifie gravity, 1030; small amount of albumin, leukocytes, a few red blood corpuscles, urates, a few hyaline casts. There is a trace of bile.

16*th.* Abdomen tapped; twelve pints fourteen ounces removed.

January 3, 1904. Abdomen tapped; sixteen pints fifteen ounces removed. The fluid does not contain bile.

14*th.* Abdomen tapped; eighteen pints eight ounces removed. Right pleural cavity tapped; fourteen ounces of blood-tinged fluid removed. Soon after this the patient passed out of observation.

The most interesting feature in this case was the fact that she had been under my observation a year previous to her admission to the hospital, at which time I found great enlargement of the spleen without a single symptom of consequence. It was not until long after that time that she first showed evidences of beginning cirrhosis and portal obstruction. There was not in the history of this case any hemorrhage nor the usual gastrointestinal symptoms met with in splenic anæmia.

Classification of Splenic Anæmia. Analysis of the clinical descriptions and pathological features of many of the cases classified as splenic anæmia discloses the fact that these cases properly belonged to one or the other of the following conditions:

1. *Progressive Pernicious Anæmia or Intense Secondary Anæmia.* The oft-cited case of Strümpell belongs to this group. In that case, probably one of pernicious anæmia, simple congestion with great dilatation of the splenic sinuses constituted the pathological condition of the spleen. Other cases in which pronounced anæmia and moderate enlargement of the spleen have been found should

be included in this group, and these constitute the basis for the view now seldom expressed, that splenic anæmia and progressive pernicious anæmia are closely allied. As a matter of fact, in the conditions nowadays classified as splenic anæmia impoverishment of the blood is rarely a predominating feature except after repeated hemorrhages.

2. *Pseudoleukæmia.* The earliest writers (Griesinger, H. C. Wood) suggested that the condition is usually a splenic variety of Hodgkin's disease, and this view is occasionally expressed at the present day. This opinion was adopted by Sippy in his admirable review of the subject, but is now generally abandoned for the reason that the pathological anatomy as far as known almost invariably negatives the supposed pseudoleukæmic nature of the disease. Nevertheless there are some cases reported in older (Müller) and more recent literature in which the symptoms and such pathological data as were obtained show that splenic pseudoleukæmia may be, clinically, nearly if not quite identical with that we now call splenic anæmia. Such cases are, however, exceptional.

3. *Leukæmia.* All systematic writers call attention to the occasional subsidence of leukocytosis in this disease. Under these circumstances the case might for a time have many of the clinical features of splenic anæmia, and some authorities (Griesinger) regarded the latter as an aleukæmic variety of splenic leukæmia.

4. *Cirrhosis of the Liver.* Some degree of splenic enlargement is habitual in cirrhosis of the liver. Formerly this was attributed to congestion of the spleen caused by obstruction of the portal circulation, but more recently the view has gained ground that the splenic condition results from the action of the same irritant as that which causes the cirrhosis (alcohol, etc.). Under these circumstances it might seem natural that certain cases of cirrhosis should present an unusual degree of splenic enlargement. The studies of Banti, showing a frequent association of splenic anæmia and cirrhosis, gave additional color to this view, and seemed to justify the expression *splenomegalic cirrhosis of the liver.* On the other hand, however, the investigations of Banti, Bovaird, and others showed that clinically as well as pathologically the cirrhotic process may be demonstrably secondary to the splenic disease. Under such circumstances the condition is rather one of *splenomegaly with cirrhosis.* The cases in which pronounced splenomegaly is simply an incident in cirrhosis are probably rare as far as accurate studies would indicate.

5. *Hypertrophic Cirrhosis of the Liver* (Hanot's disease). In this condition the long duration of the disease and the considerable

degree of splenic enlargement are the basis upon which inclusion under the head of splenic anæmia has sometimes been suggested if not justified. Some of the cases of familiar splenic anæmia in particular may perhaps be more properly classified here.

6. *Chronic Splenitis.* The greatest confusion exists in the case of splenic enlargement in children. Such enlargement is common in rickets and congenital syphilis, and occurs in the uncertainly classified condition called anæmia infantum pseudoleukæmica (von Jaksch). In the case of rickets and congenital syphilis the splenic lesion is a chronic splenitis leading to fibroid change and some lymphadenoid hypertrophy. Clinically the dominating symptoms are those of the underlying affection. It is, of course, possible that exceptionally the splenic enlargement and its consequences might overshadow other features, but the evidence at hand does not bear out such an assumption. In the case of von Jaksch's disease, pathological studies and accurate clinical observations also are still wanting.

The chronic splenitis of malaria belongs in the same group. How far malaria may prove to be a factor in the etiology of splenic anæmia remains unsettled. Undoubtedly, however, there is some added element that operates in the development of the condition even if malaria is a factor.

Leaving out of consideration the cases of splenic enlargement, which by their clinical features or pathological lesions could be plainly referred to the above groups, there remain certain cases in which the splenic disease is of such dominating character that the cases must be regarded as forming a separate group or separate groups. The fact that cirrhosis of the liver supervenes in the late stages does not militate against such a classification, since very good evidence has been brought forward to show that splenic disease may occasion secondary cirrhosis of the liver. Conspicuous predominance of splenic involvement from the beginning warrants the separate classification of such cases even when some evidence of cirrhosis of the liver is an early feature.

It would be hopeless in the present state of knowledge to attempt a classification of all of the cases that have been reported. On the other hand, it is very evident that there are very different sorts of cases that have more or less superficial resemblance, and I cannot share the view that all are probably instances of one disease in different stages.

The ultimate solution of the matter must, seemingly, come from more careful clinical and pathological study of these cases, with recognition of the fact that the long continuance of the disease

may cause very different lesions at different stages. The following varieties may be recognized provisionally:

1. *Simple Splenomegaly.* In a certain number of cases, including some described by Müller, Banti, Osler, Rendu, Peter, Sippy, and others, the conspicuous feature in the clinical history is the splenic enlargement. Anæmia is not by any means an invariable symptom, though usually present, especially when hemorrhages occur. The hemorrhages may be a purely splenic feature in the sense that they are caused by mechanical obstructions brought about by traction on the splenic vein, or they may be caused by general conditions less readily explained, as, for example, in the case of hemorrhages from the gums. Pathologically speaking, this variety belongs in the category of chronic splenitis such as occurs secondary to malaria, syphilis, rickets, and chronic gastrointestinal diseases. The lesion is essentially a fibrous hyperplasia. In some instances the endothelial cells of the sinuses are swollen and large macrophages are found; in others these cells are not observed, possibly on account of the late stage at which the disease has terminated. Analogy suggests that some form of chronic infection or intoxication is the cause of this variety. The tendency to some endothelial proliferation does not exclude this view, for in all kinds of chronic splenitis such endothelial processes may occur. In some cases the disease may persist for a long time and the patient may ultimately die without additional lesions; in other cases changes in the liver develop as a final stage and cause a marked alteration in the clinical features. These latter cases are, I believe, in some sort different from the former in their pathology, and may for convenience be separately classed as

2. *Simple Splenomegaly Terminating in Cirrhosis of the Liver.* Perhaps the cases which ultimately develop cirrhosis of the liver and assume the fully developed character of Banti's disease are cases which from the start had a prominent grade of endothelial proliferation in the splenic sinuses. Banti has shown that there may be an endophlebitis extending from the spleen to the splenic vein and eventually to the portal vein, and he referred the cirrhosis of the liver to this cause. In the cases recently reported by Dock and Warthin, stenosis of the portal vein was discovered, and this may have been preceded by a similar endothelial process. In one of my own cases there were, within the terminals of the portal vein in the liver, large endothelial cells corresponding to those found in the splenic sinuses and in the regional lymphatic glands. In Bovaird's case large endothelial cells corresponding with those found in the sinuses of the spleen were a conspicuous feature in the

portal spaces of the liver. The probable embolical origin of these formations could not be overlooked. All of these facts suggest that cirrhosis of the liver as a termination of splenomegaly is particularly likely to occur when the process from the beginning has been inclined to affect the endothelial cells in the splenic sinuses particularly. A review of the cases reported in the literature discloses the varying degree of endothelial proliferation that may be present, and it seems likely to me that this is not the result merely of the different stages at which the examinations happened to be made, but rather the consequence of natural difference in the pathology of different cases. Even accepting this, however, the difference may be only one of degree.

That splenomegaly may actually precede cirrhosis of the liver, or at least any considerable degree of cirrhosis, was shown distinctly by one of my cases (Case V.) here reported, in which the patient had been under my observation for over a year preceding the final development of the well-known symptoms of Banti's disease. When she came under observation there was a decided enlargement of the spleen, but no other signs of illness.

3. *Splenomegaly with Marked Constitutional Disturbances.* A certain number of cases of splenomegaly have been described in which, in addition to the enlargement of the spleen, there has been a profound disturbance of the general health, causing a stunted growth, clubbed fingers, osseous changes, and pigmentation of the skin. Gilbert and Fournier report a group of such cases in children in whom the symptoms were those enumerated, together with enlargement of the liver and jaundice. Frederick Taylor has also reported a series and refers to the case of H. R. Smith, another presented in the Medical Society of the Hospitals of Paris, and some other less certain instances. In some particulars the group of family splenomegaly described by Brill is analogous, though in other particulars more suggestive of the variety of simple splenomegaly. In considering these cases, which have for the most part been observed in young persons or children, the difficulty of distinguishing the disease from hypertrophic cirrhosis of the liver (Hanot's disease) must be kept in mind. Furthermore, pigmentation of the skin of non-icteric character may be accounted for in various ways, and in some of the reported instances the possibility of its being arsenical must be remembered, while in other cases the whole condition may belong to that uncertainly defined affection called hæmochromatosis, in which cirrhosis of the liver is often an incident. Leaving out uncertain cases, however, there seems to be a group or variety in which splenomegaly is associated with stunted growth, pigmen-

tation of the skin, clubbing of the fingers, and other evidences of general systemic disturbances. In this group probably belong two of the cases here reported. These presented very different clinical features from those shown by other instances of so-called splenic anæmia or splenomegaly.

4. *Splenomegaly Primitive.* While it is not possible perhaps to distinguish this variety clinically, there is a sharp distinction in the pathological features. It will be recalled that the essential characteristic of this condition is the presence of irregular oval spaces surrounded with fibrous tissue, and more or less filled with large endothelial cells containing one or more nuclei. All writers agree that these alveoli are formed by the proliferation of the endothelial lining of the splenic sinuses, with fibrous hyperplasia of the surrounding tissue, causing the formation of a coarse reticulum.

Bovaird has suggested that the proliferated endothelial cells eventually form fibrous tissue, and Rolleston and Osler are disposed to admit this as a probability. Harris and Herzog dissent from this opinion. When the descriptions and figures of the cases of Gaucher, Picou and Ramond, Collier and Bovaird are examined, it may not seem impossible that the endothelial process might be the forerunner of an ordinary fibrous change; that, in other words, as Rolleston states, the endothelial proliferation may be replaced by a fibrous tissue process. When, however, the macroscopic as well as the histological features in my own case are considered, it will be seen that the transformation into the ordinary characters of a fibrous splenitis could not have occurred after a lapse of any amount of time. From every point of view the case suggests a neoplasm. In reporting his case Bovaird considered the respective merits of the neoplasm and hyperplasia theories, and concluded that the condition was rather one of endothelial hyperplasia. He referred to the doctrine of Thoma, that a tumor must be an autonomous growth. On the other hand, all pathologists are agreed that there is no sharp dividing line between the processes which may be properly called hyperplastic and those which are strictly speaking neoplastic. In reviewing the cases of splenic anæmia in which the endothelial hyperplasia has been a feature it will be seen that there are all grades of conspicuousness of this part of the pathological processes—from those cases in which the predominating feature is a fibrous hyperplasia, with a certain element of endothelial proliferation superadded, up to those cases like my own (Case III.), in which the macroscopic features of the condition were those of a tumor and the microscopic characters those of an

active neoplastic formation, essentially and primarily involving the endothelial cells.

Pathological Anatomy. Compared with the mass of clinical material the pathological data are scant and unsatisfactory. In part this is due to the chronicity of the disease and in part to the fact that the examinations have been made at various stages, when presumably diverse conditions might be expected. The most extensive of the more recent studies are those of Banti. In brief the following notes contain the results of his examinations:

The spleen is much increased, weighing from 1 to 1.5 kilograms. The shape is preserved, the surface smooth and regular. The capsule is thickened and on section the substance is dark brown and hard, showing thickened trabeculæ and whitish nodules which correspond to the Malpighian bodies.

Microscopically the Malpighian bodies were found in various stages of fibrous transformation, the process beginning around the vessel within the body. A certain amount of hyaline transformation was also apparent. The splenic pulp showed no special enlargement of the venous channels. In the earliest stage there may be found in some of the veins a lining of large cells, making the vessel appear almost like an epithelial channel on cross-section. These large cells have a limited amount of protoplasm and a large nucleus of a diameter of from 5 μ to 8 μ. The same kind of cells are found in the reticulum surrounding the veins, and in some of the channels the cells have become loosened from the walls and fill the lumen of the vessel, giving the appearance of a cancerous alveolus. In some spaces actual giant cells and occasionally cells containing normal or degenerated red corpuscles were observed. The reticulum of the pulp was evidently thickened and of hyaline appearance. This was always a conspicuous feature and distinguished the tissue absolutely from normal spleen. The thickening of the reticulum is in proportion to the duration of the disease, and finally areas of the splenic pulp may become entirely fibrous. In view of the process of fibrous transformation and the multiplication of cells within the veins, Banti proposed the name "fibroadenia." He does not believe there is a new-formation of fibrous tissue in the ordinary sense of the term, but rather an increase of the reticulum from exudation from pre-existing cells.

The liver is reduced in size, granular, and hard. In earlier stages of the disease it may be normal in size and smooth. Microscopically there is found a marked interlobular cirrhosis like that due to alcohol.

Banti calls particular attention to sclerotic endophlebitis of the

splenic vein, causing irregular thickening and sometimes even atheromatous and calcareous foci. These conditions also extend into the portal vein, and in the ascitic stage of the disease even the mesenteric veins may be affected, though in less degree than the splenic.

The bone-marrow showed all the characteristics of fetal marrow, but nucleated red corpuscles were present in small numbers.

Bacteriological examination of various tissues and the blood proved negative.

Most of the reports published since Banti's correspond in all essential details.

According to Osler[1] two conditions have been described in the spleen: (1) a fibrosis and hyperplasia with atrophy of the pulp and a hyaline degeneration of the Malpighian bodies, and with this description, according to MacCallum, Osler's cases Nos. 4, 5, and 16 correspond; (2) on the other hand, very remarkable change is found in certain cases which agree in every clinical particular with the definition of the disease as given for ordinary cases. The normal texture of the spleen is replaced by fibrous tissue and large endothelial cells with clear protoplasm containing two or more nuclei and among them giant cells. This was the condition first described by Gaucher as primary endothelioma.

Sippy[2] could find records of but ten post-mortems in which he felt reasonably certain that the cause of death was "splenic pseudo-leukæmia." The liver was usually enlarged, the surface smooth, the edges rounded, and no evidence of cirrhosis, though under the microscope slight increase of the interlobular connective tissue may be found. The spleen is always increased in size, and there may be perisplenitis. Its surface is usually smooth, but sometimes peritoneal adhesions have been recorded. In a case reported by Banti there was visible increase in the connective tissue, and small white areas about the size of a pea were noted, and these proved to be made up of connective tissue. In Sippy's[3] case there was no macroscopic evidence of connective tissue, but microscopically considerable fibrosis was the feature of interest. Banti summarizes the findings in the spleen as follows: (1) atrophy and sclerosis of the Malpighian corpuscles, and (2) substitution of a fibrous reticulum for the delicate reticulum of the splenic pulp. As a rule, according to Sippy, the Malpighian bodies have been found but slightly altered. In his own case a few were sclerosed, the greater number showing no change.

[1] Transactions of the Association of American Physicians, 1902, p. 429.
[2] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, November, 1899.

The following is quoted from the description of West ("A Case of Splenic Anæmia, Splenomegalic Primitive," *Medico-Chirurgical Transactions,* 1896): "The spleen showed slight increase in the trabecular tissue—*i. e.*, slight fibrosis. Malpighian corpuscles are much diminished in size and badly developed. Iron reaction negative." Kanthack examined the tissues in West's case and referred to the presence of giant cells in addition to the fibrosis.

Sippy does not quote extensively from others regarding the pathological anatomy, leaving the impression that the histology as observed by others was practically the same as given in the above.

Dock and Warthin[1] report two cases with anatomical studies. In the first the liver was small and showed a moderate increase in connective tissue, especially in one area. The spleen had a thickened capsule and showed a dense fibrous network enclosing enlarged blood spaces. These were lined and in many cases partly filled with large endothelial or reticular cells containing one or more lightly staining nuclei, and in the majority of cases nucleoli. "The fibrous tissue represents a hyperplasia of the reticulum of the pulp, the endothelial cells lining the blood spaces apparently taking part in the formation of the new fibrous tissue."

The bone-marrow was red and contained an increased number of normoblasts and very few giant cells. The retroperitoneal glands were enlarged and of the type known as hæmal gland.

In their second case the liver was small, adherent to the diaphragm by tough adhesions, and the surface on section was granular. It was the picture of an atrophic cirrhosis on microscopic examination.

The spleen showed marked fibrosis with hyaline change of the new-formed connective tissue. This process was uniform throughout the organ. The blood spaces were lined by large hypertrophic endothelial cells. A few giant cells were found in the blood spaces, and the author suggests that these may have been embolic and of bone-marrow origin.

In both of the cases there was a stenosis of the portal vein, and as the pathological lesions are entirely compatible with chronic congestion of the spleen they suggest that the condition of the portal vein may have been the cause of the lesion.

They find nothing in recent accounts of splenic anæmia suggesting the occurrence of this condition of the portal vein, but several cases were reported by Sir Andrew Clark.[2] The lesions of the splenic and portal vein described by Banti differed somewhat from

[1] Transactions of the Association of American Physicians, 1903.
[2] Transactions of the London Pathological Society, 1867.

that reported by Dock and Warthin, though perhaps later stages of the conditions observed by Banti might correspond.

Williamson[1] describes a case which came to autopsy and in which the histological features were sclerosis of the Malpighian bodies, general fibrous hyperplasia, great congestion of the pulp, and sinuses filled with large corpuscles containing cells. The last-named cells contained from six to ten red corpuscles and were mononuclear. I find no other recorded case with such conspicuous macrophages. Allusion is made by some authors to occasional large endothelial cells containing red corpuscles or fragments of such, but not to the numbers found by Williamson nor to cells of the peculiar character figured by him. In a case studied by Rolleston, the spleen, weighing thirty-seven ounces, "showed fibrosis with widespread proliferation of the endothelial cells and disappearance of the leukocytic elements."

Taylor, in referring to one of his cases of "splenomegalic cirrhosis of the liver," states that "the spleen was loaded with red corpuscles; otherwise it appeared normal."

One cannot read the accounts of pathological examinations, scanty and unsatisfactory as they are, without receiving the impression that they very probably refer to different pathological conditions, however similar the clinical features. There are three sorts of changes that may be clearly distinguished: (1) congestion, (2) fibrous transformation, and (3) endothelial proliferation. The first of these was conspicuous in only a few of the cases, and is more prominent in instances (like that of Strümpell) of doubtful character. Fibrous hyperplasia of the splenic reticulum and sclerosis of the Malpighian bodies constitute a marked condition in nearly all of the cases—a fact which is, of course, easily explained by the chronicity of the disease and the late stage at which the histology has usually been studied. What the conditions might have been at earlier stages cannot be determined by such examinations. The endothelial proliferation is not peculiar to cases of so-called splenic anæmia. A certain amount of such proliferation is found in cases of infectious splenitis of all kinds, and this doubtless contributes, in such cases as in splenic anæmia (Bovaird, Rolleston, Osler, Dock and Warthin), to the fibrous change in the reticulum.

A very different condition is that first described by Weichselbaum as "Primary Multiple Endothelial Sarcoma of the Spleen," and later by Gaucher as "Epithelioma primitif," and by Debove and

[1] Medical Chronicle, May, 1893.

Bruhl as "Splenomegalie primitive." Among the cases of this description are those of Weichselbaum, Gaucher, Collier, Picou and Ramond, Bovaird, and my own (Case III. of this series). The case of Weichselbaum and mine differ from the others in having a more marked neoplastic appearance on macroscopic examination. The opinion of Birch-Hirschfeld that Weichselbaum's case was one of endothelial hyperplasia rather than a tumor does not accord entirely with the gross appearance of the organ, though it is more applicable to Weichselbaum's case than to my own. This will appear from the recorded description.

Weichselbaum[1] remarks, by way of preface, that he was unable to find any instance of primary sarcoma of the spleen in the literature. The specimen was obtained from the body of a soldier twenty-one years old. No clinical data are given. The spleen was "somewhat enlarged," hard, dark brown in color, and presented visible follicles. On section the surface was found studded with small nodules the size of a millet-seed or pea, grayish-red in color, rather soft, and projecting above the cut surface. Their color distinguished them sharply from the splenic tissue, but there was no other sharp demarcation. On microscopic examination there was found a fibrous reticulum, coarser than that of the normal reticulum of the spleen, but no distinct alveolar arrangement. In the meshes of the reticulum were found large endothelial cells of round, oval, or irregular shape, some of the latter having projecting processes. The nuclei were large and often double. In the periphery of the masses large cells containing remnants of red corpuscles or yellowish pigment were found. In the same region extension of the processes of the cells into the fibrous reticulum was observed. All other organs were uninvolved.

In Collier's case the involvement of the spleen was in the form of a zone of cortical infiltration, and Bovaird describes pyramidal formations of white or yellowish-white color extending deeply into the substance of the organ, and involving the greater part of its anterior half, while the posterior half was comparatively free. In Picou and Ramond's case the macroscopic appearance of the organ is not described with sufficient accuracy. In none of these cases was the condition so similar to that of definite neoplasms as in mine. It is not impossible though difficult to conceive how in any of these cases a longer duration could have led to an effacement of the conspicuous cellular process, and a conversion by fibrous hyperplasia into an organ such as those previously described in cases of ordinary

[1] Virchow's Archiv, 1881, vol. lxxxv. p. 563.

splenic anæmia. It may be admitted as probable that endothelial proliferation is a precursor of some of the fibrous-tissue formation in splenic anæmia as well as in chronic splenitis, just as the same process may lead to sclerosis in the peritoneum; but it seems to me just as unlikely that the endothelial process in the six cases under consideration could have terminated in complete fibrosis as that endotheliomata of the peritoneum may have a like conclusion.

It is always difficult to draw sharp lines between cellular hyperplasias and tumors. In the case of glandular affections of the gastro-intestinal mucosa, in certain epithelial proliferations in the liver, thyroid gland, and breast, this difficulty is well recognized. The microscopic features alone do not suffice, and an appeal must be made to the gross appearances, the etiological relations, etc. Viewed in this way, I cannot avoid the conclusion that my own case belongs in the category of tumors rather than of simple cellular hyperplasia. The peculiar prominence of giant cells naturally raised the suspicion that the process might be infectious or parasitic, but no form of bacterial organisms nor anything suggesting protozoa could be discovered.

One of the arguments advanced in opposition to the tumor theory in such cases is the preservation of normal splenic appearances. As one author states, "After all these years the organ is still a spleen." This preservation of normal appearance is, however, more superficial than real, as sections through the organ showed in several cases almost complete transformation of the splenic substance.

The conclusion to which I have come is that the cases of splenomegaly of the type of Gaucher represent a primary neoplasm of the spleen somewhat comparable to the diffuse myelomata, and to certain infiltrating sarcomata of the liver

FROM THE WILLIAM PEPPER LABORATORY OF CLINICAL MEDICINE, PHOEBE A. HEARST FOUNDATION.

MUCOCELE OF THE APPENDIX.

WITH REPORT OF A CASE POSSIBLY CARCINOMATOUS IN NATURE.*

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The somewhat indefinite term mucocele may be retained because it sufficiently suggests the general characters of a condition, the exact nature of which is probably not always the same. In some cases the pathology seems clear; in others there is much uncertainty as to the process of formation; but in all there is a cyst-like appendix with mucoid contents. Such cysts, and in fact all kinds of cysts, of the appendix are comparatively rare. According to Kelly and Hurdon, Ribbert found six cases among 400 autopsies; Bryant, one case among 124 autopsies; Steiner, three among 2,286; Bordy, one among 528, and they themselves found sixteen cases recorded among 3,770 autopsies at the Boston City Hospital. I have seen but one well-defined case, that herewith reported, among about 2,000 autopsies.

The appearance of the diseased appendix is that of a rounded or pyriform cyst with a more or less definite constriction of the proximal portion of the organ. Sometimes the distal part or tip alone is dilated; in other cases the whole appendix is enlarged. The lumen may be completely occluded at the cecal end or merely narrowed. In some of the cases the obstruction was due to a kink produced by a bend or by a fibrous band. In one, at least (Treves and Swallow), the cyst contents flowed out when the appendix was straightened.

The contents of the cysts are either of a muco-purulent, sero-mucous, serous or purely mucoid character. Occasionally they are blood-tinged. A review of the reported cases will show that in all probability the cysts

* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

are of different pathologic character. Some are undoubtedly merely inflammatory retention cysts, caused by occlusion of the mouth or proximal part of the appendix. A number of such have come under my observation, all being of moderate size and quite evidently of inflammatory origin. Exceptional cases, however, may be of such size and may have lost the characters of inflammatory retention cysts to such an extent that they may be classified as cysts and may admit of much doubt as to the mode of formation.

LITERATURE.

Leube,[1] in referring to these inflammatory retention cysts, states that the contents at first consist of tenacious mucous, and that later the sac contains only a watery serum, because when the appendix becomes much distended its wall becomes thinned and its vessels more superficial. Thus the watery portion of the blood may escape more easily, and the formation of mucus is reduced to a minimum (*hydrops processus vermiformis*).

Sonnenberg,[2] in referring to hydrops of the appendix and to retentive cysts, after detailing the results of obstruction of the appendix, states that the retained secretion does not always cause a severe disease of the appendix. If the obstruction occurs at a time when the lumen of the appendix is free, or when virulent microorganisms are not present, there is no decomposition of the secretions. A continued accumulation of secretion takes place and overdistension of the appendix in the form of a retention cyst may occur. The mucous membrane becomes compressed, epithelial cells are thrown off and the connective tissue elements hypertrophy. The muscular and serous coats of the appendix also thicken. Hernious protrusions of the mucous membrane through the muscular layer are occasionally met with, as in the case described by Kelynack and Ribbert. Such protrusions are also found in cases reported by Shoemaker and Kelly and in my own.

Among others the following reports refer to cases supposed to have had this character of retention cysts:

Wenzel-Gruber[3] describes a case in which the appendix was 10 cm. long, the spherical sac at the top being

1. Ziemssen's Cyclopedia of the Practice of Med., vol. vii, p. 361.
2. Path. u. Therap. der Perityphlitis. Leipzig, 194.
3. Arch. f. Path. Anat. u. Physiolog., 1875, vol. lxiii, p. 97.

4.2 cm. long, the constricted neck 1.8 cm. and the pedicle or proximal portion 4 cm. in length. The diameter of the sac was 5 cm., of the neck 2 cm. and of the pedicle 1 cm. The wall of the sac was from 2 to 3 mm. thick, as were the walls of the proximal portion. The serosa was thickened, the muscularis hypertrophied and the mucosa convoluted. The cyst was filled with viscid glassy mucus. The patient had tuberculosis of the lungs and intestines. The author notes that the opening of the appendix into the cecum, 1 mm. in diameter, was very small, but must have been thus narrowed by the chronic inflammation.

Feré[4] presented a mucocele of the appendix, found at autopsy on a man 55 years of age, dead of disease of the kidneys. The appendix was sigmoid and fusiform, with a circumference of 9 cm. at the central dilated portion. The length was 10.5 cm. The appendix was quite free from adhesions and normal in color. On opening the cecum there was seen a fluctuating tumor the size of a walnut, covered with reddish mucous membrane, which was almost ecchymotic in spots. The contents of this tumor were continuous with the contents of the appendix. On section of the unthickened walls of the appendix a colorless gelatinous mass, resembling boiled starch, was turned out. This was found to be composed of mucin and a few cells. The mucocele was probably consequent on an obliteration of the appendiceal opening, due to ulceration of the mucous membrane at this point. The tumor distended the wall formed by the mucous membrane of the cecum and the appendix, and thus produced the intracecal tumor. The condition had caused no symptoms.

Other cases of cysts or of dropsies of the appendix are referred to by Bossard, Kraussold and Ribbert; and Wölfler describes a cyst found in an operation for herniotomy and which, on consideration of its characters, seemed to be a cyst of the appendix.

Bristowe[5] calls attention to dilatation of the appendix which may occur when its orifice is obliterated or obstructed. "Then the appendix becomes elongated and plump (perhaps as thick as the little finger), presents often false diverticula (resembling, on a small scale,

4. Progres Med. Paris, 1877. vol, v, p. 73.
5. Reynold's System of Medicine.

those of a sacculated bladder), and is distended with a glairy transparent fluid, the secretion of the mucous membrane."

Treves[6] states that it is common to find the fore end of the appendix greatly enlarged and distended from the retention of mucus and other matters in the distal end of the canal.

Kelynack says that this has not been his experience. He refers to one case under his own observation and to Fenwick's case,[7] in which "the appendix was distended by a milky fluid, the communication with the cecum being obliterated."

Maylard[8] describes a retention cyst of the vermiform appendix from a patient who had died of chronic Bright's disease. The appendix was free, four inches in length, normal for its proximal two inches, "but the distal portion was dilated into an egg-shaped, tense, cyst-like structure." The dilated part was shut off from proximal portion which communicated freely with the cecum. A mass of clear gelatinous substance was turned out of the cyst, leaving behind some "white, creamy-like material, in which was embedded a small calcareous concretion." The peritoneal surface was deeply injected with blood vessels. Maylard notes that Coats[9] has described a similar specimen.

Shoemaker[10] describes a cystic condition of the appendix, discovered postmortem, not having given rise to symptoms during life. The cyst of the appendix was 4 inches long and 1¼ inches in its broadest diameter. "A small portion of the distal end was not dilated, and at about the broadest portion of the cyst was a thinned area seemingly about to rupture." The cyst contained a "clear jelly-like mass."

Biggs[11] reports two cases of stricture of the appendix. One appendix was 9 cm. long and 2 cm. in diameter, and the lumen was occluded .5 cm. from the origin by firm fibrous bands. "The contents of the appendix measured 2 drams, were of a slightly pinkish color, and consisted of fat globules, granular matter, and cholesterin crystals." The second appendix was obstructed

6. Lancet, Feb. 9, 1889, p. 268.
7. "Clinical Lectures," 1889.
8. Trans. Glasgow Path. and Clin. Soc. vol. iv, 1891-3, p. 111.
9 "Manual of Pathology," 2d ed., p. 753.
10. Occident. Med. Times, 1892, vol. vi, p. 387.
11. Med. Rec., 1893, vol. xliii, p. 536

by a kink near the tip, produced by traction of the peritoneum.

Hawkins[12] reports 2 cases of a condition which he calls "cystic appendix," which were cases of empyema of the appendix. He thinks these cysts may be caused by obstruction of the lumen due to kinking of the tube by an acute bend. He refers to a case reported by Treves and Swallow[13] in which the cyst was 2 inches in length, very hard, and filled with mucus, which escaped when the appendix was made straight after its removal. The bent position had been maintained by old adhesions.

It is somewhat remarkable that in almost all the cases the condition was discovered accidentally at operations or autopsy or at least had occasioned no pronounced symptoms. If the accumulating liquid is of inflammatory nature, one might expect, in a greater number of the cases, active clinical symptoms, especially as the cysts often reach considerable size and not rarely have been attached by adhesions to surrounding structures. There is little doubt, however, that most of these cases were probably of inflammatory origin.

In some cases, a tumor was recognized in the right iliac fossa or the growth was of such size as to have made it probably palpable during life.

Coats[14] mentions a case in which the appendix had been converted into a large cyst, measuring 5 inches in its long diameter. The cyst contained a tenacious material and the wall was thick and firm.

Wilks[15] saw a case in which the appendix was dilated to the size of the ileum and distended with 3 or 4 ounces of white odorless mucus.

Wien[16] reports a case of cystic degeneration of the appendix vermiformis, which caused a tumor in the right iliac fossa. There was great swelling along the crest of the ilium, and an opening near the posterior spine of the ilium, from which 3 or 4 ounces of quite clear mucus, occasionally stained with pus, were discharged daily. The discharge was said to look almost exactly like vitreous humor.

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12 "Diseases of the Vermiform Appendix," London, 1895.
13. Lancet. Feb. 9, 1889.
14. Glasgow Med. Jour., 1875, vol. viii, p. 126.
15. Quoted by Fagge, vol. ii, p. 174.
16. Med. Rec., 1880, vol. i, p. 44.

Guttmann[17] reports a specimen of enormous hydrops of the appendix, found on section of a woman 70 years old. The vermiform appendix was 14 cm. long and 21 cm. in circumference, and the opening into the cecum was completely constricted by strong fibrous bands produced by chronic inflammation of this part of the appendix. The secretion of the mucous membrane had become quite watery.

Montgomery[18] describes a cyst of the appendix found in a woman during the operation of panhysterectomy. The cyst was 5½ inches long and 4¾ inches in its largest circumference. The contents were "apparently thin and watery." The cyst was removed.

Deaver's[19] case presented a cystic dilatation of the appendix, the size of a small orange, which was adherent both to the neighboring coils of small intestine and to the right broad ligament. The lumen of the appendix was entirely occluded ¼ of an inch from its cecal end. The contents of the cyst were quite clear and somewhat tenacious. The author says that the mucous membrane is usually smooth and generally greatly atrophied as a consequence of mechanical pressure. There is also marked atrophy of the lymphoid follicles. If the distension be but moderate, it is not uncommon to find the wall much thickened as a result of compensatory hypertrophy of the muscular coats and also of some connective-tissue hyperplasia.

Occasionally, as in a case reported by Fowler,[20] there are active symptoms which necessitate operation. In Fowler's case the dilated portion, about the size of a small walnut, was at the distal end. There were no adhesions.

Though accurate studies of the pathology of the appendix have until recently been wanting, and especially in the class of cases above referred to, it is very probable that most of the cases cited were retention cysts with inflammatory contents. Every one who has studied series of appendices must have encountered minor grades of cystic distension with contents of mucopurulent character. More advanced stages may cause empy-

17. Deutsch. med. Wochft., 1891, vol. xxii, p. 260.
18. The Journal A. M. A., vol. xxix, p. 174.
19. "Treatise on Appendicitis," Philadelphia, 1900.
20. "Treatise on Appendicitis," Philadelphia, 1894.

ema, and hydrops may occur in the appendix, as in the gall bladder.

There is, however, some reason to believe that there exists a quite different sort of dilatation of the appendix with which the inflammatory form may readily be confused. Long ago (1867) Rokitansky reported four cases which he regarded as instances of colloid cancer and in which the gross appearance was that of cysts of the appendix. Virchow described these cases as colloid degeneration and figures one in his "Krankhafte Geschwülzte."

In Rokitansky's series of cases[21] the appendix was transformed into a thick-walled cyst, varying in size from 2 to 6 cm. in length and from 1 to 2 cm. in diameter. The wall was made up of fibrous tissue, which replaced the coats of the appendix. The inner portion of this capsule was a loose areolar layer, with brownish pigment here and there, and in places it was lamellated. His observations pointed to the fact that this layer might be the remains of an atrophied reticulum. The contents of these appendices consisted of a whitish-yellow gelatinous substance, supported in two cases by a fine reticular network, with small rudimentary blood vessels visible in places. After considerable discussion of the subject, Rokitansky comes to the conclusion that this affection is a colloid-cancerous degeneration of the appendix, and that the tension of the mass of gelatinous carcinomatous material causes a dilatation of the walls of the vermiform process, with a consequent transformation into a fibrous capsule.

At the time of Rokitansky's report little was known regarding the occurrence of carcinoma of the appendix, only two cases, those of Merling (1838) and of Prus (1865), having been reported. Recently, however, a considerable number of cases have been recorded, and Kelly and Hurdon tabulate a total of 52, including 2 which were designated endothelioma. They refer to Rokitansky's cases, though erroneously stating that these were not examined histologically.

In 1884, Draper[22] reported a case of colloid cancer of the appendix vermiformis. "The upper third or head of the appendix was enlarged and dilated to such a de-

21. Med. Jahrb., Wien., 1867, vol. xiii, p. 179.
22. Boston Med. and Surg. Jour., 1884, vol. cx, p. 131.

gree that externally it was of the size and shape of a large plum; its cavity, deeply injected, was irregular in its surface, and would admit the little finger. The opening to the intestine from the appendix was also dilated. The thickened wall of this enlargement presented the characteristic appearances of colloid disease." The tumor had caused symptoms and was probably the cause of death.

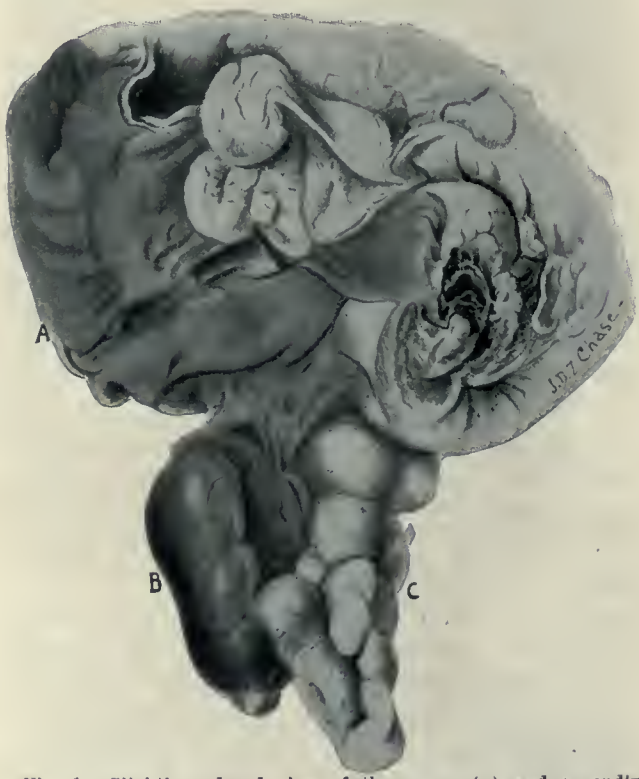

Fig. 1.—Slightly reduced view of the cecum (*a*) and appendix (*b*). The mesentery of the appendix was heavily loaded with fat (*c*).

The features of this case differed somewhat from those usually described. The thickening of the walls of the diseased appendix and the dilation of the cecal opening contrast strongly with the usual conditions.

Vimont[23] reports a case of mucocele of the appendix,

23. Bull. Soc. de la Soc. Anat., Paris, 1887, vol. lxii, p. 608.

found at the autopsy of a woman who had been operated on for bilateral gelatinous cysts of the ovary, which had ruptured into the peritoneal cavity. The tip of the appendix was found attached to the uterine cornus. The shape of the appendix resembled that of the stomach, with the small end attached to the cecum by a small pedicle. The appendix was 11 cm. long and 12.5 cm. in circumference at the larger extremity. The contents were gelatinous, like boiled starch, and weighed 38 grams. The walls of the appendix were thickened, whitish, and at one place presented two small papillomatous masses. The author asks if this dilatation may not have been due to compression caused by the ovarian cysts.

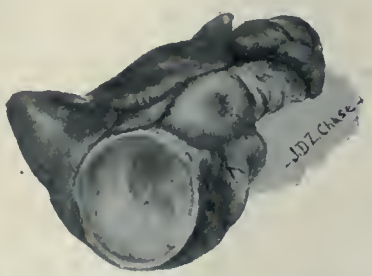

Fig. 2.—Transverse section of the appendix showing the stiff walls and opalescent mucoid contents. Life size.

This case even more definitely establishes the neoplastic nature of certain mucoceles.

Baillet[24] exhibited a cyst of the appendix found during an operation performed to remove a papillomatous ovarian cyst. The orifice of communication with the cecum was occluded. The cyst was found to be made up of mucoid tissue, embedded in which were many large cavities lined with non-ciliated cylindrical epithelium.

PERSONAL CASE.

The case which came under my own observation occurred in a woman aged 50, who had had glycosuria for a number of years and finally died of rapidly developed acidosis. I had not seen her during life, but made the

24. Bull. de la Société Anat. de Paris, 1891; 55, vol. v, lxvi, p. 67.

postmortem examination, at which the enlarged appendix was discovered.

Autopsy.—Performed March 18, 1899.

The body was that of a very large white woman, probably 5 ft. 10 in. in height, and quite fat. Rigor mortis was well developed. On section into the body, the subcutaneous fat was

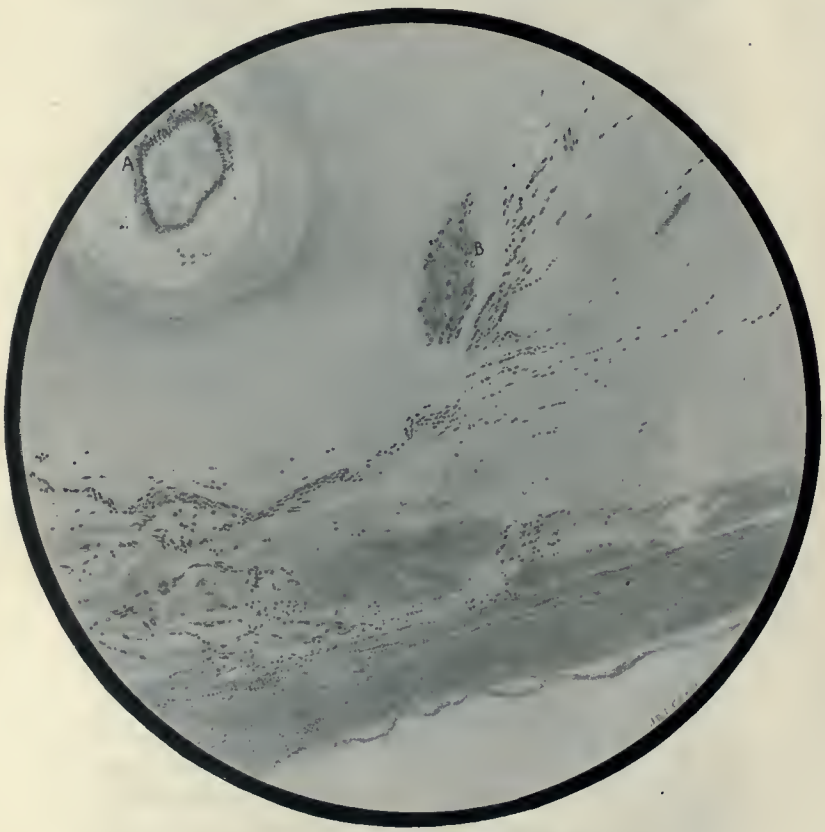

Fig. 3.—Section of the wall of the appendix and part of the substance within. Toward the center of the appendix is seen (*a*) an acinous or section of a glandular tubule; at (*b*) an irregular mass of epithelial cells suggesting by its position and the relations of adjacent structures that it had been separated from the mucosa. No remains of normal mucous membrane are observable.

found excessive, being in places as much as an inch and one-half in thickness. The fat itself was of a light yellow color, and the muscles were rather lighter colored than normal. The

pleural cavities were free of exudation, and there were no adhesions. The anterior mediastinum was occupied with a considerable excess of fat, so that the heart and pericardium were completely covered. On section into the pericardial sac, a little clear fluid was discovered. The epicardium contained an excessive deposit of fat at the auriculo-ventricular furrow on the right side and over the root of the great vessels, but not much anywhere else. The coronary vessels were distinctly seen as white streaks, the whiteness being due to the fibrous character of the walls of the vessels. The root and larger

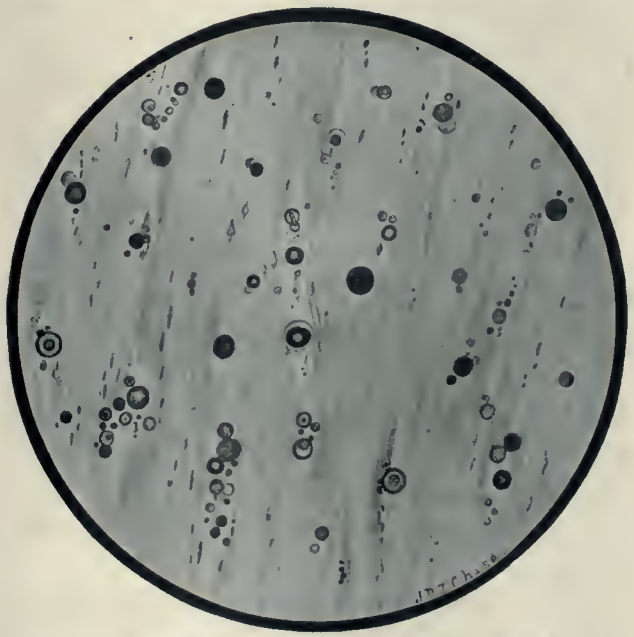

Fig. 4.—Calcareous spheres imbedded in the gelatinous substance within the appendix. Zeiss. oc. 1; obj. 1/12. Specimen stained with hematoxylin.

branches were so sclerotic that when cut transversely and compressed they immediately sprang open from the stiffness of their walls. The heart muscle was flabby on both sides, and there were some fatty patches here and there. The endocardium was white in places, and there were marked patches of atheroma in the anterior mitral leaflet, as well as in the root of the aorta around the mouths of the coronary vessels and at the edges and floor of the sinuses of Valsalva. The valvular orifices were normal, as were also the leaflets of the

aortic and pulmonary valves. The tricuspid leaflets showed slight thickness at the edges.

The lungs were congested at the bases and somewhat edematous, but there was no marked change.

The abdomen contained an immense quantity of fat in the mesentery and omentum. The gastro-intestinal tract presented no abnormalities, except in the region of the appendix. The latter was found greatly distended in a somewhat cystic fashion, and at one point a small hernious protrusion of the mucosa, through a defect in the serous and muscular coats, causing a clear vesicular projection of about the size of a grape seed, was discovered. The mouth of the appendix seemed to be occluded, but the bowel was kept unopened for subsequent dissection. The coils of intestines were everywhere more or less matted together by thin, veil-like adhesions, but there were no gross adhesions of any sort.

The liver was much enlarged and compressed by the ribs (*Schnurr Leber*). On section, its substance was rather flabby, and spots and streaks of light color were discovered. There was evidently some slight sclerosis and also a considerable degree of fatty change.

The pancreas was soft and presented no macroscopic change.

The spleen was enlarged, fully twice its normal size, and the capsule was rather hard. The substance was soft and rather light in color, with spots of dark, almost hemorrhagic, appearance. The splenic artery was atheromatous in a high degree, and the splenic vein greatly increased in size. The kidneys were a little enlarged. The cortex was rather wider than normal, and the substance deeply congested. There was no definite visible disease. The suprarenal capsules were normal.

The abdominal aorta and its branches, as far as they could be felt, were sclerotic, though much less so than the splenic artery.

The uterus and its appendages were normal.

Description of Cyst.—The appendiceal cyst was found to be about 2½ inches in length and a little over 1 inch in diameter at its thickest part, which was near the middle of the organ. The cyst extended from the cecum to the tip of the appendix. At the cecal attachment the lumen was occluded and the expansion to the cyst was sudden, as if a much enlarged appendix had been constricted at its origin by a tightly drawn encircling ligature. The unopened cyst was quite firm and elastic, giving the impression of a sac tensely distended with gelatinous matter (Fig. 1). The wall was white and glistening on the outside, and the small blood vessels showed plainly in the serous covering. On transverse section, the cyst was found to be of semi-solid consistence; its walls tough and fibrous, 1 to 2 mm. thick, and in most places cleanly separated from the

whitish or opalescent gelatinous contents (Fig. 2). The latter were easily shelled out when the thickness and firmness of the walls prevented their collapse, leaving a firm shell.

Microscopic Examination.—Microscopic examination showed the wall or capsule of the cyst to consist of a thickened and fibrous muscularis and serosa (Fig. 3). The submucosa was of loose areolar character, containing considerable leucocytic infiltration and new-formed spindle cells. The mucosa was nowhere intact. In its place was found a layer of varying thickness, composed of polymorphous epithelial cells without definite arrangement. Generally this epithelial lining was thin and in some places wanting; in a few places it was more massive, and at such places there could be traced into the gelatinous cyst contents, irregular extension of columns or strata of epithelial cells.

Cyst Contents.—The contents of the cyst were made up of a lamellated gelatinous substance of compact character. Between the lamellæ were found cells (leucocytes) and many minute spherical bodies staining deeply with hematoxylin (calcareous spheres, Fig. 4), and here and there masses of irregular epithelial cells or less frequently ill-defined glandular acini. While the epithelial cells were more numerous near the periphery, that is, just within the capsule, they could be found at the very center and scattered everywhere through the gelatinous substance. There was no evidence of a well-developed reticulum, but in places the irregular course of the gelatinous lamellæ and the presence of short strands of spindle cells lying end to end suggested an old reticular arrangement. Nearly all the cells within the gelatinous material were degenerate, the groups of epithelial cells in particular.

The appearances strongly indicated some active cellular process with mucoid degeneration rather than an exudation from a diseased, but more or less intact, mucous membrane. The presence of acini deeply embedded in the gelatinous material and of irregular heaps of polymorphous epithelial cells further confirmed the suspicion that the process was akin to that of gelatinous carcinoma elsewhere.

There was no evidence in any of the sections of invasion of the walls of the appendix by a heterotopic epithelial process, though here and there in the submucosa small collections of epithelium-like cells could be identified. It is possible that a more extensive sectioning of the appendix might have discovered definite invasion, but at the time when the sections were made no suspicion was entertained of a possible malignant nature of the condition.

It may be recalled that in some of the reported cases, such as that of C. C. Norris,[25] but little invasion of the walls was

25. University of Penn. Med. Bull., 1903.

evident, the growth appearing, in the main, as a mass within the lumen of the appendix.[26]

Chemical Examination.—Chemical examination of the contents of the cyst showed the presence of considerable quantities of calcium which the microscopic examination had indicated. The fact that the mucoid material was a mucoproteid of the same general character as those met in gelatinous tumors of the ovary and the like seems to me of some importance, though not a certain proof of the nature of the condition.

Dr. Edsall reported his chemical study of the cyst contents as follows:

"The substance from the interior of the appendix was (after preservation in alcohol) of somewhat the same consistency as a dense jelly. It was of grayish-white color, partially opaque. It was soluble in water, forming a slightly glistening solution. On boiling, the solution became opalescent, but did not coagulate. It did not coagulate on the addition of acetic acid. Absolute alcohol produced a precipitate which was still readily soluble in water after standing under alcohol for more than 24 hours. After boiling with 2 per cent. sulphuric acid, the substance reduced Fehling's solution readily. The lack of coagulation after adding acetic acid is sufficient to indicate that it was not mucin; the solubility in water distinguished it from colloid. The reactions are those characteristic of pseudomucin. After allowing the preserving alcohol to evaporate from two small portions of the substance, these portions were weighed, incinerated, and the calcium of the ash determined. In the two instances the weight of the calcium (as Ca 0) was, respectively, 1.1 per cent. and 0.85 per cent. of the total."

It must be admitted that the nature of the process in the appendix I have described is somewhat uncertain. At first I was disposed to think it simply a dilated appendix filled with mucoid material unusual in amount

26. Since the above was written, an interesting specimen has been shown me by Dr. A. J. Smith, to which I am permitted to refer by his and Dr. B. C. Hirst's courtesy. Dr. Smith writes as follows:

"Appendix was removed in Howard Hospital in June, 1905, by Dr. B. C. Hirst, from a negro woman; character of case was not appreciated prior to operation. The woman was supposed to have fibroid pelvic growths. At operation both ovaries were found much enlarged and the seat of widely infiltrating papillary adenocarcinoma, with surface papillary extensions, with both tubes and peritoneal surface of uterus similarly involved. Appendix was free, short, with smooth and pale and glistening exterior, but with distal extremity distended into a small rounded cyst-like dilatation. On section the latter was found filled with clear mucus, the walls grossly showing no thickening save at one or two points where there were tiny white subserous nodules, which may possibly be foci of starting invasion from the cancerous growth of the genitals."

The appearance of the gross specimen was strikingly similar to that of my own.

and character. Closer study, however, and in particular the discovery of irregular acini, epithelial tubular structures and collections of epithelial cells scattered everywhere through the gelatinous substance made me suspicious that the condition might be allied to colloid carcinoma. A review of the scant literature of the subject and especially the features of the cases reported by Vimont and Baillet seem to lend some support to my suspicion.

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THE CLINICAL CHEMISTRY OF DISEASE OF THE LIVER.[1]

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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

While I do not wish to trespass upon the territory of the speaker that is to follow me, I may be permitted to refer to the fact that if we liken the conditions in disease of the liver to those in diseases of most of the other important organs, we find that we are limited to a remarkable degree in the number and character of the measures at our disposal when we attempt to establish an early diagnosis. We have either reasonably accurate methods of physical examination or important aids from the clinical laboratory in most of the other classes of diseases that are common and important. In the case of the liver, however, the conditions under which we work offer an unfortunate contrast. In the combined complexity and magnitude of its functions the liver is undoubtedly the most important of all the vegetative organs; yet the methods of investigating its derangements are very restricted. Physical examination is limited to a few procedures and is often unsatisfactory unless comparatively gross changes are present, while the laboratory methods that have become so helpful in many other conditions have had but little direct bearing upon disorders of the liver. As is but natural, numerous attempts have been made to provide through the laboratory special clin-

[1] Part of a Symposium on the Early Manifestations of Cirrhosis of the Liver. Read before the Section on Medicine of the College of Physicians, Philadelphia, January 11, 1904.

ical means of determining that there is derangement of the hepatic functions; but, unfortunately, we can still get little serious and reliable aid from any such special methods of observation, except when bile-elements are present in the urine or are more or less completely shut off from the intestine.

The way that has been and still is most evidently open to those that would attempt studies of this character lies through chemical investigations of the functions of the liver and of the derangements in these functions that may be shown in changes in the urine, feces, or blood. There are, however, great stumbling-blocks in the path of such studies. On the one hand, most of the products of the liver that reach the intestine in the bile have become greatly altered during their long journey through the intestine by digestion and by bacterial action before being excreted in the feces or absorbed; while, on the other hand, if the products of deranged hepatic function reach the circulation, or if on account of derangement of the liver other substances that would normally become altered in the liver circulate in the body fluids in abnormal amount, they, too, are likely, before they can be excreted in the urine, to be destroyed or to become so changed that their meaning can no longer be clearly traced.

The difficulties caused thereby are easily appreciated. Examination of the urine, for example, would afford but a frail support in diagnosis if the urine, instead of being secured almost as it secreted from the kidney, were subjected to active and more or less prolonged bacterial processes before its excretion. We know that casts, blood corpuscles, epithelial cells, and probably even small amounts of albumin, originally present in the urine as it comes from the kidney, may escape our observation when there are local infections along the urinary tract, through their being broken up by the bacteria present; indeed, the same thing may occur even when actual local infection is absent if the urine contains many bacteria and remains in the bladder for any considerable length of time or is not examined almost immediately after it is passed. We can more or less completely overcome such difficulties in renal disease, but in disease of the liver the constituents of the urine or feces must remain, as a rule, only indirect indicators of the condition of the liver.

At present, also, the chemistry of the blood offers almost no aid, owing to the great technical difficulties in blood chemistry, while direct examination of the bile is impossible, though, if the latter were feasible, it might, of course, be extremely valuable. Hence, in studying the excretions we are forced to adopt more or less indirect methods of investigation.

I shall refer to some of the more important of the studies that have been made and mention their present status, which is, unfortunately, in almost all instances sadly unsatisfactory; but I shall first sketch briefly our knowledge concerning the chemical functions of the liver in order to indicate the reasons why most of these studies have been undertaken. Obscure as the functions of the liver in large part remain, we have at least gained some conception of their complexity, and, within the last few decades, we have been taught a number of strikingly important facts.

The liver has long been known to bear a distinct relation to carbohydrate metabolism, constructing and storing glycogen from the simpler carbohydrates brought to it through the digestive tract, and, again, rapidly forming dextrose from this glycogen and throwing it back into the circulation whenever the supply of blood-sugar runs low. As a storehouse and supply depot for carbohydrates, the liver is by far more important than any other organ in the body.

The liver also stores fat and yields it again for consumption when needed. It probably constructs fats from fatty acids and glycerin, and it is possible—although as yet unproved—that it produces fats from proteids or proteid derivatives. Its relation to fat metabolism is, however, less important than the relation it bears to carbohydrate metabolism, and the relation to the fats is shared largely by other tissues.

The connection of the liver with proteid metabolism is far more complex and more obscure. Its most satisfactorily established function in proteid metabolism is the production of urea from ammonia compounds formed in the digestive tract or in the course of metabolism. In this function the liver is normally almost or perhaps quite as conspicuous as it is in its relation to carbohydrate metabolism. It likewise apparently produces and

probably also destroys a certain amount of uric acid. In fowls this is an extremely important part of the liver's functions; but in fowls uric acid is the chief end-product of proteid metabolism, occupying much the same position in this respect as does urea in mammals. It is still problematical whether the liver bears an especially striking relation to uric acid production in man; but it now seems probable that its importance in this respect is not dependent upon any peculiarly individual relation to nuclein metabolism, but is solely or almost solely dependent upon its size, the large number of cells that it contains, and its general metabolic activity. The relation of the liver to most of the remaining nitrogenous constituents of the urine is very obscure, and the changes through which proteids pass after digestion, before reaching the urea stage, as well as the places where these changes occur, are almost equally obscure, our only reasonably well-established knowledge being that it is somewhat probable that the terminal stages are the formation of ammonium lactate, ammonium carbamate, ammonium carbonate, and then urea.

The most generally recognized function of the liver is the formation of bile pigments and bile acids. It suffices here to say that this is an exclusive function of the liver, and that the bile pigments are indirectly produced from hæmoglobin, while the bile acids are formed by a union of cholalic acid with glycocol or taurin, the two latter substances coming almost certainly from proteids, while cholalic acid is of unknown source.

In addition to those mentioned, the liver has the very remarkable function of protecting the organism against various kinds of poisons, some of these poisons being produced within the body and others coming from and being formed in the digestive tract or being merely ingested and absorbed as such. The best known of the poisons that are formed in the organs is ammonia. It has been clearly determined experimentally that the exclusion of the liver from the circulation or the extirpation of this organ is followed by the accumulation of an enormous amount of ammonia in the system; and there is considerable evidence that ammonia compounds are the chief cause of death after such experimental procedures, and also that in the intoxications occurring in grave disease of the liver, particularly in many cases

of advanced cirrhosis, the remarkable clinical manifestations seen are due to ammonia poisoning. There can be little doubt that other poisons produced in the organism are destroyed by the liver, but our knowledge concerning them is comparatively indefinite. Of the poisons coming from the digestive tract that are held up by the liver and either directly antidoted or destroyed, there are unquestionably a vast number. It has been clearly determined that many metallic poisons held in combination by the liver cells are excreted in the bile, or are, through the action of the liver, oxidized or combined to comparatively harmless substances, and are then passed on into the circulation and excreted by the kidneys. Similar facts have been demonstrated concerning alkaloidal poisons, the liver in this case also sometimes destroying the substance, sometimes excreting it in the bile, and sometimes producing relatively harmless combinations; or, in other instances, perhaps merely holding the bulk of the poison for a time, gradually passing it on into the circulation in relatively small and harmless amounts.

The liver likewise has an extremely important duty to perform in this connection in shielding the organism from the effects of the products of putrefaction that are developed in the gastro-intestinal tract. Ammonia is again important as one of these, for a considerable part of the ammonia that normally goes to form urea comes from the digestive tract, and is made harmless by this conversion into urea before being allowed to pass from the liver into the circulation. The other best known toxic substances thus coming to the liver from the digestive tract are the aromatic products of proteid putrefaction, such as indol, phenol, and skatol, and the volatile fatty acids produced in the breaking-up of various forms of food. It has been determined that indol and phenol enter into combination with sulphuric acid in the liver, and probably here, also, with glycuronic acid after they have undergone some oxidation; they are then passed on, in relatively harmless form, into the circulation and excreted in the urine, representing, when combined with sulphuric acid, the fraction of the urinary sulphates known as the ethereal or conjugate sulphates. Herter considers that he has demonstrated that some of the phenol reaching the liver is actually destroyed by this

organ. It is highly probable that this is true of phenol as well as of the other bodies; the amount absorbed is certainly much greater than that excreted.

Besides the functions mentioned there are most active and important fermentative processes of various kinds taking place in the liver, although their exact nature and the extent of their importance can at present be but indicated. The liver is undoubtedly the seat of the most energetic oxidative processes that go on within the body, and these oxidative processes are unquestionably of many kinds and are apparently due to many varieties of what we now call oxidative ferments. It has also been mentioned that there are important synthetic and catalytic fermentative actions here, other than oxidation, upon the carbohydrates and fats and probably upon the proteids. In the latter connection may be mentioned the brilliant observations begun by Salkowski and especially elaborated by Jacoby, which have demonstrated that post-mortem and even intravitam there are active self-digestive processes going on in the liver. These yield large amounts of leucin, tyrosin, hexon bases, and other advanced products of proteid digestion. It has, to be sure, been shown that practically all other organs exhibit this autolytic action, and that, therefore, it is not peculiar to the liver. A point of importance about it is, however, the fact that in these self-digestive processes the liver exhibits a remarkable facility for rapidly transforming proteids into advanced products of digestion, such as leucin and tyrosin, while many of the other organs form these advanced products only slowly, but they form the earlier products (albumoses and peptones) in comparatively large amount. This fact is an aid in understanding the frequent appearance of leucin and tyrosin in the urine in very grave destructive disease of the liver.

To turn to the possible diagnostic importance of the functions mentioned.

If disturbances of these functions occur they are likely, in the earlier stages, to be shown only by indefinite clinical signs. Among the changes in the secretion of bile biliary obstruction, of course, produces the most evident symptoms. Unfortunately

we cannot study alterations in the bile itself as it is secreted, and are limited chiefly to observations of the effects of more or less complete obstruction to its outflow. Reduction in the amount of bile passed into the intestine or its complete absence from the intestine is followed by marked disturbances of digestion, which chiefly consist in greatly reduced fat absorption and excessive putrefaction of the intestinal contents. There is, of course, also marked alteration in the color of the stools.

Although it has long been known that the stools are fatty in cases of jaundice, the work of Friedreich Müller first directed attention to the extent and importance of this fact in its relation to pancreatic disease, and demonstrated that the absorption of fat often suffers even more severely in jaundice than in many instances of severe disease of the pancreas. The extent of this disturbance may be extreme. I have found in moderately severe jaundice that less than 15 per cent. of the fat ingested has been absorbed. In relation to the diagnosis of liver disease this is, however, not of much importance, for aside from the complicating conditions in pancreatic disease we do not know that it occurs unless the outflow of bile is obstructed, and the presence of biliary obstruction can be determined much more readily and definitely in other ways.

Excessive putrefaction in the digestive tract also is not helpful in diagnosis, for it does not by any means occur constantly in liver diseases even when jaundice is present; and it is met with in many other conditions. The color of the stools is often an extremely useful indication that the amount of bile reaching the intestines is abnormally small, although the influence of diet upon the color should be considered more frequently than it is, and this method of observation is at best crude.

The only satisfactory method of determining the presence of slight grades of jaundice is by examining the urine.

The clinical tests for bile are accurate enough when a considerable amount of bile pigment is present, but when the amount is small or when a large quantity of other pigments is present Gmelin's test is often unsatisfactory, and the iodine test is still less reliable. A number of clinicians have recently taken up and recommended the old Hayecraft test with flowers of

sulphur. This test has been shown by Fraenkel and Cluzet and others to respond to alcohol, acetic acid, phenol, and various other substances that are particularly likely to be present when the urine has undergone fermentation, and they consider it useful only when fresh urine is to be tested, but to furnish then a useful preliminary test. It is certainly very unreliable. Dr. Willetts has made a series of tests of urine in cases in which bile pigments were absent and in which there was no reason to suppose that bile elements would be present, and has repeatedly obtained a more or less strikingly positive result; and in several of these cases in which there was some doubt I have determined that bile pigments were absent and have had a negative result from Neumann's method for bile acids. When bile tests of urine are doubtful, the only satisfactory measure is to use Huppert's method or some one of the modifications of this. Of these modifications that recently described by Nashayama is easily carried out and probably very reliable.

I may refer to the fact that even in severe obstruction of the biliary passages bile often does not appear in the urine until some time after the obstruction has become established, and when bile pigments have once been deposited in the tissues they disappear but slowly. Evidently, then, bile pigments are excreted slowly. A fact of much interest in this connection and one that is of great importance is that in many cases of chronic liver disease there is often a subicteric tint of the skin and of the conjunctivæ, and yet the urine shows no bile pigments or contains them only occasionally. Urobilin is often present in the urine in these cases in noteworthy amount, and certain authors, particularly several of the French school, have called this condition urobilin icterus, and have attributed the staining of the tissues to this pigment. Some of these authors have, in fact, taught that in some diseases the liver produces urobilin. I shall briefly discuss the source of urobilin and the meaning of urobilinuria later. At this point I wish merely to refer to the fact that in cases of the class that I have mentioned it has been found that the blood serum really contains bile pigment; that, in other words, the discoloration is due to actual mild jaundice, but the bile pigment is altered or destroyed before it can be excreted in the urine. A

reliable clinical method for demonstrating the presence of a small amount of bile pigment in the blood, when the urine contains none, would be extremely valuable, as it would often greatly hasten the definite determination that disorder of the liver is present. Hamel's recently described method of drawing blood into capillary tubes and observing the color of the serum after its separation may prove to be of some use, but it is too crude to be reliable.

Since, therefore, the existence of the very early and slight grades of chronic jaundice is at times difficult—or, in our present circumstances, even practically impossible, clinically—to demonstrate, and since many cases of chronic disease of the liver exhibit no jaundice, investigators have been led to study the other functions of the liver in diseases of that organ in the hope of discovering tests of clinical importance. The most evident chances of success were seen in connection with the function of storing carbohydrates and with that of transforming ammonia compounds into urea. It seemed probable that the diseased liver might, on the one hand, lose much of its power of transforming the simpler carbohydrates into glycogen, and, therefore, that the administration of a large amount of sugar might result in its appearance in the urine; or, on the other hand, that the ammonia reaching a diseased liver might, in large part, pass through it unaltered and be excreted in the urine in abnormal amount at the expense of the other nitrogenous constituents, particularly urea. These hopes have proved to be in a large part vain. It was at one time believed by many observers that the administration of glucose frequently produces alimentary glycosuria in liver disease; but even if this had proved true, its importance would, of course, have been greatly restricted by the fact that alimentary glycosuria is common in many other conditions. The conclusions of the earlier observers have, too, been energetically disputed, and to so large an extent disproved that it is extremely questionable whether alimentary glycosuria is even common in liver disease.

More useful knowledge seemed to be in sight, if not at hand, when Sachs reported that he had demonstrated that in frogs extirpation of the liver is followed by loss of the power of assimilating levulose, while other sugar can still be assimilated.

Lépine and Strauss followed this by administering levulose as a test of the functional capacity of the liver; and Strauss concluded that a consequent alimentary levulosuria constitutes a useful test for disease of the liver. His conclusions were more or less fully concurred in by Bruining and Ferrannini, but Landsberg has had decidedly contrary results. In six cases in which I used the test the results were entirely negative in three, and in the others they were but weakly and indefinitely positive (slight Seliwanoff reaction; minimal reduction of copper; trace of fermentation). The latter conditions may certainly be met with in other diseases, and perhaps in normal persons. All my cases had severe disease of the liver, which in five was advanced cirrhosis, and in the other secondary carcinoma. In human beings the liver apparently retains most persistently its power of making and storing glycogen from either glucose or levulose (except in diabetes); or, if it loses it, other organs—probably, chiefly, the muscles—take this function upon themselves. Sachs believed that he had demonstrated that other organs cannot act in place of the liver in regard to levulose. He did not, however, show that this is true in chronic and slowly increasing disease, when the function, if lost at all, would disappear slowly. Alimentary levulosuria may be of some value in testing the functional capacity of the liver; but its importance is, at most, probably very limited.

The same statement may be made concerning the relative amounts of urea and ammonia in the urine. In animals, when the liver function is experimentally excluded by establishing an Eck fistula or by destroying a large part of the liver parenchyma, the ammonia of the body fluids and of many tissues rises to an extremely high point; and, at the same time, the excretion of ammonia in the urine becomes greatly increased, while that of urea sinks correspondingly (Hahn, Massen, Nencki, Pawlow, and Zaleski). Similar results have been produced in geese by extirpating the liver (Minkowski and Naunyn); in this case the ammonia of the urine increasing at the expense of uric acid, which is the chief normal nitrogenous end-product in fowls. A marked increase in the urinary ammonia, with a fall in urea, has also frequently been observed in profound acute disease of

the liver, such as acute yellow atrophy or phosphorus poisoning.

It is, indeed, as I have stated, not improbable that excess of ammonia compounds produces the most striking of the symptoms in the remarkable intoxication that occurs in advanced hepatic disease and in the experiments mentioned. Again, however, we meet the unfortunate fact that this change in the urine does not occur in all cases of extensive liver disease, even when the lesion is so grave and of such rapid progress as that in acute yellow atrophy; and in chronic disease, such as cirrhosis, while the ammonia of the urine is not infrequently excessive as compared with the total nitrogen, it has frequently been found normal or almost normal by various observers. I have made many estimations of the total nitrogen and ammonia in cases of cirrhosis of the liver, and have had the same results as others, even when death was not far distant. There is no question that the function is often maintained even when the changes in the liver are extremely advanced. It is probable that urea is in part formed normally in other tissues, and that these tissues assume most of the liver's large share of this function when that organ loses its powers, particularly when this occurs gradually from slowly advancing disease. It is also possible that a very small fraction of healthy liver tissue will suffice to carry on this function, as is the case with the pancreas in sugar metabolism; and the clinical aspect of the question is further complicated by the fact that the ammonia of the urine becomes greatly increased in almost all conditions in which marked acid intoxication is present, not because of any known difficulty in urea formation, but because the ammonia is needed to neutralize the acids and to protect the organism from their action. Acid intoxication occurs in many conditions in which liver disease is absent; and it probably appears, also, in many cases of grave disturbance of the liver function and in experiments in which the liver function is excluded. This has recently been quite clearly shown to be the cause of the increased excretion of ammonia in some cases, at least, of advanced liver disease (Schittenhelm), for ammonia salts administered by mouth yielded their ammonia in the urine as urea. This, of itself, suffices to make the urinary

ammonia at best an equivocal indicator of the urea-forming capacity of the liver.

There are several other facts connected with the metabolism of proteids that have suggested a possible means of attacking the question of the diagnosis of chronic liver disease. Proteids contain sulphur in complex combinations; and in the course of digestion this sulphur is largely oxidized and appears in the urine as sulphates, though a small fraction remains unoxidized, this fraction constituting the neutral sulphur of the urine. In many disorders of metabolism, particularly when there is pathological destruction of tissue and hasty elimination of half-formed excretory products, or when the oxidative processes are reduced in activity, an abnormal amount of sulphur escapes oxidation and is eliminated in the urine as neutral sulphur, and this fraction of the sulphur of the urine is, in such circumstances, relatively or absolutely increased. Considering the importance of the liver in metabolism, and especially its great oxidative activity, it is not surprising that this has frequently been observed in disease of the liver. There was no good reason to suppose, however, that this would be sufficiently confined to diseases of the liver or so conspicuous in such diseases as to make it important in diagnosis, and it is not important in this respect. With many others, I have found the neutral sulphur much increased when hepatic disease was absent, and it is often little, if at all, increased in liver disease, particularly when jaundice is absent, even if the lesion is severe and destructive. The neutral sulphur of the urine is not, however, furnished by one substance only, but by many, which differ more or less widely in their character and significance. The development of methods of studying these various fractions would furnish many facts of physiological interest, and probably of clinical value; and some of these might have special importance in connection with hepatic diseases. The technical difficulties in the way of complete studies of this kind are at present insurmountable; but there is one subfraction of the neutral sulphur that can be accurately estimated. Early in the course of the disintegration of proteid a portion of the sulphur is found in a combination such that it is easily split off from the proteid molecule, and can thus be separately estimated

—a fact that may prove to be of much importance in general physiological chemistry. A small subfraction of the neutral sulphur of the urine is usually found in this form, and this subfraction was found by Goldmann and Baumann to be increased in severe liver disease. The method used by these authors was, however, unreliable; and in several cases in which the liver was severely diseased, or in which oxidation processes were probably much reduced, I found (using the accurate method of F. N. Schultz) that this readily eliminable sulphur was not increased—an observation that accords with those of Petry and with the results of Lang's experiments. I think it probable that this portion of the sulphur of the urine is derived from the urinary tract; it seems, at any rate, to be of no importance in general metabolic disturbances except in rare conditions, such as cystinuria.

Abnormal proteid metabolism, in certain diseases of the liver, causes other changes in the urine, however, which have been known by physicians for years, and have had much significance, although we are just beginning to learn why these changes occur. It has long been known that leucin and tyrosin appear in the urine in acute destructive lesions of the liver, chiefly acute yellow atrophy and phosphorus poisoning, while they are rarely found in other conditions. The readiest explanation for this, that was apparent for many years, was that leucin and tyrosin, which are normally formed in the intestinal tract, are carried to the liver and are there transformed, by synthesis or catalysis, into other substances; and that their appearances in the urine in profound liver disease means only that the liver is unable to do its work, and, therefore, allows them to escape into the circulation and thence into the urine The work on autolysis in the liver, set in motion by Salkowski and Jacoby, together with the experiments of Jacoby on phosphorus poisoning and the observations of Alonzo E. Taylor and others in cases of acute yellow atrophy have made it seem extremely likely that this process of self-digestion explains their occurrence. Autolysis certainly takes place in the liver, and in other organs as well, after death, and it probably occurs in normal living organs to a moderate extent. It now seems fairly clear that in some circumstances these local self-digestive processes undergo pathological excitation. Whether

the immediate cause of this proves to be bacterial, toxic or other, we have good reason to believe that the most prominent lesions and many of the symptoms in acute yellow atrophy and in phosphorus poisoning are due chiefly to abnormally active autolysis, and that this explains the appearance of leucin and tyrosin in the urine. As I have stated, the liver during autolysis rapidly forms a relatively large amount of amido-acids (to which group of bodies leucin and tyrosin belong) as well as hexon bases and other products of advanced proteolysis. In acute yellow atrophy and phosphorus poisoning large amounts of these are produced, and, either because the crippled liver cannot carry out the further disintegration of such large quantities or their synthesis to more complex bodies, or because the other tissues that, perhaps, should do this part cannot, they are carried away from the liver and excreted in the urine. I mention these matters partly on account of their general interest and partly because they have a possible bearing upon less rapidly destructive disease of the liver. It must readily occur to one that the difference in this respect between acute yellow atrophy and some chronic destructive diseases of the liver is likely to be chiefly one of quantity rather than of kind; that abnormal amounts of amido-acids and of other products of the destruction of liver tissue are likely to reach the circulation in chronic liver disease; and that this might be of diagnostic importance if it does not occur too readily in disease of other tissues, and if these substances are not altered and made unrecognizable before they can be excreted in the urine.

The first difficulty in the way of such studies was the lack of suitable methods; but a method for the quantitative estimation of the amido-acids of the urine was quite recently furnished by Pfaundler, and a large number of observations of cases have since been made, chiefly by v. Jaksch, Ascoli and de Grazia, and Halpern, using this method or modifications of it. The results have not been extremely important, but they seem to me to have some suggestiveness. A number of cases of hypertrophic cirrhosis, for example, have shown an increase in the amido-acids, while there was no increase in many other instances of serious disease of other organs, such as chronic nephritis and

severe anæmias. An increase was observed in several diseases that do not conspicuously involve the liver (diabetes insipidus, typhoid fever, etc.), but in most of these instances diagnostic confusion with liver disease was very improbable. It is, however, on general physiological grounds, not to be expected that this will prove to be frequently of value; and certainly Pfaundler's method, while probably accurate, is not suited to clinical observations. A simpler and less tedious one would have to be found before this plan could be widely used, even if it were of value.

It remains for me to mention the possible diagnostic relation of the detoxicating function of the liver. We cannot, of course, even consider the propriety of administering extraneous toxic substances in order to study the influence of the liver upon them, even if it were possible to determine this; but nature requires the liver to destroy or antidote many of the toxic substances formed in the digestive tract and in the course of metabolism, and we can at least attempt to determine the extent to which the liver carries out this function.

I think it best to discuss briefly the significance of urobilinuria at this point, for, although there is no ground for the statement that the relation of the liver to urobilinuria belongs under the general heading of detoxication, the prevailing views concerning the source of urobilin bring this substance into close relation with the enterogenous decomposition products, which are in most part more or less toxic.

The source and the significance of urobilin have been discussed and experimented upon for years with great activity; but these questions are still far from being definitely settled, and even a brief sketch of all the suggestive work done upon them would involve too extensive a discussion. Certain salient points may, however, be mentioned.

It has been determined with almost final positiveness that in normal circumstances nearly, and possibly quite, all the urobilin formed in the organism is produced from bilirubin in the intestinal tract; and this almost certainly occurs chiefly through the action of bacteria. Normally, some of the urobilin thus produced is excreted with the feces, the pigment lending to them the chief

portion of their normal color. Some of the urobilin, the amount not being definitely known, is absorbed. A small portion of this is excreted in the bile, and another small portion in the urine; and it is probable that a more or less considerable portion is, somewhere in the organism, so transformed as to be lost sight of.

Under certain conditions the amount excreted in the urine increases to a noteworthy degree, lending to the urine a golden-brown or brownish color. These conditions are, chiefly: (1) during some of the infectious fevers; (2) after extravasation of blood or during the course of destructive diseases of the blood, such as pernicious anæmia; and (3) in many cases of disease of the liver. In the second of these three classes of conditions it is extremely probable that the urobilinuria is almost entirely due to the fact that the increased destruction of blood causes an increased formation of bile; and that, in consequence, more urobilin than the normal amount is manufactured in the intestinal tract. It is rather customary to attribute the urobilinuria of infectious diseases to the same cause, although this is, to a considerable extent, based upon assumption rather than upon fact. It is by no means impossible that the liver and, perhaps, other organs are concerned in it. The urobilinuria of hepatic disease is of uncertain significance and importance. The readiest explanation of its occurrence is that it is due to changes in the quantity or the quality of the bile flowing into the intestine, and consequent increased urobilin formation; and another possible explanation is that there are variations in the decomposition processes in the intestinal tract, some of these being associated with a larger product of urobilin than others. If the latter of these views, in particular, be correct, the urobilinuria in hepatic disorders is merely one of the indices of the conditions existing in the intestinal tract, in which case its relation to liver disease is of rather secondary importance.

In the main the other views concerning the origin of this urobilinuria are: 1. That normally the liver converts the urobilin after its absorption back into bile-pigment or otherwise transforms it, thus preventing its escape into the circulation and thence into the urine; but that under certain conditions the liver is unable to do this, and urobilinuria results. 2. That the liver itself,

in certain pathological conditions, produces urobilin. 3. That the other organs and tisues, particularly the kidney, may produce urobilin from bile-pigment.

There are a great many reasons for believing that the last two theories, although possibly correct in some instances and in a rather minor way, are not sufficient to explain many known facts. I do not believe, either, that mere changes in the character of the decomposition processes in the intestine constitute a sufficient explanation. In addition to other facts that speak against this view, I have, with Dr. Fife and Dr. Wile, made some observations that indicate its incorrectness. In sixty-three pregnant women, many of whom showed urobilinuria, sometimes of intense degree, we made a series of about one hundred and twenty-five observations of the urine. In each we determined the degree of urobilinuria and also the intensity of the reactions for indican, phenol, and acetone, when these were present; and, quantitatively, the ethereal and the preformed sulphates, the volatile fatty acids, the ammonia, and the total nitrogen. I have since made about fifty similar observations, chiefly in cases of chronic alcoholism with or without cirrhosis of the liver, and in other cases of early and late hepatic disease. Urobilinuria, when present, was usually found to be associated with an increase in some or all of the enterogenous decomposition products. Most commonly marked amounts of phenol were found with it, and somewhat less frequently abnormal amounts of volatile fatty acids. There was, however, no approach to constancy in the relations with any one of these decomposition products. Often, too, when several or all of the latter were increased urobilinuria was absent; and, on the other hand, an increase in any of these decomposition products was repeatedly found absent when urobilinuria existed. These variations were not due to changes in the condition of the bowels.

These results seem to me good evidence that the character of the decomposition processes in the intestinal tract is not the determining factor in the production of urobilinuria, even when actual disease of the liver is absent. It likewise seems probable that urobilinuria is not due to the entrance of an excessive amount of bile into the intestinal tract, except in cases of the

class due to excessive hæmolysis; for bile has some restraining influence upon the decomposition processes, while in the cases mentioned the products of decomposition were usually found in the urine in excessive amounts, and such conditions correspond better with decrease in bile than with excess. This latter point is not at all conclusive of itself, but, together with the fact that many of the actual diseases of the liver that are associated with urobilinuria may much more readily be thought to produce too little rather than too much bile, it leads one to consider it improbable that excess of bile produces this urobilinuria.

It is impossible to decide which of the remaining theories is the more satisfactory. Probably both are to some extent correct. It is known that there are variations in the quality of the bile, but we do not know how extensive these are or whether they actually cause marked variations in the amount of urobilin produced. It is known that the liver is actively engaged in transforming many substances that come to it from the intestinal tract; and it seems to me highly probable that it exercises this function with a considerable portion of the urobilin from the intestinal canal. The observations concerning the intestinal decomposition products that I have mentioned agree with those of Strauss and Philippsohn and some other recent investigators in indicating that the excretion of an excess of these substances is often an evidence of reduction in the detoxicating action of the organism rather than of increase in decomposition within the intestine; and this is particularly true when, as was noted in most of the cases referred to, there are no other recognizable signs of a noteworthy increase in the intestinal decomposition processes. It seems to me, then, probable that much of the urobilin normally meets the same general fate as does the major portion of the other decomposition products, and that its appearance in the urine in abnormal amount means that it has escaped this fate. If this is true, its transformation, whatever this transformation may be, probably occurs chiefly in the liver, for urobilinuria bears an undeniably close relation to hepatic disease.

In the confusion that exists concerning the exact causes of urobilinuria, it is, of course, impossible to determine its precise clinical significance. It is extremely common in cirrhosis and carcinoma

of the liver, and in various conditions associated with jaundice. In the latter instance it is particularly marked very early after the obstruction producing the jaundice has been set up; and also at a time when the obstruction has been partially or completely relieved, as well as for a considerable period after this. I have mentioned the fact that urobilinuria is also common in infectious diseases and in diseases associated with excessive blood destruction. It occurs, too, in a variety of other conditions in which it is not known that there is any disorder of the liver; for example, as I have indicated, it is common during pregnancy. If in these latter conditions it indicates hepatic disturbances, this disorder must usually be functional.

A temporary urobilinuria certainly has no known important significance, except in connection with internal hemorrhage and such conditions. If, however, urobilinuria is persistent and is unassociated with evidences of rapid hæmolysis, it justifies a strong suspicion of chronic disease of the liver; and in the absence of signs of biliary obstruction, of passive congestion (from cardiac disease, etc.), or of carcinoma, this disease is likely to be cirrhosis. In connection with a suggestive clinical history, urobilinuria in such circumstances assumes a larger degree of suggestiveness. Garrod refers especially to the fact that other pigments are not usually present with the urobilin when the urobilinuria is due merely to excess in hæmolysis, but that these pigments are present when hepatic disorder exists. He considers that hæmatoporphyrin, in particular, bears a close relation to disease of the liver.

The clinical determination of the presence of urobilin has always been somewhat troublesome, because the methods in use are rather clumsy. Schlesinger, however, has recently described a method that is extremely simple and, so far as I have tested it, seems to be satisfactory. It consists merely in adding to a small portion of urine an equal amount of a 10 per cent. solution of zinc acetate in absolute alcohol. The precipitate is then filtered or centrifugated off, and the clear fluid at once shows the usual green fluorescence due to urobilin and the characteristic absorption band. Schlesinger's observations indicate that the test is extremely delicate. The flourescence is seen with especial readi-

ness if the filtrate is illuminated by means of a pocket electric light.

Other substances than urobilin that are more distinctively related to the detoxicating function of the liver have received some attention in connection with diagnosis. I shall refer to these but briefly. It is known that the liver contains a larger amount of volatile fatty acids than do the other tissues, and that these substances are formed in considerable amount in the intestine and, perhaps, in the course of metabolism. It is not difficult, therefore, to conceive the idea that the volatile fatty acids may normally be arrested in the liver and destroyed, and that their excretion in excess indicates hepatic disorder. Strauss made some observations that led him to think this true, but, on further investigation, he dismissed this view. I have made many estimations of the volatile fatty acids in disease of the liver as well as in other conditions, and do not believe that they have any value in the diagnosis of hepatic disorder; nor do I agree with Rosenfeld in attributing to them diagnostic importance in gastric carcinoma or, in fact, in any other condition that I can now recognize, except as a general indication of excessive decomposition in the digestive tract.

A number of observers, especially several Italians, have recently attempted to give some dignity to indicanuria as an indication of hepatic disorder. This view has, at least, the justification that indicanuria, as I have already stated, probably often means that indol has escaped destruction by the liver or other tissues, rather than that it has been formed in excessive amount. Granting, however, the truth of this, there is little reason to attribute the indicanuria in any individual cases to disorder of the liver, for it readily occurs with comparatively slight digestive disturbance and, even in the absence of any definite disorder of digestion, it is found in a variety of conditions. Hence it is a very poor index of disorder of any special organs.

Rather more interest, I believe, may properly be directed to the excretion of phenol. It is known that the phenol formed in the digestive tract is in part antidoted in the liver by combination with sulphuric acid and glycuronic acid, and is in considerable part apparently destroyed by that organ. Excess of phenol

seems, too, to appear in the urine less frequently than does excess of indican, and in less varied disorders. It is common in some infectious diseases and in severe digestive disturbance; but I have been impressed with the frequency with which, in the absence of any noteworthy disturbance in digestion, I have found a large amount of phenol in the urine—often, but by no means always, in association with urobilin—in passive congestion of the liver, in chronic alcoholism with hepatic enlargement, or, at times, in cases of chronic alcoholism without definite signs of hepatic enlargement, and also in a number of cases that seemed to be probably early cirrhosis of the liver. Phenol was persistently present in large amount, even when these cases had been for some time on gentle purgation. In very far advanced cirrhosis I have frequently found it absent.

The excretion of phenol in the urine has been much less extensively studied than has that of indican, largely on account of the greater difficulty attending such observations; and it may be that the apparent suggestiveness of my experience would vanish with more extended study. At present I feel, at least, inclined to suspect disorder of the liver if, in the absence of noteworthy evidences of excessive intestinal decomposition, there is a persistent excretion of a large amount of phenol, especially in a case with a suggestive history. This unquestionably occurs, at times, when disorder of the liver cannot be definitely demonstrated to be present. It remains to learn whether it frequently occurs when there is actually no noteworthy hepatic disorder, functional or other. Even when marked gastro-intestinal disturbance is absent, I think it is not improbable that it does.

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SOME FURTHER EXPERIMENTS UPON RECTAL ALIMENTATION.

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In some previous contributions to this subject, in which we published the results of our own work and reviewed the literature, we emphasized the fact that reliable experiments on the absorption of nutritive enemas have, in the majority of instances, demonstrated that food administered in this way is very poorly absorbed, as compared with the results when food is taken in the normal manner, namely, by the mouth. The bulk that can be given by rectum is also small. Hence, the patient ordinarily obtains an extremely insufficent amount of food. As we have previously stated, we believe that in most cases the greatest value of rectal alimentation consists in furnishing fluid to the tissues. Patients occasionally appear to receive a good deal of nutriment in this way; but this is certainly the exception, rather than the rule.

The form of food that is apparently most imperfectly absorbed is fat—a most unfortunate fact, because a given weight of fat provides the organism with more than twice as much energy as does an equal amount of either proteid or carbohydrate. If even a moderate quantity of fat could be absorbed from the lower bowel and utilized by the tissues, a result of great importance in rectal alimentation would be thus obtained, owing to the high food value of fats. It seemed to us, therefore, to be worth while to attempt to find some method of artificially preparing fats so that a greater degree of absorption might be secured.

With this purpose in view, we carried out experi-

ments upon two different lines. 1. We tried to provide our fats in the form of a soap that would be easily prepared and administered, and to investigate its absorption when given by rectum. 2. We searched for a good emulsion of fat that would remain emulsified after its introduction into the bowel, and determined the extent to which it was absorbed.

The experiments with soap were undertaken on account of the insistent claim of Pflüger that practically all the fat taken into the digestive tract is split and is absorbed chiefly in the form of soap. It is not necessary to discuss the literature of this question or to attempt to determine here whether the evidence favors this view or that of Munk and his followers who believe that much of the fat is absorbed in emulsion, without being split. If, however, Pflüger should be right, and most, or even a large part, of the fat were split before absorption, it would be essential to provide for this splitting and soap formation in administering fats per rectum; and the customary method of administering native fats would, of course, be quite irrational, even though these were well emulsified. The possibility of administering soap for nutritive purposes by the lower bowel had, we think, never been investigated, and for this reason we undertook our observations. It also seemed that the method might yield some points of interest in relation to the theoretic side of the discussion between the Pflüger and the Munk schools.

The experiments with emulsions of fat were undertaken because the emulsions usually administered (milk and egg yolk), while, of course, excellent natural emulsions, are so entangled with a mass of easily coagulated proteid that they do not remain emulsions in the bowel for any considerable length of time. Much of the proteid, particularly that of milk, soon coagulates, carrying with it the fat, entangled in large clumps, in such form that it is practically impossible for it to be absorbed without further digestion. The emulsion used by us was chosen for the purpose of overcoming this difficulty. As we shall note later, it apparently did so; although it was not very satisfactorily absorbed.

In the experiments with soap, it was our purpose to secure a good quality of soap that would readily go into solution, and would contain no appreciable amount of free alkali; for the latter would, of course, irritate the bowel. If our method was to have any practical value, it was necessary to adopt some means of preparing this

soap that would permit of its being readily made under the conditions met in practice, and by persons without skill in chemic manipulations. After trying a variety of methods, we adopted the following:

A stock solution containing 500 gm. of sodium hydrate in 1,000 cc. of water was made; also a saturated solution of commercial sodium chlorid. The soap was made from oleic acid, as follows: 50 cc. of the sodium hydrate solution was taken and 100 cc. of water was mixed with it, this, of course, producing some warmth. To this, small portions at a time, and with vigorous stirring, was at once added 50 cc. of the oleic acid. The stirring was continued for one or two minutes. The soap produced was yellowish or brownish-yellow, and somewhat pasty, though capable of being well subdivided if energetically stirred. Directly after the stirring the fluid was decanted, and several hundred cubic centimeters of the sodium chlorid solution was added. The mixture was again thoroughly stirred, any clumps being broken up. During the course of this stirring the soap changed in character, losing its stickiness, and becoming finely granular and lighter in color, these changes being due to the partial abstraction of water by the salt solution. The salt solution was then decanted, and a fresh quantity of it was added, and the process was repeated. The fluid was again decanted, and a third washing was carried out. The soap was then washed once with half saturated sodium chlorid and drained as thoroughly as possible to free it of the sodium chlorid. It was then placed in a beaker and its bulk increased to 200 cc. with warm, distilled water.

A considerable portion of the soap at once went into solution, and the whole mass could be readily injected through a Davidson syringe. The entire course of the preparation of the soap took only about a half hour, and could be readily carried out by any one. The soap thus prepared was injected into a series of three dogs. The results of these injections, which were on the whole unsatisfactory, will be briefly mentioned.

In the experiments on dogs the soap was prepared as already stated, but after the sodium chlorid solution had been drawn off, and before water had been added, the whole mass was weighed, and a small portion (about 2 gm.) was taken to determine the amount of oleic acid present, using the following method, which may be rapidly carried out and is fairly accurate:

The portion used for the determination was weighed and placed in a small beaker. About 20 cc. of water was added, and then a small quantity of strong hydrochloric acid. The beaker was then placed in a boiling water bath until its contents were entirely decomposed (an hour and a half to two hours). The fatty acid was then found floating on top of a slightly opalescent liquid. The contents of the beaker were then allowed to cool and poured into a 50-cc. buret with a glass cock. The beaker was well washed out with small portions of ether, the washings

being also poured into the buret. More ether was added, until the buret was filled to near the top. The buret was then corked and repeatedly inverted, until the ether had taken up all the fat, this being shown by the entire absence of opalescence in the underlying fluid. The buret was then allowed to stand vertically for a few minutes, until the separation of the watery fluid from the ether was completed. The volume of the ether solution was read off, and all the aqueous solution was then run out, as well as a little of the ether solution, to wash out the cock. A known quantity (about 10 cc.) of the ether solution was then drawn out into a platinum dish. The ether was evaporated, and the contents of the dish dried at 100° C. and weighed. From the weight so obtained the amount present in the whole solution originally contained in the buret was computed.

With each of the dogs, soap solutions were made up as already described, and their bulk increased to 200 cc. with warm water. A third of this amount was given at each injection, two injections being given daily; one at about 10.30 a.m., and the other at about 5.30 p.m. The average amount of moist soap contained in the total 200 cc. of mixture was about 80 gm., and the average amount of oleic acid about 30 gm. Hence, in the individual injections, containing a third of the total, the dogs received 25 gm. to 30 gm. of the moist soap, and about 10 gm. of actual oleic acid.

The first animal was purged freely before the beginning of the experiment, and then starved for a day. After this, for six days, or until the completion of the experiment, he received nothing but rectal enemas of soap. The total amount of oleic acid that the dog had in this time was 108.98 gm. On the last three days of the experiment he was weighed, and was found to have lost in this time 681 gm.

The bowel movements during this time were saved. There were six of these during the period of the experiment. The first occurred on the second day of the experiment; it weighed 71.7 gm., and was firm and of normal appearance. The second occurred the same day; it was small and of pasty consistency, and weighed 18.2 gm. The third occurred on the fifth day of the experiment; it was small, hard, and well formed. The fourth occurred on the following day; it was well formed. The other two were very small, and occurred at the end of the experiment; they were of rather pasty consistency.

The feces were collected on the water bath. Hydrochloric acid was added and the whole mass was evaporated to dryness. The dry residue was weighed; and small weighed portions were boiled on the water bath with hydrochloric acid, dried, and extracted in the Soxhlet apparatus. The total fatty acid recovered weighed 5.556 gm.

This was, then, apparently only 5.1% of the total amount given; so the absorption in this instance seemed to have been remarkably good, fully equaling the absorption of fats when given by the mouth and, indeed, exceeding the ordinary absorption. During the course of the experiment the animal showed no evidence of irritation of the bowel, and seemed to be in entirely normal condition.

These results, however, we are obliged to consider more than questionable; because in two experiments carried out shortly afterward on other dogs, the soap solution evidently produced irritation of the bowel, the bowel movements were so frequent and large that there seemed to be very little absorption of the soap, and the results were obviously so unsatisfactory that these experiments were abandoned without completing the figures for the absorption. We also found at this time that the janitor, contrary to orders, had been occasionally cleaning the cages of these dogs. He had perhaps done the same with the first animal, although he denied this. It is possible that the first dog had actually absorbed the soap extremely well, and we saw no evidence of irritation as the result of its use. The results in the other two animals, however, were such as to make us conclude that it is not practicable to use the soap solution that we prepared, in attempting to nourish human beings by rectum; for it is probably too irritating to the bowel, and it was evidently poorly absorbed by most of the dogs. Whether the poor absorption was due chiefly to the irritation or to the nature of the substance, we cannot state.

This side of our investigations was then abandoned, as we were unable, after repeated attempts, to find any other method of making a soap that could be readily prepared for clinical purposes or would be unirritating.

The latter point is the one that is most difficult to overcome. With the soap solution mentioned, and with all others that we tried, as the soap goes more completely into solution, the reaction of the mixture becomes more and more alkaline—a result partly, perhaps, of the setting free of the alkali that has been mechanically entaugled in the small portions of soap; but partly, also, as the result of dissociation. The latter point cannot be overcome, and we now see no method by which it will be practicable to study the absorption of large quantities of soap from the lower bowel, without running the risk of producing so much irritation of the bowel as to interfere with the accuracy of the experiment. This would likewise interfere with the use of soap for the nourishment of human subjects. As to the question at issue between the Munk and the Pflüger schools, our observations furnish no satisfactory evidence bearing upon either side.

We pursued the question somewhat further however, by tying off two loops of small intestine in a dog; intro-

ducing into one loop egg albumin and egg yolk, the two being thoroughly beaten up together. Into the other loop the same emulsion was introduced, some of our soap having, however, been throughly incorporated with it. The dog was killed after 18 hours. In the loop containing only the egg, the absorption had been practically completed; in the other, there had evidently been irritation of the mucous membrane, a good deal of mucus being present, and the membrane being considerably injected. Little, if any, of the soap-egg mixture had been absorbed, although the exact amount absorbed was not determined.

Our observations on the absorption of artificial fat emulsions were undertaken, as previously stated, because natural emulsions are in large part quickly destroyed in the intestine; chiefly on account of the coagulation of the proteid. Hamburger has reported some experiments with dogs, using an emulsion made with soap, and introducing this emulsion into loops of intestine. He claims that the absorption of the fat, when emulsified with soap, was extremely good. We wished to avoid using soap, as our previous work made it seem likely that it would at least irritate the intestine and perhaps cause the expulsion of the enemas. We therefore made emulsions after the method devised by Moore and Rockwood, emulsifying the fat in a solution of alkali albumin. We first tested the method by taking white of egg, adding an equal volume of 0.5% sodium bicarbonate solution, warming on a water bath, and then adding the fat to this and shaking vigorously. We were readily able to confirm the statements of Moore and Rockwood that oils emulsified in this way remain in excellent emulsion for many days at least.

Owing to the readiness with which good butter fat is digested and absorbed, we at first attempted to make an emulsion of melted butter fat, but found that this preparation remains emulsified for but a short time at most. We carried out an intestinal-loop experiment with this emulsion of butter fat in alkali albumin, however, introducing into the large intestine of a dog 27.4 gm. of the emulsion, after having tied off the intestine at the ileocecal valve and at the rectum.

The emulsion was analyzed for fat by drying a weighed portion on sand in an evaporating dish, rubbing it in a mortar, and then extracting in the Soxhlet apparatus. For proteid, it was analyzed by Kjeldahl nitrogen estimations.

The dog was killed eight hours after the introduction of the emulsion, and the loop of intestine was then found to contain a large amount of fairly dry substance, of the same appearance as that introduced, except for the dryness and a somewhat darker color. There appeared to be quite as much solid material as had been introduced. The greater portion of this was expressed through one end of the loop, and the bowel was then well washed with warm water. The washings and the substance expressed were mixed, and portions were taken for Kjeldahl estimations, and the remainder for fat estimations.

It was found that we had introduced: Of fat, 6.386 gm.; of proteid, 1.107 gm.

We recovered: Of fat, 4.331 gm.; of proteid; 1.112 gm. Of the fat, therefore, there had been absorbed 2.055 gm., or 32.17% ; while there was no evidence of the absorption of any proteid, the amount recovered being even a little larger than that introduced—evidently owing to the excretion of nitrogenous material into the intestinal lumen. The absorption of fat, however was not wholly unsatisfactory.

We then made some observations with an emulsion made with alkali albumin and oil. The most readily available inexpensive neutral oils are olive oil and codliver oil. We chose the latter because olive oil seems clinically to have more tendency to act as a laxative, and we wished to avoid this effect. The absorption of the codliver oil was investigated in an intestinal-loop experiment in a dog, and it was also given to a human subject.

In our daily work the emulsion was made by taking the whites of nine eggs and an equal volume of 0.5% sodium bicarbonate solution, heating on the water bath, adding 100 cc. of codliver oil, and shaking thoroughly for about five minutes. The preparation so made remains in excellent emulsion for many days at room temperature.

In the experiment on the dog, we tied off a loop of the lower part of the jejunum, and in the same animal, a loop consisting of the entire lower bowel, except the rectum. Into the loop of small intestine, we introduced 10 cc. of emulsion; into that in the large gut, 5 cc. of emulsion. The operation was done at midday, and the dog was killed at the same time the day following, that is, after 24 hours.

The fat in the emulsion introduced was determined by drying two portions of 5 cc. each on kaolin for 24 hours, rubbing up the mass with sodium sulfate, and, after another 24 hours, extracting in the Soxhlet apparatus. The results of these estimations were as follows: 1. 2.276. 2. 2.294. Average, 2.285 gm. The nitrogen was determined by the Kjeldahl method, in two

portions, of 5 cc. each. The results for these were: (1) 0.0344 gm. (2) 0.0336 gm. Average, 0.340 gm.

The fat and nitrogen in the mass recovered from the two loops in the intestine were determined—the nitrogen by Kjeldahl estimations, and the fat by drying on sand, grinding in a mortar, and extracting in the Soxhlet apparatus. The amount of fat and proteid introduced into the two loops of intestine was as follows:

Into the small intestine: of fat . 4.570 gm.; of proteid . 0.680 gm.
Into the large intestine: " " . 2.285 gm.; " " . 0.340 gm.

The amount recovered was as follows:

From the small intestine: of fat, 2.884 gm.; of proteid, 0.238 gm.
From the large intestine: " " 0.844 gm.; " " 0.392 gm.

The absorption of fat from the small intestine, therefore, was indifferent; strange to say, it was much better from the large intestine. This, however, may have been due to the fact that the small intestine showed much irritation, containing a good deal of mucus, and exhibiting a considerable amount of injection. The very poor figures for proteid in the large intestine are, perhaps, due to the excessive amount of mucus found in the loop.

So far as our experiment goes, therefore, the figures for fat, with the lower bowel, are favorable; but the conditions in intestinal-loop experiments are so entirely abnormal that they do not seem to us to offer any real indications of the results that would be secured by introducing food into the normal intestine. Hence, the results in the following experiment while not extremely favorable, we consider to provide a much more satisfactory demonstration of the actual absorption per rectum that may be expected from artificial emulsions of fat made by the method that we employed.

The patient upon whom our observations were carried out, was a woman of 26, with persistent hysteric vomiting which had responded to no treatment. She was put on rectal alimentation in order to control the vomiting, nothing but the emulsion previously described being used. Salts were first administered, and she was well purged; then a cleansing enema was given. Every eight hours thereafter, we gave a third of an emulsion made as previously described, namely, with the whites of nine eggs, an equal volume of 0.5% sodium bicarbonate solution, and 100 cc. of codliver oil. This was continued for two days.

The bowel movements following the cleansing enemas were discarded during this time. Then for seven days the movements (which did not occur spontaneously, but were produced by cleansing enemas) were collected in an evaporating dish, small portions of sulfuric acid being added, and the whole evaporated until water-free. The movements evidently contained a large amount of fat, but they afforded an excellent demonstration of the persistence of the emulsion; as the contents of the lower bowel, when washed out nearly eight hours after the adminis-

tration of the emulsion, showed practically no free oil, all the oil present being in milky emulsion.

The urine of each day was likewise saved, and its nitrogen determined.

During the seven days throughout which the absorption was determined, then, the woman received 157.74 gm. of proteid, or 29.024 gm. of nitrogen. Of fat she received 700 cc. (of codliver oil), or 644 gm.

When freed of water, the feces contained so much oil that their consistency was syrupy. It was impossible, by ordinary methods, to carry out accurate fat and nitrogen estimations, of this mass; for, while most of it was syrupy, it contained a great many lumpy masses, and we could find no way of making it homogeneous. We therefore undertook the following somewhat laborious procedure:

The mass was extracted three times with alcohol, and was then filtered, The residue on the filter was well washed with ether, the ether being allowed to flow into the alcoholic extract. After draining, the residue was extracted twice with ether. The ethereal and alcoholic extracts were collected separately. The extraction was carried out on a large filter, under suction, and took several days. The residue was finally dried on the water bath, and ground, and the amounts of nitrogen and fat in this determined.

The fat in the ethereal extract was determined by running an eighth of the whole extract into a platinum dish, evaporating, drying, and weighing. It was free from nitrogen. The alcoholic extract was evaporated into a moderately thick syrup, and was well stirred, and portions were taken for fat extraction and for nitrogen estimations. A considerable amount of precipitate formed in the alcoholic extract before work with it had been begun. This was removed by decanting, and dissolved in water. It appeared to be resinous; and, since it was soluble in water and had separated from the alcohol-ether solution, it was assumed to be free from fat. The nitrogen in it, was estimated.

The results of these various estimations were as follows:

For fat:

In the dried feces	79.98 gm.
In the ether extract	35.70 gm.
In the alcoholic extract	339.79 gm.
Total	455.47 gm.

For nitrogen:

In the dried feces	17.881 gm.
In the alcoholic extract	1.259 gm.
In the resinous mass	1.334 gm.
Total	20.474 gm.

The patient therefore received 644 gm. of fat and excreted 455.47 gm., and hence absorbed 188.53 gm. in seven days, or 26.939 gm. per day, or 29.27% of the amount given. Of nitrogen she received 29.024 gm., and excreted in the feces 20.474 gm., and hence absorbed

8.55 gm. in seven days, or 1.221 gm. per day or 29.11% of the amount given.

The amount of nitrogen absorbed is much less than that excreted by persons who are on an extremely restricted and insufficient diet, and even much less than that usually excreted by those who are starving. It was, evidently, much too small an amount to prevent tissue loss. The quantity of fat absorbed was, however, fairly considerable, and was somewhat more than we found in the cases that we studied previously that were on predigested milk and eggs. The amount of fat absorbed was indeed larger than is thought possible by many students of this question. This furnishes some justification for the belief that the use of an emulsion that will not readily be destroyed in the bowel will result in a larger absorption of fat than will the use of milk and eggs, even when these are predigested.

Our results in this experiment offer some encouragement, therefore, for further attempts to improve the methods of preparation of nutritive enemas. At the same time it is evident that the amount of fat absorbed by this patient was, of itself, far too little to furnish the amount of energy necessary for even a person absolutely at rest; and if this method, or one developed from it, is to have any clinical value it will be necessary to devise some means of adding a considerable amount of carbohydrate in a form that will be capable of being absorbed in fair quantity, and also of adding proteid in a form capable of being absorbed in amounts sufficient to repair tissue waste. These are difficult practical problems. Our results with the oil emulsion, as detailed, while better than with predigested milk and eggs, were not very decidedly better, and an improvement upon them is very much to be desired. As to the carbohydrates, Reach's observation that dextrins are well absorbed, may prove to be of value, though the amount of dextrin that can be used will almost necessarily be too small to make up the deficit that will exist even with fairly good fat absorption. It seems, from our own previous observations and from a study of the literature, to be improbable that any proteid preparations that are available are capable of absorption from the lower bowel in amounts greater than 25 gm. daily, and usually the quantity will certainly be less than this.

On the whole, it seems possible that methods of preparation of nutritive enemas may be devised which will permit of the absorption of a total amount of food

having a daily value in calories of 500 to 700. This would, in view of the more recent observations on minimal metabolic equilibrium, particularly those of Chittenden, be sufficient in some cases to prevent loss of weight, for a considerable time at any rate. Whether this means maintenance of normal nutrition is, we believe, still doubtful; and at any rate, as we have previously shown, nutritive enemas, as at present given, are almost certainly rarely absorbed as well as this, and usually very much less well.

The functions at present served in most cases by nutritive enemas are, we believe, as follows: First and most important, to provide fluids and various inorganic salts for the tissues. 2. To provide perhaps a third to a sixth of the requisite amount of food. 3. To prevent the anxiety of friends and patient that would be produced by giving no food.

Whether the function of providing actual food will ever be increased, by improved methods of preparing or administering rectal enemas, to the point where it will be possible to prevent tissue loss in a large proportion of cases, even in emaciated patients who are absolutely at rest, we consider very doubtful.

Certainly those occasional cases in which nutrition seems to be well sustained or improved during the use of exclusive rectal alimentation cannot properly be used as examples of what one should frequently expect when using the methods now in vogue; nor are they even ideals which it will be generally possible to reach by improved methods. They are at present very exceptional, and they are likely to remain exceptional. It seems to us, as previously stated by one of us, that these unusual cases are probably due most commonly to reverse transport of the enemas past the ileocecal valve into the small intestine and their absorption there as under natural conditions; not to exceptionally satisfactory absorption in the lower bowel. This view has been very emphatically opposed by a number of prominent writers, who deny the possibility of the occurrence of true antiperistalsis. That, however, actual antiperistaltic transport of large quantities of substances past the ileocecal valve does at times occur in human subjects is, we believe, certainly demonstrated by cases previously referred to as well as by the cases since mentioned by Rolleston, in the American edition of the Nothnagel volume on Diseases of the Intestines; and experimental demonstration of the possibility that antiperistalsis may

result from the use of rectal enemas has been clearly given by Loewi, who was able both to see active antiperistalsis and to demonstrate in the small intestine considerable amounts of substances that had been introduced into the lower bowel, while lesser amounts were found even in the stomach and esophagus.

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THE DIETETIC USE OF PREDIGESTED LEGUME FLOUR, PARTICULARLY IN ATROPHIC INFANTS:

WITH A STUDY OF ABSORPTION AND METABOLISM.[1]

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AND

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Beans and other legumes have throughout many years past been occasionally recommended as useful in dieting infants, and in Germany especially they are said to be a constituent of a number of preparations of "Kindermehl." So far as we know, however, they have been given in a form in which it is impossible for even adults to take considerable amounts without tending to cause more or less digestive disturbance, particularly if they are given for some time; and statements concerning their effects in infants have been based almost entirely upon somewhat loose and casual observations of clinicians or upon the so-called experience of the laity.

The work that we are reporting was carried out partly in order to determine the possibility, in infants that have persistent difficulty in digesting milk proteids, of administering a useful quantity of vegetable proteid in a form suited to their digestion. We also investigated the question whether this proteid in its influence upon metabolism shows any important differences from milk proteids that are dependent upon the character of the proteid as distinguished from its digestibility and from the mere fact that it is proteid food.

Our results have shown the feasibility of successfully administering vegetable proteid to infants in considerable amounts and for at least a fairly long period. They also suggest that the favorable influence upon nutrition observed in a large proportion of cases is more largely referable to the character of the proteid that we used than to the amount, though this is a point that necessarily has in it an element of undemonstrable theory, and that can be provisionally accepted only after further control studies.

The investigation of the use of vegetable proteid in infants was undertaken at the suggestion of Dr. J. P. Crozer Griffith. The coincident consideration of the probable dependence of the nutri-

[1] Read by invitation before the Buffalo Academy of Medicine, December 13, 1904.

tional improvement that occurred in a large proportion of the cases studied, upon the character of the proteid, we based upon the following theoretical grounds: Native food proteids are of various kinds, the chief among them being albumin, nucleoalbumin, nucleoproteid, and a less important group most satisfactorily called albuminoids. Albumins, represented for example by egg-albumen, are distinguished by a series of reactions, but, for our purposes, particularly by the fact that they do not contain phosphorus compounds. Nucleoalbumins, conspicuously represented by casein, are especially distinguished by the fact that they contain phosphorus compounds, but do not yield any xanthin bases upon disintegration. Nucleoproteids, represented among animal foods most strikingly by various organs rich in cells, such as the pancreas and the thymus, but found also widespread in the vegetable kingdom, are distinguished chiefly by the fact that they contain a large amount of phosphorus compounds and do yield xanthin bases upon their disintegration. The albuminoids are represented by gelatins and a series of other substances which are of less specialized form than the substances mentioned above.

In human or other animal tissues the protoplasm of the cells is made up largely of albumin, in some cases of nucleoalbumins also; while the nuclei of the cells are formed chiefly of nucleoproteid. Adults receive in their food, in addition to albumin and nucleoalbumin, considerable quantities of nucleoproteid. It is not known how they manufacture the nucleoproteid of their tissues, but it is at least not improbable that the nucleoproteid of the food, or at any rate the nucleic acid that this nucleoproteid contains, is used for a part or the whole of this process. This would at any rate appear to be an economical method as compared with the wholly synthetic manufacture of nucleoproteid from relatively simple substances. In infants, however, the cell nucleoproteid must be manufactured, for the food contains no true nuclein, the proteids of the milk being entirely albumins and nucleoalbumins. If, then, the adult uses his nucleoproteid more or less directly in cell construction, the infant has in this point greater complexity in its metabolism than the adult; and it is possible that this is one reason that the assimilative powers of an infant are so much more subject to uncontrollable breakdown than those of an adult. It seemed possible, therefore, that when the assimilative functions are already incompetent it might be feasible to help the child by giving it nuclein in a form that would be readily absorbed without disturbing the digestion. The difficulties in the way of using animal foods for this purpose in noteworthy amounts are too great, but vegetables of the class of the legumes (beans, peas, lentils) contain extremely large amounts of nitrogenous substances and among these there is a considerable amount of nucleins. That starch can be given to infants in large amounts if predigested is known, and this fact has been used in a special manner by Keller, for example, with apparently very successful results. There was,

therefore, no evident obstacle in the way of the use of legume flour except the possibility that the proteid that it contains might disturb the digestion. Heating, however, causes much of this proteid to go into solution if it is finely ground, and, from a mechanical standpoint, the remainder would appear to be at least no more disturbing than the easily coagulated milk proteid. The practical effects of its use remained to be determined.

In studying this question we have given predigested bean flour to a series of infants, having first convinced ourselves, by the administration of small amounts of the bean flour, that it did not disturb digestion, and having also first studied its absorption and determined that this was, in the infants investigated, satisfactory.

We will discuss first the method of preparing the flour and the manner in which it was used, and then refer briefly to the studies of absorption and metabolism, subsequently discussing the clinical results.

We were unable to find on the market any satisfactory bean flour or pea flour. We, therefore, secured white kidney beans, dried them, and in our first experiments ground a few pounds of flour ourselves in an ordinary spice mill, removing the shell, and using only very fine flour secured by bolting; subsequently we had about two hundred pounds ground for us. It is essential that the flour should be finely ground in order that it may be subject to satisfactory predigestion, and also in order that the proteid may be properly absorbed. There has been much discussion of the question whether vegetable proteid is well absorbed or not (in adults). It seems probable that the correct answer to this question is that unfavorable results are due to the form in which the vegetable proteid is administered. The studies have usually been made with vegetables cooked in the ordinary manner, and in this form the proteid is enclosed in large part in a tough mass of cellulose. Rockwood has shown that, if administered free from cellulose, vegetable proteid is well absorbed. It is, therefore, important to see that the flour is finely ground. The object of predigestion was, of course, to convert the starch, the method of preparation having no effect upon the proteid excepting that due to the heat. In our work we usually prepare a 10 per cent. solution of predigested bean flour, first mixing the weighed or measured bean flour with water until made into a smooth paste, then adding more water until it can be easily stirred, and then heating in a double boiler at a good heat for fifteen or twenty minutes, stirring very frequently. During this time the flour of course swells and a 10 per cent. mixture of flour and water becomes a rather thick paste. It is then cooled to between 60° and 70° C., and the ferment is added and allowed to act for about ten minutes, stirring the mass frequently and loosening the portions that have adhered closely to the sides of the vessel so that they may undergo thorough digestion. Within a few moments after adding an active diastatic ferment the mass becomes perfectly

fluid and resembles a rather thin soup. After this, in order to stop the action of the ferment, it is brought to the boiling point; it is then cooled and is ready for use. The ferment that is to be used is largely a matter of choice, the only essential being that the ferment shall be active and in convenient form. We generally used cereo, sometimes maltine. Any of the other good diastatic ferments on the market would probably do as well. We have used the first mentioned chiefly because it is in very convenient form for this individual purpose and is very active. The nature of the mixture after the digestive process is past has not been investigated farther than to determine that there is little, if any, iodine-reacting starch present and that practically all the flour is in a fluid form. The proteid present would seem from the physical standpoint to be in a condition very suitable for absorption, for it is largely in solution, the solid particles that remain are few and extremely small, and it is impossible to bring down any coagulum by heating, while even strong acids precipitate the proteid only in the form of fine flakes.

In using this preparation with infants we have done as follows: A quantity of the infant's milk mixture approximately equal in food value to the amount of bean flour that we were about to add was discarded and was replaced by 10 per cent. solution of bean flour. For example, with a 3.6.1 milk mixture, the 10 per cent. bean flour is somewhat less than a direct equivalent of an equal quantity of the milk mixture; therefore, in such a case we gave the food as follows: if the child was receiving 48 oz. of 3.6.1. per day this was reduced to 36 oz., and 15 oz. of 10 per cent. bean-flour solution was added; the child therefore got 51 oz. a day, but received about the same energy value (actually slightly less) in its food. In a good deal of the work bean flour was not added at one time to the total quantity of the day's food, but was kept separate and a proper amount was added to each feeding. For example, with previous feedings of 4 oz. of 3.6.1. mixture the child was now given 3 oz. of 3.6.1. and 1¼ oz. of 10 per cent. bean-flour solution. In almost all our work with infants the feedings contained 2.5 per cent. to 3 per cent., at most, of bean flour. From the determinations that we made of the nitrogen in the flour, which will be mentioned immediately, we found that 3 per cent. of bean flour meant about 0.65 per cent. of proteid.

We made, in all, five analyses of the nitrogen in the bean flour. They resulted as follows: I., 3.447 per cent.; II., 3.448 per cent.; III., 3.394 per cent.; IV., 3.559 per cent.; V., 3.327 per cent.; the average being 3.435 per cent. of nitrogen, or 21.468 per cent. of proteid.

In our absorption work we used diapers made of rubber tissue, large wads of absorbent cotton being placed over the genitals to avoid any mixture of the urine with the feces. By this method we could collect the feces on the rubber diapers with entire success and without loss. The only difficulty that we had was that in one instance, when the observations were continued for ten days, the

child had rather marked irritation of the skin about the buttocks. In the one instance in which we did a complete nitrogen metabolism experiment in an infant, we collected the urine by introducing the penis into a piece of rubber tubing, strapping the tubing on with adhesive plaster, the lower end of the tubing discharging into a vessel which collected the urine. In the metabolism experiment in an adult we followed the customary methods. In the case of the infants the nitrogen in the food was determined each day. In the experiment with the adult we used a diet containing substances of which we had many times estimated the nitrogen-content ourselves, or which have a well-known and practically constant nitrogen-content.

The results of our absorption experiments in infants were as follows: Case I. was a boy, aged six months when studied, who had been in the house three weeks, and in this time had gained and lost repeatedly an ounce or two at a time. When the study was begun he weighed six pounds fifteen ounces. He had usually three soft bowel movements daily that were fairly satisfactory. In the preliminary period of study the child received 4 oz. of 4.7.2. mixture every three hours. This period of study was three days in length. The child was then put on 3 oz. of 4.7.2. mixture and 1¼ oz. of 10 per cent. bean-flour solution every three hours, and the absorption was studied for a period of six days following. In the two periods the conditions of nitrogen absorption were as follows:

Preliminary Period.		Bean-flour Period.	
Received in three days	8.601 gm.	Received in six days	19.111 gm.
Average daily	2.867 "	Average daily	3.185 "
Excreted in feces in three days	0.503 "	Excreted in feces in six days	1.203 "
Average daily	0.167 "	Average daily	0.200 "
Absorption in three days	8.098 "	Absorption in six days	17.908 "
Average daily	2.699 "	Average daily	2.984 "
Absorption of the intake	94.2 %	Absorption of the intake	93.7 %

The second case was studied at the same time and in the same way. The same amounts of food were given in both periods, but the child vomited about two ounces after one feeding; therefore, the intake in the preliminary period was slightly less than in the first case. This child was four months old when studied; had been in the house six weeks, and had varied between six pounds thirteen and one-half ounces and seven pounds three ounces, and showed the latter weight when the bean flour was begun. There were three or four bowel movements daily, which were yellow, quite well digested, but contained a little mucus. The conditions of nitrogen absorption in this case were as follows:

Preliminary Period.		Bean-flour Period.	
Received in three days	8.422 gm.	Received in six days	19.111 gm.
Average daily	2.807 "	Average daily	3.185 "
Excreted in feces in three days	0.415 "	Excreted in feces in six days	0.548 "
Average daily	0.138 "	Average daily	0.091 "
Absorption in three days	8.007 "	Absorption in six days	18.563 "
Average daily	2.667 "	Average daily	3.093 "
Absorption of the intake	95.1 %	Absorption of the intake	97.2 %

In these two cases the absorption was very good in both periods. In the first case there was only a fraction of 1 per cent. difference in the two periods; in the second case absorption during the bean-flour period was better than during the preliminary period. These figures show that in these children the bean proteid was fully as well absorbed as the milk proteid, and both were extremely well absorbed.

In another child we investigated both absorption and metabolism while bean flour was being given. We had no opportunity to study a control period when the child was taking only milk. The figures for the period of investigation, which was five days in length, are as follows:

Received of nitrogen in five days	14.430 gm.
Average daily	2.886 "
Excreted in feces in five days	1.844 "
Average daily	0.368 "
Absorption in five days	12.586 "
Average daily	2.517 "
Absorption of the intake was therefore	87.92 %

This child's urine was studied daily, with the following results:

First day	0.3192 gm. nitrogen.
Second "	0.2240 " "
Third "	0.1092 " "
Fourth "	0.1041 " "
Fifth "	0.3032 " "
Total in five days	1.0597 " "
Average in one day	0.2119 " "

The nitrogen in the food was	14.4305 gm.
" " feces "	1.8441 "
" " urine "	1.0597 "
Total loss through excretions was	2.903 "
Total retention was	11.527 "
The retention of the intake was	79.87 %

Whether these figures relating to the child's metabolism are wholly reliable or not cannot be said. Some studies of infants in the first few weeks of life have shown extremely high grades of nitrogen retention as compared with those that are observed in adults, even exceeding the retention shown by our figures in this case. This is natural because of the very rapid growth of their tissues at that period, but 79.8 per cent. of retention is so astonishingly high for an infant of the age of our subject that we cannot help suspecting that some of the child's urine was lost. If it was, we could not discover it, a careful watch having been kept on the apparatus regularly without any evidence of loss of urine at any time during the experiment. We do not feel, however, that the figures for metabolism can be further commented upon than to say that if they are correct they show most unusually favorable conditions, particularly for an atrophic infant. The figures for absorption are much poorer than those in the other children and

are not very satisfactory. This was expected in this child, as he came in with a good deal of digestive disturbance, with about five movements daily, which were greenish and contained many curds. The bowels improved after his admission, but this study was begun soon after he came in, when there was still some digestive disturbance.

The further study that we made of metabolism and absorption was carried out in an adult patient, a subject of phthisis. This man had been on a very free diet, having had three meals a day and as large a quantity of milk and raw eggs in addition as he cared to take. He had been gaining quite rapidly in weight on this diet, and his general condition had improved. Because his previous diet had been a very heavy one, we put him, in both the preliminary and bean-flour periods, upon a very free diet as to quantity. In the preliminary period this consisted of milk 2400 c.c.; rice, 30 gm.; eggs, eight daily; bread, 300 gm.; butter, 60 gm.; sugar, 30 gm.; steak, 200 gm.; baked potato, 70 gm. In the bean-flour period the diet remained the same, excepting that the milk was reduced by 550 c.c. each day and in its place he was given each day a solution of predigested bean flour which contained 100 gm. of (dry) bean flour. The nitrogen in the food was estimated by weighing accurately each portion of the food and calculating the nitrogen from the weights. We have ourselves made a large number of nitrogen estimations of the bread, milk, butter, and steak used in the hospital in previous metabolism experiments that we have carried out, and we took the average of these figures for these foods. The nitrogen of the eggs and rice, which is very constant for a given weight, we took from the tables of König and Blyth. The nitrogen excreted in the urine was estimated daily. That of the feces was estimated in the total amount after the feces had been collected throughout the proper period, dried on the water bath (sulphuric acid having been added) and then ground fine. One detail of the work on the feces may be of some interest to investigators in this line. We have repeatedly had the experience, as we had in this instance, of finding that feces contained so much fat that it was impossible to grind them fine after drying them, or to get a homogeneous mixture by occasional stirring while they were drying. We have in some instances overcome this by extracting with alcohol and ether, then drying and grinding the residue and making nitrogen (and when desired, fat) estimations of both the residue and the alcohol and ether extracts. This burdensome procedure, however, proved unnecessary in this instance, and very good results in control estimations were obtained by first extracting with alcohol and ether, then grinding the residue fine after drying it, and then adding the alcohol and ether extracts again to the ground residue and evaporating as quickly as possible, with constant stirring so as to keep the mass thoroughly mixed. In this way a homogeneous mixture was

obtained, and it could also be ground in a mortar much finer than it could before. Control estimations of the nitrogen corresponded very closely.

The results in this case were as follows:

PRELIMINARY PERIOD.

	Nitrogen in the Food.	Nitrogen in the Urine.
October 31	33.0347 gm.	25.4710 gm.
November 1	33.7943 "	23.1336 "
" 2	32.7100 "	22.1450 "
" 3	33.1116 "	21.0112 "
" 4	32.2051 "	25.5780 "
" 5	33.1345 "	18.8160 "
" 6	32.1041 "	21.1232 "
Total	230.0043 "	157.2780 "
Average	32.8577 "	22.4682 "

The total nitrogen in the feces in this period was 12.1866 gm.; the average daily excretion in the feces was 1.7409 gm. The combined urinary and fecal nitrogen in the whole period was 169.4646 gm.; and the daily average excretion was, therefore, 24.2092 gm. Since then the daily average in the food was 32.8577 gm., the average daily retention was 26.3 per cent. of the intake. The absorption of nitrogen was 93.7 per cent. of the intake.

BEAN-FLOUR PERIOD.

	Nitrogen in the Food.	Nitrogen in the Urine.
November 7	30.3704 gm.	22.3264 gm.
" 8	27.5247 "	17.1888 "
" 9	28.6844 "	23.7832 "
" 10	30.7284 "	21.7140 "
" 11	32.4540 "	18.2864 "
" 12	33.2469 "	22.9600 "
" 13	33.9411 "	17.3600 "
" 14	33.2166 "	29.9880 "
" 15	32.9460 "	21.7728 "
Total	283.1125 "	195.2796 "
Average	31.4569 "	21.6977 "

The nitrogen in the feces in this period was 17.0581 gm.; the daily average was 1.8953 gm. The combined urinary and fecal nitrogen was 212.3377 gm.; the daily average excretion was 23.5937 gm. The daily average in the food was 31.4569 gm. Hence, the average daily retention was 7.8639 gm. and the total retention was 70.7748 gm., which was 24.9 per cent. of the intake. The absorption in this period was 94.0 per cent. of the intake.

These figures for metabolism are, therefore, somewhat against the bean flour, since the retention, which was high in both periods, was about 1.5 per cent. better in the preliminary period than in the bean-flour period. The conditions in the early part of this experiment were, however, not satisfactory, for we met the same difficulty that has been noted many times before in attempts to administer legumes as ordinarily cooked, over a considerable period con-

tinuously; that is, after the first few portions, the man objected so greatly to the taste that it was almost impossible for him to take the beans. He made a willing effort to do so, however, and succeeded; but it upset his appetite so much that he was unable to take the proper amount of the other food, as is readily seen by referring to the table for the food nitrogen in the bean-flour period. These figures drop decidedly on the first day, and much more in the next two days; rising again on the next day, and reaching the proper point on the fifth day. The explanation of these figures lies in the point noted; in the first three days it was impossible by any of the means that we used to flavor the beans so as to make them agreeable. The rise in food nitrogen on the fifth day was coincident with the use of cinnamon as a flavor; this was agreeable to the man, and subsequently throughout the period of investigation and a long period afterward he took the predigested bean flour in his milk with entire satisfaction. The last five days of the experiment, therefore, offer a fairer comparison with the preliminary period than does the whole bean-flour period. The figures for these five days are as follows:

Average daily food nitrogen	33.1609 gm.
Average daily urinary nitrogen	22.0534 "
" " fecal "	1.8953 "
Total excretion daily	23.9487 "
Average retention (27.4 % of the intake) was	9.2122 "
Absorption of the intake was	94.2 %

The figures in this part of the bean-flour period are, therefore, 1 per cent. better as regards nitrogen retention than in the preliminary period, and almost 3 per cent. better than in the total bean-flour period. The figures for absorption in this period are very slightly below those in the preliminary period, but the figures for absorption in all three of these periods are so similar that they provide sufficient evidence that this man absorbed the bean nitrogen practically as well as the nitrogen from the milk, eggs, steak, and bread. All were absorbed very satisfactorily, particularly considering the very large food intake.

We cannot draw very definite conclusions from this experiment excepting to say that the bean proteid was quite as satisfactory as the other proteids in its influence upon metabolism. In the last part of the bean-flour period it seemed to have a slightly better effect upon metabolism than the other proteids, though the difference is so slight that little weight can be laid upon it. We could not expect much difference, however, even if nuclein has a noteworthy influence upon proteid metabolism as compared with the influence of other forms of proteid, for this man was already getting some animal nuclein in his food. The experiment serves chiefly to demonstrate the entire metabolic suitability of a large quantity of

legumes in maintaining a large nitrogen retention, and also the satisfactory absorption of the proteid in the legume. The last result directly supports the view previously referred to concerning the absorption of vegetable proteid, and the results with metabolism also support the observations that have been made in considerable number, in adults, in regard to the influence of vegetable diet upon nitrogen metabolism, most such experiments having demonstrated the ready possibility of maintaining a nitrogen equilibrium and of sometimes producing a nitrogen retention, on a vegetable diet. This was usually done, however, by using vegetables cooked in the ordinary manner. The preparation that we used has the advantage of being an extremely concentrated food containing a very high energy value for its bulk and it is at the same time in fluid form. It is, therefore, in these points an excellent food for improving the nutritive condition when it is impossible to take a large bulk or to take solid or semisolid food in considerable quantities. The chief difficulty with it, and one that has as yet been hard for us to overcome, is the flavor, which is distasteful to most adults and older children from the beginning, or soon becomes so. Infants take it without trouble in practically all cases after one or two feedings, but it is difficult to persuade older children and adults to do so. Attempts to accomplish this become largely a question of flavoring, but when flavoring ingredients are necessary over a long period of time a great variety must be used or they too become distasteful. This limitation of the usefulness of this food in older persons may, therefore, remain permanent. The point cannot now be settled.

In infants, however, our clinical results up to the present have been such as to encourage us decidedly. We have not as yet used it in a very large series of cases, as our attention has been chiefly directed to the determination of its influence upon absorption and metabolism, and during this particular period of the year we have not had a large number of cases available for study. Those that have been studied are the following: nine in the service of Dr. Griffith at the University Hospital; five at the Seashore House at Atlantic City studied through the kindness of Dr. William H. Bennett; one private case of Dr. Charles H. Schoff. In these cases the gentlemen who had charge of the cases, or their assistants, usually the latter, prescribed the diet, excepting only that we suggested the amount of bean flour to be used. Another series, that could be studied for only a brief period, was seen at St. Christopher's Hospital. The results in the first fourteen cases, briefly abstracted, are as follows, first mentioning the least favorable cases:

CASE I.—J. P., aged five months; weight ten pounds nine ounces. Treated at Children's Seashore House, Atlantic City. Lost weight for ten days continuously, but slowly. Then weighed ten pounds four ounces. Had been on Meigs' mixture, then on partially peptonized milk. Was put on whey upon the appearance

of decided acute digestive disturbance, in which the stools became green and contained mucus and curds and occasionally a trace of blood. This continued and he was put by one of the residents on three parts of Meigs' mixture and one part of 10 per cent. predigested bean flour, giving three ounces of this mixture every three hours. No noteworthy change occurred in his condition, and after ten days he was taken home, having lost in all one pound from the time of his admission. In our view this case was at this period an unsuitable one for this food or any other except the most dilute.

Case II.—L. C., a girl aged ten months; weight nine and one-half pounds. Admitted to Children's Ward, University Hospital, with three or four greenish stools daily, containing curds. No acute disturbance. Put on barley-water for twenty-four hours. Then on a 3.6.1. mixture, three parts; 10 per cent. bean-flour solution, one part; five ounces being given every three hours.

The stools rapidly became normal and the child in ten days gained exactly a pound. At this time it developed fever, cyanosis, and rapid respirations. There was no digestive disturbance for five or six days after the onset of this acute illness, when a mild diarrhœa developed and the child one day vomited. The diet was then changed to a plain milk mixture without any noteworthy change in the condition of the digestion; the cyanosis and rapid respiration also continuing. This child died after continued illness. This case is mentioned among the unfavorable ones because one or two of those who saw the child thought that the bean flour was responsible for the acute illness. We personally felt that the attack was not originally a digestive one at all, but was probably due to an obscure bronchopneumonia. Autopsy showed numerous pyæmic abscesses of the lungs originating in middle-ear disease. This case cannot be used for or against the bean flour, though the child temporarily gained very rapidly on the mixture containing bean flour.

Case III.—J. O., aged three months; weight eight pounds one ounce. Admitted with greenish stools containing curds; five movements daily. This child was the one mentioned as having been studied as to both absorption and metabolism. After one day of barley-water, the child was put on three parts of 4.6.2., one part of 10 per cent. bean-flour solution; why the diet was increased suddenly to this point is not recorded. In the next six days the child gained six ounces; it had never gained as much before. The bowel movements after the first two or three days became soft, yellow, and contained no curds, but there were three or four movements a day. In the following nine days he gained but one ounce more and the bowels were the same. On October 4th he had not gained further and the mother took him home. A more gradual increase in the food might have been more successful.

The others of the cases that were treated at the University Hospital and at Atlantic City are all more or less favorable. We will mention first the University Hospital cases and then the Atlantic City cases.

Case IV.—Girl, aged four months; weight six pounds thirteen and one-half ounces. This child was the second of our absorption studies. She was admitted having three or four movements a day; they were yellow, half-formed, contained a little mucus. She had lost weight gradually since birth, and had at no time gained; was extremely emaciated and weak. Upon admission she was put on barley-water, followed by Keller's malt-soup; after a week this was changed to a simple milk mixture, containing barley-jelly, which was afterward malted. As the bowels improved, the milk mixture was increased to a 4.7.2., containing malted barley-jelly. Throughout six weeks her weight had varied, with slight rises and falls, between six pounds thirteen ounces and seven pounds three ounces. Bean-flour solution was then added to the 4.7.2. mixture; her weight at this time being seven pounds three ounces. Six days later our bean flour gave out; at this time she weighed eight pounds. She continued gaining after this for four weeks, when she weighed nine and one-half pounds, a simple 4.7.2. mixture having been used during this time. She then lost half a pound in a week, and regained it only very gradually in the next three weeks. This was at the beginning of summer, and her slow gain was thought to be due to hot weather and "hospitalism," and she was sent to the seashore.

Case V.—The first of our absorption experiments. Was admitted with three to five stools daily that were greenish and loose. He was six months old; weighed six pounds fourteen ounces. He was much emaciated and weak. He was put on barley-water and then on weak milk mixture; gradually increased as the bowels soon became nearly normal to a 4.7.2., which was ordered eleven days after he was admitted. Eighteen days after admission his weight was six pounds fifteen ounces, there having been only slight fluctuation in this period. He was then given bean flour in the 4.7.2. mixture. Six days later, when the flour gave out, he weighed seven pounds fourteen ounces, the bowels remaining the same. Afterward, on a simple 4.7.2. mixture, he gained gradually, in five weeks, to nine and one-half pounds. He was then taken home in satisfactory condition and was lost sight of.

Case VI.—L. D., aged four months; weight six pounds; very weak. Admitted with mild digestive disturbance; three to five stools daily, which were yellow and partly formed, but contained some curds. Put on barley-water, then on dilute milk mixture, gradually increased. Five weeks after admission was given 4.7.2. mixture. The child was then having two or three movements a day, which were yellow and quite well digested, but there had been

no gain. Six weeks after admission was given bean-flour solution in the 4.7.2. mixture. Four days later she weighed eight and one-half pounds. Was taken home just after this, weighing eight pounds nine and one-half ounces. Readmitted a week later with loose, greenish stools, and having lost half a pound; she had been on a simple milk mixture outside the hospital. Was put on barley-water, then on her previous milk mixture, and gained half a pound in five days. After this stayed stationary for a week and was then given bean-flour solution again, in her milk mixture, and gained a half-pound in four days, and a quarter of a pound in the next five days, and was again taken home in satisfactory condition, weighing nine and one-quarter pounds. The gain in this case when bean-flour solution was first given was almost incomprehensible. At each weighing before this time the record had been within an ounce or two of six pounds. At each weighing after five days of bean-flour solution the record was regularly above eight and one-half pounds. She was carefully weighed by the nurse, the resident physician, and by one of us, all records agreeing. The scales may have been at fault, but they were correct when tested afterward. If the gain was as recorded it was certainly not all due to increase of tissue, for in all her food during this time she received a little less than enough solids to have made this gain if all had been deposited in the form of tissue. Hence, some of it must have been retention of water. Water retention, however, is a very desirable thing in most atrophic infants, as their tissues are usually very abnormally dry. Whatever may be said of the weight records, the improvement in the child's condition was perfectly astonishing; within four days she became a wholly different-looking infant, and she retained her improvement.

Case VII.—Girl, aged thirteen months; weight eleven pounds, one ounce; very ill-nourished and weak. Admitted with five or six greenish stools daily, which contained mucus. Put on barley-water and then on a milk modification which was increased to 4.7.2. mixture, although the stools remained about the same. She gained a half-pound in the first ten days; then remained stationary for a week. Was then put on bean-flour solution. The bowels improved, but the movements still remained greenish and loose for a week, and in this time she lost a half-pound. From this period on, however, the bowels rapidly improved and soon became normal, and in the next three and one-half weeks she gained one and one-half pounds, and was discharged weighing one and one-half pounds more than when admitted, her bowels for two weeks having been entirely normal.

Case VIII.—C. B., girl, aged six months; admitted weighing seven and one-half pounds, with three or four greenish, half-formed movements daily. Put on barley-water for twenty-four hours, followed by simple milk modification. Bowels did not improve,

and the child lost a half-pound in four days. Bean-flour solution was then added. The bowels within three days became normal, and in ten days the child gained slightly over a half-pound; in five days more another half-pound; in three days more another half-pound. Was discharged, with normal bowels, weighing eight and one-half pounds.

CASE IX.—D. L., boy, aged seven months. Admitted weighing nine pounds, with four or five movements daily, which were green and contained mucus and an occasional trace of blood. Put on barley-water, then on milk mixture; the bowels improved at first, but after three days remained stationary, continuing loose and greenish, with some mucus. Nine days after admission the child was on a 4.7.1. mixture; weighed nine and one-half pounds, but had been stationary for nearly a week. Then bean-flour solution was added; three days later the bowels were recorded as nearly normal, the child still weighed nine and one-half pounds. Six days later had gained a half-pound; four days later another half-pound; four days later than this another half-pound. Was discharged in satisfactory condition.

CASE X.—K. D., boy, aged nine months; weight twelve pounds; ill-nourished and weak. Three to five yellowish stools daily, containing curds. Put on barley-water and then on milk mixture, which was increased to 3.6.1. mixture and afterward up to 4.7.2. He had gained three ounces in five days. Wheat flour, predigested as the bean flour had been, was then added. The child gained four ounces in four days; then remained stationary for three days. Then predigested bean flour was substituted, and in the next three days there was a gain of nine ounces; in the next week four ounces; in the next week twelve ounces. Was discharged weighing fourteen pounds. The bowels had improved on the milk mixture and remained in good condition with the use of both wheat flour and bean flour.

The following four cases were treated at Atlantic City, by Dr. Wm. H. Bennett and Dr. Sidney Repplier:

CASE XI.—E. W., girl, aged seven months; weight fourteen pounds four ounces. Stools fairly normal; weight decreased regularly for a week, during which time she lost half a pound. At that time the bowels became loose, contained mucus, and were greenish. She had been on Meigs' mixture. To this was added, through a misunderstanding, over 4 per cent. of bean flour, with the result that vomiting occurred after every feeding. She was then put on peptonized milk and two days afterward was put back on Meigs' mixture containing $2\frac{1}{2}$ per cent. of bean flour. Her weight was then thirteen pounds; stools greenish and contained mucus and curds. One week later had lost four ounces, but the stools were improved. Three days later gained two ounces, stools much improved. One week later gained five ounces, stools normal;

four days later gained five ounces more, stools normal. Was then taken home in good condition.

Case XII.—Boy, aged five months; weight ten pounds eight ounces. Stools greenish and loose. Lost on Meigs' mixture six ounces in a week. Was then given 2½ per cent. bean flour in Meigs' mixture. Three days later stools much improved, had lost two ounces; three days later stools normal, had gained four ounces. Was then taken home by the mother.

Case XIII.—A. E., aged seven months; weight twelve pounds; stools greenish, with curds. On Meigs' mixture, from July 1st to 26th, lost a pound. Bowels remained bad. Put, through misunderstanding as in the first case, on excessive amount of bean flour, getting over 6 per cent. Vomited occasionally for a day. Amount of bean flour reduced to 2½ per cent. Vomiting stopped at once, stools improved rapidly. Three days later stools normal excepting for a little mucus; had gained nine ounces; three days later had gained seven ounces more. Stools normal. Developed chicken-pox and was sent home.

Case XIV.—E. H., aged six months; weight eleven pounds four ounces; stools normal. Gained four ounces in a week; stools then became loose, and contained a little mucus. Lost six ounces in ten days. Had been on Meigs' mixture. Then bean-flour solution added. Gained four ounces in three days; stools improved. Gained ten ounces in the next five days; stools normal. Discharged in good condition.

In addition to these cases there were treated at St. Christopher's Hospital, in the service of one of us (Edsall), thirteen infants (Cases XV. to XXVII., inclusive), who for a short time got milk mixtures containing predigested wheat flour or predigested bean flour, the wheat flour having been used at first because bean flour could not be secured at that time. Unfortunately bean flour was obtained only a very short time before the term of duty on this service was ended, and hence these observations are of little value. They serve chiefly as a contrast between the effects of wheat flour in these cases and of bean flour in the cases that have already been detailed.

Of the thirteen cases, six were treated with mixtures containing predigested wheat flour, but got no bean flour, receiving the wheat flour in various cases for from ten days to three weeks. Five of these six lost persistently; one gained nicely from five pounds twelve ounces to six pounds twelve ounces in ten days, after having lost for the preceding ten days. The bowels in this case remained slightly loose. Three other infants got wheat flour for from ten days to two weeks, one gaining a few ounces at first and then losing, the others losing persistently. When bean flour was secured all these three were apparently near death, and all ultimately died; but upon the use of bean flour one held its weight for a week and then rapidly lost, while the others gained four ounces each in the first

three days, and then died unexpectedly without any new symptoms. In all these cases the bean flour seemed to be well digested, and in all of them the bowel movements became more satisfactory under its use. Two other infants that had been on predigested wheat flour showed decided improvement of the bowels under bean flour, but were sent to the seashore in three days after its use without any record of their weight at the time. Another child had lost rapidly on predigested wheat flour and showed no gain on bean flour, though it held its weight for a week, when it suddenly died. It seemed *in extremis* when bean flour was started. Another child came in with a mild acute enterocolitis. It got barley-water for forty-eight hours, then whey, afterward whey and albumin-water alternating. The bowels remained persistently bad for a week, and the infant lost a pound. It was then given whey with 1½ per cent. of fat added and 2 per cent. predigested bean flour. The bowels became normal almost at once, and the infant gained a pound and a quarter in three days, and was taken home by its mother and lost sight of.

In none of these cases, excepting the last, was the child in a condition that permitted of any special hope from any treatment at the time that bean-flour solution was started. The results with wheat flour (that was given in almost the same form that Keller gives it in his malt-soup; though it was digested with another ferment) were very unsatisfactory in eleven out of twelve instances. One child, as stated, showed rapid improvement, but the others lost persistently, and no very satisfactory influence upon the bowels was observed; though in no instance did it seem to produce any further digestive disturbance. Hence, the results with wheat flour appear to be much less satisfactory than those with bean flour, though it is, of course, not wholly fair to contrast a group of cases in one institution with those in another. On the whole the St. Christopher's cases were more advanced when the wheat flour was started than were most of the cases at the University Hospital or at Atlantic City that were on bean flour; but in none of the cases at St. Christopher's Hospital was there any very recent acute disturbance of the digestive tract, excepting in the one last described. All the cases, including the last, were atrophic infants, their weights ranging from five and one-half to nine pounds. Three of the infants were under ten weeks of age; one of these was the infant that gained rapidly on wheat flour; the other two did not gain. One other was four months old, and the remainder were between six and eleven months of age.

In addition to atrophy in infants, we have thought that predigested legume flour might be of value in the management of cases in older children or in adults in which there is persistent digestive disturbance and difficulty in taking a sufficient amount of food, particularly proteid food; or in which there is malnutrition from other causes, and the food intake is unsatisfactorily low.

Our observations on this point have been as yet very fragmentary and we do not now feel extremely hopeful in regard to its practical usefulness in most of such cases unless some means of flavoring it satisfactorily can be devised; for, as stated, adults and older children object at once, or after taking a few portions, to the taste of the beans. The man on whom we did the metabolism experiment gained four pounds in the preliminary period (that in which no bean flour was used). In the first four days of the use of bean flour, when his appetite was much upset, and he took a much reduced amount of food, he lost two pounds; but in the next five days he gained three pounds, so that the gain in the first period and the last part of the bean-flour periods was practically the same. Afterward he went back to his usual diet and lost a pound a week for two weeks. He then requested that he be allowed to take predigested bean flour again. Without making any other change in the diet, he did this, and gained one pound each week for two weeks (the bean flour being then flavored), and his appetite improved together with his gain. The conditions in this case are hardly worthy of special comment, though rather favoring the bean flour.

In another case, however, very remarkable results were obtained, and this case is sufficient to encourage the further use of the preparation in children past infancy.

Case XXVIII.—A girl, aged two years, who in brief had the following history: She had been running down for a year; had had persistent digestive disturbance during this time, with constant diarrhœa and occasional vomiting, and nothing seemed to agree with her. She had constantly lost weight at the time when seen by Dr. Charles H. Schoff, of Media, who treated her with predigested bean flour. She had been for three months before this at Atlantic City, under the care of several skilful clinicians, and was then seen by Dr. J. P. Crozer Griffith, who tried a variety of diets without success. The child seemed entirely unable to take milk even when it was greatly diluted, and other liquids agreed but little better. She was then tried on semisolid and solid food, but grew decidedly worse. She was referred to Dr. Schoff at this time, and was then having from ten to fifteen bowel movements a day, which were loose and green. She was vomiting several times daily; was emaciated and extremely weak; her hands and feet were cold, and she was apparently in a desperate state. She weighed eighteen pounds. Several days of careful dieting and medication brought no improvement, and at our suggestion Dr. Schoff tried predigested bean-flour solution, alone, in small amounts. Finding that this did well it was rapidly increased, and the child was given eight ounces of 10 per cent. solution every three hours. Dr. Schoff states that within twenty-four hours the bowel movements were much reduced and much improved in appearance, and the vomit-

ing had stopped. Within a few days more the bowel movements were reduced to about three daily and the child's general condition was greatly improved, and after this there was continuous general advance in health and improvement of the digestive tract. In the first week a gain of slightly less than a pound was made; in the second week a similar gain; in the third week a little over two pounds; in the fourth week two pounds. At this time it was attempted to give the child a very small amount of milk with the bean flour, but it immediately disturbed the digestion. Two weeks later other foods were gradually added, and the child when last heard from had continued to gain and was to all appearances perfectly normal excepting for a tendency to intestinal disturbance from slight causes. This child objected to the taste of the bean flour at first, but took the subsequent feedings readily.

In this case the usefulness of the preparation probably depended upon the fact that it is extremely easy of digestion, has a high nutritive value for its bulk, and contains (that which most other very easily digested preparations do not) an amount of proteid that is entirely sufficient for the needs of the organism. In similar cases, even when much less severe, it would be worthy of trial. It would also be worthy of trial (if agreeably flavored) in cases of acute infectious diseases, particularly in typhoid fever, when there is difficulty in digesting the proper amount of milk. In these cases the addition of a small amount of this preparation would increase the nutritive value of the food, and would sometimes improve the digestion—if in no other way, through its action upon the curd of the milk. It has become the custom of one of us, in a hospital service in which large numbers of cases of typhoid fever are seen, to treat any digestive disturbance on exactly the principles that are used in the treatment of digestive disturbances in infants, reducing the fats or the proteids or both as seems wise, and frequently adding a cereal to prevent the formation of large, tough curds. The latter is a particularly useful procedure in a certain number of cases, and we have seen it rapidly control serious disturbance of digestion, with diarrhœa, distention, etc., in typhoid cases. Predigested bean flour in the form in which we use it has, as we could readily determine, the same influence upon the curd as barley-jelly and the like, and it has also another influence—it is necessary to add much more acid to milk to curdle it when predigested bean flour is present than when it is not. This is probably due to the acid combining with the proteid of the bean.

These clinical results seem to us on the whole to be decidedly favorable. It is to be remembered that all the infants treated were hospital babies, and that with one exception (the last St. Christopher's Hospital case) they had all been losing before the bean flour was started, or had at best merely maintained a very low weight. We would also have it especially noted that no change was

made in the diet excepting that a portion of what the infants had been getting immediately before was cast out, and in its place an equivalent, or usually very slightly less, value of bean flour was given. All the St. Christopher's Hospital cases, excepting the last, are of little importance, since all were in extremely bad condition when the bean flour was started, and only three of them got this preparation as long as a week. These three did a little better than they had done for some time before, though they all died. Of the cases treated elsewhere, three have been classed as unfavorable. The first of these was at the time probably not in condition to receive this or any other food, except the most dilute, and hence was certainly not a suitable case for trial of the food. In the second case there was a rapid gain at first, and then an acute illness which was not due to the diet. In the third case there was some gain, though on the whole the infant did not do well; but the milk mixture used was certainly very concentrated for an infant of the age and digestion of this one, and a lower modification might have done better. In none of these instances was there any actual evidence that the food did harm. The other infants all gained and all were continuously improving when they passed from observation, most of them having increased largely and rapidly in weight and strength and many of them having much improved digestions. Eleven out of fourteen infants, therefore, showed decided improvement, and most of them showed very striking improvement.

Atrophic infants, when treated in hospitals, certainly do not usually show so high a percentage of improvement and such large gains. Indeed, in our experience, and certainly in that of most other observers, such cases are, in hospitals, most unsatisfactory to treat, and usually show persistent downward progress. We think, therefore, that there is good reason to encourage a more extensive trial of the preparation.

There are, of course, several evident reasons why one may be doubtful whether the legume flour had any influence in these cases that was peculiar to itself. The readiest objection that could be raised we have already met—the improvement was certainly not due merely to increase in the amount of food, for the amount of bean flour was purposely kept only equal to or a very little below the amount of milk mixture that it displaced. Those who use very low modifications may consider that some of the infants, at least, had had too strong a milk mixture previously, and that the improvement was due to dilution of the milk. There may be some truth in this, for some of the milk mixture was displaced by the bean-flour solution, and there was, therefore, a little dilution of the milk, but if this is the explanation of the results it means that these babies digested and absorbed the bean-flour solution better than they did modified milk, for the food as a whole was not appreciably diluted, the bean flour, as stated, maintaining

the actual concentration of the total food at practically the previous point. Another possibility that might be suggested is that improvement did not occur because of any influence of bean flour as such, but merely because of its mechanical effect on the curd. This is almost certainly not the case, for most of the babies had already received either barley-water, barley-jelly, malted barley-jelly, predigested wheat flour, or arrowroot.

Three points are, however, subject to somewhat serious criticism. In the first place the number of cases is small, and a larger number may show that our results were due simply to chance good fortune. Again, our cases were necessarily under observation for but short periods, and longer observation is necessary before it can be stated whether infants can often be brought back to good health by this means. Further, we have suggested that the bean flour probably exercised a special influence directly upon metabolism; that is, that it did not act solely through its influence upon digestion, or through the fact that an increased amount of food was being absorbed by babies who had previously been unable to take enough. This we have not definitely proved, but in support of our suggestion we have the following facts: While it is true that in most instances the digestion was more or less decidedly improved under the use of bean-flour solution when there was previously distinct digestive disturbance, it is equally noteworthy that in a number of instances the digestion was but little disturbed beforehand. In most instances also the gain in weight and strength was almost immediate, and it was usually very rapid, while the digestion in repeated instances improved only much more gradually; so that it appeared in such cases that the improvement of digestion was a part of the general improvement rather than the cause of it. Further, and most important, there was in some instances little or no change in digestion, and yet very marked improvement occurred; for example, in the first two cases in which absorption was studied the bowel movements of the two periods remained about the same, and the figures show that the actual absorption was already good and practically did not change when bean flour was given, yet both infants gained nearly a pound in six days, and afterward continued to gain while they had previously been stationary. That this food is capable of causing much improvement of digestion was shown by a number of the cases, most strikingly by Dr. Schoff's very remarkable case in the two-year-old child, in which the result was probably due chiefly to the influence on digestion. Disturbance of digestion, however, does not constitute the whole of the pathology of infancy. In dealing with adults there is an increasing and proper conviction that a good deal more digestive disturbance than was once thought is dependent upon some general disorder of nutrition; that is, that the disorder of digestion is not the primary condition, but is itself a result of some other disease; and the fact that digestive dis-

turbance is of enormous importance in infancy and early childhood need not, as it often does, render obscure the similarly important fact that in not a few instances in infants also the most important disturbance is one of general nutritive processes rather than of the digestive organs.

In order to give satisfactory evidence that the successful results in our cases were due to a special influence of the bean flour, and, particularly, to a special influence of the bean proteid, we must, however, demonstrate that similar results cannot be obtained in a similar proportion of cases by means of predigested starches of other forms. To a limited extent we have given evidence of this in the cases so far studied. One infant had been on Keller's malt-soup, and also on malted barley-jelly, with no improvement; another infant was treated with predigested wheat flour with slight improvement, then became stationary, and immediately afterward gained rapidly, as long as it was under observation, when we used bean flour. The cases seen at St. Christopher's Hospital also favor somewhat the view that wheat flour produces less successful results than bean flour.

If legume flour has this special influence upon the metabolism of atrophic infants, we think it may most readily be thought that it is due to the effect of the nuclein, or possibly to other particular substances in the flour, but not to the mere gross quantity of proteid in it, for the actual amount of proteid absorbed, as seen in the experiments detailed, was almost the same when bean flour was being used and when it was not.

Summary. Bean flour in which the starch is predigested by means of a diastatic ferment seems to be well digested and absorbed by infants and adults. An extremely concentrated food may be given in this way in fluid and partially digested form; a 20 per cent. solution, although fluid, is practically equivalent to beefsteak in nutritive value. Its influence upon the digestive tract in infants in the cases studied was usually distinctly favorable, and its influence upon metabolism in infants and adults is at least equal to that of milk. Of fifteen infants treated, one did not gain; one gained rapidly, but had an intercurrent illness and the flour was stopped; one gained nine ounces and then almost ceased to gain. The others gained as follows: one, fifteen ounces in six days; one, thirteen ounces in six days, both continuing after the bean flour gave out; one, one and a half pounds in sixteen days; one, one and a half pounds in twenty-three days; one, one and a half pounds in seventeen days; one, over two pounds in four days, and after readmission twelve ounces in eleven days; one, one and a half pounds in twenty days; one, twelve ounces in eleven days; one, four ounces in three days (then taken home); one, one pound in seven days; one, one pound in eight days; one, one and one-half pounds in three days. All these were atrophic infants that had previously been stationary or

losing. A child of two years that had had persistent and very dangerous disturbance of digestion with advanced malnutrition improved immediately, the digestive tract became nearly normal within a few days, and the child repeatedly gained over two pounds a week. The last-mentioned child took nothing but bean-flour solution; the infants took usually about 2½ per cent. of bean flour in milk modifications.

These results are certainly unusual. They need to be controlled in several ways before any definite conclusions can be drawn from them, but it seems possible that they were due to a special influence of the legume flour on metabolism, and, perhaps, to a particular influence of the nuclein contained in this flour upon the tissue-building processes.

One point that appears to be of some importance we have definitely determined: it is easily possible to administer in this way as much as 0.75 per cent. to 1.0 per cent. of proteid, a fact of decided consequence in those common cases in which it is difficult or impossible to administer a proper amount of milk proteid.

It is desirable to test this preparation further in older children and adults who are the subjects of malnutrition. This will necessitate, however, some method of preparing the bean-flour solution by which it can be pleasantly flavored, as when unflavored its taste prevents its use with older patients for any considerable period. Infants, however, take it readily in milk.

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A STUDY OF METABOLISM IN LEUKÆMIA, UNDER THE INFLUENCE OF THE X-RAY.

With a Consideration of the Manner of Action of the X-ray and of Some Precautions Desirable in its Therapeutic Use.[1]

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Recent observations and experiments have furnished most impressive testimony of the power of the *x*-rays for both good and evil, and the most remarkable of the favorable influences that have been observed in the past two years is that exerted upon leukæmia. Indeed, in the extent of the tissue changes induced the effect in leukæmia more than equals that seen in any other disease. It is true, to be sure, that, as is so commonly the case in cancer, the benign effect upon leukæmia is only temporary, most of the cases in which apparent recovery occurred having relapsed, and none of them having as yet provided any evidence that relapse can be avoided. Nevertheless, numerous cases of leukæmia have now been observed in which complete, or almost complete,

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temporary disappearance of symptoms was seen as a result of *x*-ray treatment, and an equal degree of success with other forms of treatment is rare to an extreme.

On the other hand, the evil effects of *x*-rays have attained recently a disquieting degree of prominence. For some time past occasional instances have been recognized in which, in leukæmia and in other diseases, exposure to *x*-rays produced more or less severe, and sometimes even dangerous, febrile reaction, chills, vomiting, prostration, and other pronounced general symptoms that had the appearance of being caused by an intoxication. We have also lately learned that occasionally serious lesions, such as nephritis, have followed the use of *x*-rays, and an astonishing and deplorable effect upon the reproductive function has been demonstrated by the work of Albers-Schönberg and others. Furthermore, Heineke, Warthin, and others have described rapid and widespread changes in the tissues after the use of *x*-rays; the alterations in the lymph glands and bone-marrow found by Heineke in his extensive experiments being extremely startling and impressive.

It has, therefore, become plainly evident that, in addition to the "burns" that have long given occasion for caution in the use of *x*-rays, there are other unfortunate effects that may be more rapid in their appearance and that are at times much more grave. It is not surprising that an agent that is capable of producing profoundly benign effects should also have the power of doing great harm unless used with full knowledge of the manner in which its effects are brought about, and this has not been the case with *x*-rays. The indications for employing them and the dangers associated with their use have been determined chiefly by empirical means, while the nature of their action has remained a mystery.

Our investigations of the changes in metabolism that follow *x*-ray treatment of leukæmia have demonstrated in a striking manner that the influence upon metabolic pro-

cesses is extremely rapid and very profound, and our results emphasize most forcibly the possibilities in *x*-rays for the production of both good and bad results. They indicate also, we believe, with considerable clearness the general way in which *x*-rays act.

The effect upon metabolism that we observed is probably unequalled by that known to be due to any other therapeutic agent. Radium is probably capable of equally marked effects, but it has not been studied in a similar way. Other therapeutic agents may, to be sure, have profound results when they are used in doses that largely exceed the therapeutic limit; but such results are definitely toxic, not therapeutic. With the *x*-ray, on the contrary, our observations appear to indicate clearly that tissue destruction is, in leukæmia, evidence of favorable action, while when the *x*-ray fails to act this tissue break-down does not occur. This is a most striking fact, and one that is quite the reverse of the usual conditions. Rapid break-down of body tissue is, of course, ordinarily extremely harmful, especially when protein tissue is being destroyed; in one of our leukæmics, however, we observed the interesting phenomenon of rapid symptomatic improvement, occurring coincidently with tremendous acceleration of protein tissue destruction, while in the other leukæmic, whose disease was progressing toward a fatality, the *x*-ray exerted extremely little influence upon metabolism, the destruction of tissue was scarcely at all excessive, and, as death approached, tissue break-down not only did not increase, but appeared to grow progressively less. The changes that have been seen clinically and at autopsy in the condition of the spleen, the lymph glands, and the blood, in cases of leukæmia that have improved under this treatment, and particularly the remarkable experimental work of Heineke, appear to show that the tissue destruction produced by the *x*-ray is limited largely to the lymphatic tissues and the bone-marrow; Heineke, indeed, could find no changes in other tissues. Hence the fact that symptomatic

improvement occurs in leukæmia while tissues are undergoing rapid destruction seems to be the result of the limitation of this tissue disintegration, chiefly, or possibly entirely, to the diseased parts.

Rather than lessening its importance, this apparent limitation of the effects to certain tissues adds to the interest of the subject in its relation to general metabolism.

Our studies of the behavior of metabolism in leukæmia while *x*-ray treatment was being used were, as we have already indicated, carried out in two cases. We wish particularly to emphasize the contrast between these two cases, for the opportunity to compare the conditions during successful treatment with those during unsuccessful treatment led to what is, perhaps, the most suggestive result of the study. One case had previously been subjected to this treatment with success, and nearly all symptoms had then disappeared, but they returned, and when our observations on metabolism were made the symptoms were growing worse continuously, in spite of the use of *x*-rays, and the patient soon died. In the other case, on the contrary, severe symptoms were present when *x*-ray treatment was instituted, and the patient was growing worse at that time, but the use of *x*-rays resulted in immediate and very rapid improvement, and the patient left the hospital a few weeks later, showing only slight evidences of leukæmia.

The influence of *x*-rays upon metabolism was studied also in two cases of severe gout (by Dr. Edsall and Dr. Fife), and in another case (Dr. Edsall), in which the conditions of metabolism were practically normal. The details of these cases will be published elsewhere, but the results will be referred to in this paper, in so far as they bear upon the conclusion to be reached concerning the way in which the *x*-ray acts.

Both leukæmics were private patients of Dr. Musser. Both were told that *x*-ray treatment of leukæmia is still somewhat of an experiment, and that there is an element

of danger in it, but both wished the treatment to be tried. It was impossible to subject them to rigid limitation of the diet for a long time. Both had poor appetites, particularly the first patient, and they soon rebelled against the monotonous diet; consequently the period of study was brief, and some minor details (such, for example, as the duration of the effect of the *x*-ray) that could be determined only by more prolonged study were necessarily left unsettled. The main points sought for were, however, made sufficiently clear by the results that were secured. The figures obtained in both cases in the study of metabolism will, for the sake of contrast, be put together, following the clinical synopsis of the two cases.

Only the main clinical details will be given.

Case I.—The fatal case. The patient, E. C. H., a man aged forty-four years, a plumber, was first admitted September 15, 1904, to the private wards of the University Hospital. He had no family or personal history that was of any noteworthy consequence until March, 1904, when he began gradually to lose strength; the weakness had increased from this time, but he had noticed no other symptoms, except mental irritability and occasional attacks of diarrhœa. At the time of admission he showed the conditions usual in a marked splenomyelogenous leukæmia. The spleen then extended from the seventh rib in the anterior axillary line to three inches below the level of the umbilicus, and anteriorly nearly to the median line, its greatest length being twelve and one-half inches, its greatest breadth thirteen inches. The liver was not enlarged; the inguinal and axillary glands were palpable, but not of large size. The blood examination showed hæmoglobin, 38 per cent.; red blood cells, 4,280,000; white blood cells, 407,500. A differential count made on the 21st showed:

Myelocytes	49.2 per cent.
Polymorphonuclears	27.1 "
Transitionals	21.6 "
Eosinophiles	1.0 "
Lymphocytes	0.2 "

There were also 0.8 per cent. of nucleated reds. The patient was at once put upon *x*-ray treatment and very rapidly improved, the behavior of his leukocytes being shown by the accompanying chart that was made by the resident physician, Dr. Thomas Kelly. The continuous line indicates the counts before the *x*-ray treatments; the broken line the counts taken directly after the *x*-ray treatments.

At the time of discharge, on October 13th, the leukocyte count was 138,000; the spleen had decreased greatly in size, and the patient's general condition was very much improved. The leukocytes subsequently fell to below 35,000, and the spleen became about normal in size. He left because of the demands of his business, but had *x*-ray treatments at first daily, afterward once or twice a week, until February, 1905. He then stopped coming for treatment. He was readmitted on March 12, 1905, having rapidly grown much worse, and having recently had pain and soreness in the muscles, with fever and considerable weakness, and with renewed enlargement of the spleen. Upon examination his spleen was found to reach the level of the umbilicus, and the leukocyte count was 180,400.

The differential count (Dr. A. O. J. Kelly) showed:

Basophilcs	4.0 per cent.
Lymphocytes	4.0 "
Polymorphonuclears	18.0 "
Eosinophilic myelocytes	2.5 "
Neutrophilic myelocytes	71.5 "

Several nucleated reds were seen. The man had slight fever, which continued afterward, running as high as 101°. He grew rapidly worse, and on the 21st, the day that the observation of metabolism was started, his leukocyte count was 304,000. Because of his bad condition the preliminary observation of metabolism was continued but two days, and on the 23d *x*-ray treatment was started. For several days after this he seemed to feel better, though there was no improvement in the leukocytes; on the contrary, they grew continuously more numerous, the count being

453,600 on the 26th; 496,000 on the 29th. He also developed fresh hemorrhages into the retina. Suddenly, on the 31st, he went into temporary collapse; the following day he was very weak, and early the next morning he again went into collapse and died. A postmortem could not be secured.

Case II.—The successful case. The patient, Mrs. L., aged forty-two years, was admitted to the private wards of the University Hospital on March 20, 1905. Her history previous to October, 1903, was without interest. At that time she became easily fatigued, lost flesh, and her color rapidly changed and became "greenish." She also noted enlargement in the splenic region. After general treatment she improved very greatly, and by the spring of 1904 had, she believed, regained her normal health. This continued until October, 1904, when she had a slight operation for a cyst of the eyelid, and hemorrhage continued for nine hours from the small incision. She lost a great deal of blood and was much shocked afterward, and her spleen almost at once became enlarged, while her general condition grew gradually worse up to the time that she was admitted. When seen by Dr. Musser she presented marked features of leukæmia, the spleen extending from the seventh interspace in the anterior axillary line to within an inch of Poupart's ligament, and anteriorly it reached beyond the median line. The liver was not enlarged; there was no marked glandular enlargement. The blood count showed 68 per cent. hæmoglobin; 3,410,000 red blood cells; 245,000 white blood cells.

The differential count (Dr. A. O. J. Kelly) showed:

Neutrophilic myelocytes	45.0 per cent.
Basophilic myelocytes	16.0 "
Eosinophilic myelocytes	3.0 "
Polymorphonuclears	26.0 "
Lymphocytes	9.0 "

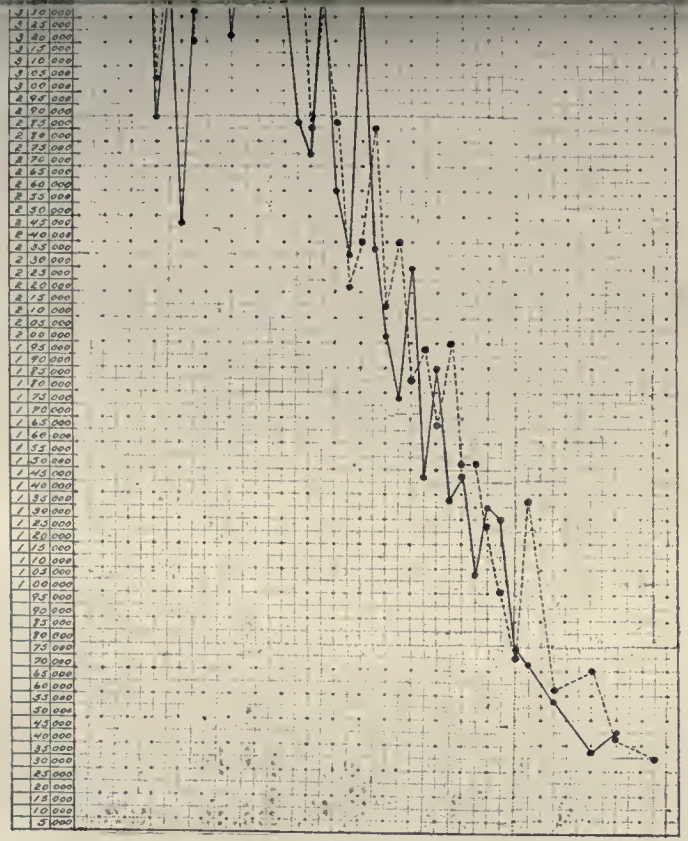
The patient was weak and very pallid, and appeared emaciated. She felt worse during the next few days, and on the 23d, when the metabolism experiment was started, the leukocyte count was 272,000; on the 26th, when *x*-ray treat-

ment was begun, it was 304,400. Directly after this continuous improvement began, and the spleen decreased rapidly in size, so that on April 20th, when she was discharged, the lower border was but slightly below the umbilicus, and the anterior border was fully two inches within the median line.

The leukocyte counts had been as follows: March 27th, 262,400; 28th, 252,400; 29th, 246,400; 30th, 214,400; 31st, 191,200; April 1st, 149,600; 4th, 96,000; 5th, 80,080; 7th, 40,080; 9th, 32,800; 11th, 30,400; 13th, 24,720; 15th, 28,440; 17th, 17,440; 18th, 15,200; 20th, 15,360. She returned for blood counts and *x*-ray treatment until May 8th. During this time the counts were: April 26, 12,480; 30th, 6480; May 8th, 9040.

For the study of metabolism both patients were put upon a diet of milk, bread, butter, eggs, sugar, rice, steak, baked potato. The amount taken each day was kept as nearly the same as possible, and the quantity actually taken was accurately weighed each day; it was not possible with either patient to make the daily intake absolutely uniform, but the variations were slight and not important.

The amount of nitrogen and P_2O_5 in the food in each case was calculated partly from a large series of analyses that we had previously made of the same foods as they are used in the University Hospital, partly from the figures of König and Blythe, chiefly from our own figures. The nitrogen, P_2O_5, uric acid (Folin-Schaeffer method), and purin bases (Salkowski method) of the urine were estimated daily. The feces for each period were collected as a whole, dried, ground, and the nitrogen and P_2O_5 contained in them estimated in a number of different portions. The total amount in the feces was determined from the average of these estimations. In both cases the diet was given for three days before the metabolism experiment was begun. In both instances there was then a preliminary control period of observation of metabolism, which was made very short in each instance, because both patients were so ill that it seemed unjust to



Leukocyte counts made before and after x-ray exposures from September 15, 1904, to October 30, 1904. The unbroken line (———) indicates counts before exposure to x-rays, the broken line (– – –) the counts after exposure.

delay the use of *x*-rays for a longer time; this period was two days in length in the first case, three days in the second. There was then a period of observation, three days long in both cases, during the use of *x*-rays. After this it was necessary to relinquish the rigid diet, since both patients refused to take it longer. Consequently the intake could no longer be accurately determined, but for some time afterward the nitrogen, P_2O_5, and uric acid of the urine were determined in each case, and the figures obtained, which provide some interesting observations, will be given in separate tables, following those that exhibit the metabolic balance.

The condition of general nitrogen metabolism before *x*-ray treatment was begun is of interest in itself. The studies of von Noorden, Magnus-Lævy, and A. E. Taylor have shown that in the ordinary course of chronic leukæmia nitrogen metabolism may show a balance, a slight loss, or a retention. It is not surprising that this is the case, for the clinical course of the disease would lead one to anticipate it. It is, however, an interesting contrast to the conditions in acute leukæmia, for most cases of the latter disease whose metabolism has been studied have shown a loss so large as to be but rarely equalled in other diseases. In a case recently studied by one of us the nitrogen loss through the urine was over twenty-two grams, and the whole loss was, indeed, much more than this if the nitrogen loss by hemorrhage be included.

The most interesting point in this connection, however, in regard to the cases now under discussion is the fact that both our patients during the preliminary studies of metabolism were very ill, and were rapidly growing worse, the first case in particular exhibiting fever, increasing prostration, and other appearances of a toxæmia that was hastening toward a fatal issue, and yet there was even in this case no evidence of excessive general tissue destruction, and in the second case there was a marked retention. The same point has been observed by others. Apparently, therefore, the

TABLE I. CASE 1. PRELIMINARY PERIOD.

Date.	Urine.				Feces.		Total loss in excretions.		Intake in food.		Balance.	
	Nitrogen.	Uric acid.	Purin bases	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.
March 22	6.6662	lost	0.0863	0.680	1.152	0.937	7.8182	1.6170	8.5754	4.4288	+ 0.7572	+ 2.8118
" 23	9.9552	1.9625	0.0618	0.7296	1.152	0.937	11.1072	1.6666	10.3262	4.1127	— 0.7810	+ 2.4461
Totai	16.6214	.....	0.1481	1.4096	2.304	1.874	18.9254	3.2836	18.9016	8.5415	— 0.0238	+ 5.2579
Average	8.3107	1.9625	0.0740	0.7048	1.152	0.937	9.4627	1.6418	9.4508	4.2707	— 0.0119	+ 2.6289
					X-RAY PERIOD.							
March 24	7.6608	1.7437	0.0430	0.8640	1.229	0.993	8.8898	1.8620	8.5693	3.7003	— 0 3205	+ 1.8383
" 25	7.4480	1.6425	0.0654	1.1712	1.229	0.998	8.6770	2.1692	8.2309	3.8854	— 0.4461	+ 1.7162
" 26	7.9520	1.8490	0.0678	1.2800	1.229	0.998	9.1810	2.2780	9.1542	4.0788	— 0.0268	1.8008
Total	23.0608	5.2352	0.1762	3 3152	3.687	2 994	26.7478	6.3092	25.9544	11.6645	— 0.7934	+ 5.3553
Average	7.6869	1.7430	0.0587	1.1050	1.229	0.998	8.9159	2.1030	8.6514	3.8881	— 0.3967	+ 1.7851

Average calories in daiiy diet: Preliminary period, 1230. X-ray period, 1230.

TABLE II. CASE 1. IN PERIOD FOLLOWING DETERMINATION OF METABOLIC BALANCE, X-RAYS STILL BEING USED.

Date.	Nitrogen.	Uric acid.	P_2O_5.
March 27	6.1340	0.5422	1.2480
" 28	5.1744	0.5445	0.8442
" 29	3.3260	1 1236	0.4800
" 30	3.7796	1.4033	0.6144
" 31	4.9440	0.9035	0.6912

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TABLE III. CASE 2. PRELIMINARY PERIOD.

Date.	Urine.				Feces.		Total loss in excretions.		Intake in food.		Balance.	
	Nitrogen.	Uric acid.	Purin bases	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.
March 24	8.8032	0.8925	0.0585	0.9744	1.684	1.737	10.4872	2.7114	12 2022	5.5623	+ 1.7130	+ 2.8509
" 25	8.1600	1.1390	0.0333	1.3008	1.684	1.737	9.8440	3 0378	12.5060	5.8678	+ 2.6620	+ 2.8300
" 26	9.2736	1.1320	0.0406	1.7220	1.684	1.737	10.9576	3.4590	12.8227	5 7196	+ 1.8651	+ 2.2600
Total	26.2368	3.1635	0.1324	3.9972	5.052	5.211	31.2888	9.2082	37.5309	17.1497	+ 6.2401	+ 7 9409
Average	8.7456	1.0545	0.0441	1.3324	1.684	1.737	10.4296	3.0694	12.5103	5.7165	+ 2.0800	+ 2.6469
X-RAY PERIOD.												
March 28	14.3920	1.6750	lost	2.944	1.660	1.624	16.0520	4.568	11 5686	5.2803	— 4.4834	+ 0.7123
" 29	15.3300	1.5800	0.1403	3.246	1.660	1.624	16.9900	4.870	11.2949	5.4140	— 5.6951	+ 0.5440
" 30	14.6588	1.6180	0.1623	3.048	1.660	1.624	16.3188	4 672	11.4077	5.6659	— 4.9111	+ 0.9939
Total	44 3808	4.8730	0.3026	9.238	4.980	4.872	49.3608	14.110	34.2712	16.3602	— 15.0896	+ 2.2502
Average	14.7936	1.6243	0.1513	3 0793	1.660	1.624	16.4536	4.703	11.4237	5.4534	— 5.0298	+ 0.7500

Average calories in diet: Preliminary period, 1750. X-ray period, 1410.

TABLE IV. CASE 2. IN PERIOD FOLLOWING DETERMINATION OF METABOLIC BALANCE, X-RAYS STILL BEING USED.

Date.	Nitrogen.	Uric acid.	P_2O_5.
March 31	13.4064	2.0040	3.1392
April 1	14.0616	2.4274	3.0400
" 2	15.3216	1.9672	2.5920
" 3	13.9216	2.2811	2.9040
" 18	10.3320	0.8329	1.9488
" 19	12.4236	1.2219	2.9538

toxæmia that occurs in the most severe stages of chronic leukæmia does not necessarily produce tissue loss. One would think at once of the possibility that in these cases a generous food allowance had sufficed to conceal the evidences of tissue loss, for it has been shown that abundant feeding in the course of toxæmias may at times transform the loss that usually occurs to a balance between the intake and outgo, or may even produce some retention. This, however, was certainly not the explanation in these cases, for, as can be seen from the figures, the amount of protein consumed was less than the normal, and the total value of the food, in calories, was very low. Hence it appears that in these cases there was severe toxæmia; and not only was there no evidence of any noteworthy increase in destructive processes, there was in one case actual decided retention that was probably due to the disease, an interesting contrast with most infectious toxæmias, with cancer, and with many nutritional diseases, such as exophthalmic goitre, Addison's disease, advanced diabetes, and gout (at the time of acute attacks). In the latter conditions, and in many other endogenous and exogenous intoxications, more or less marked nitrogen loss occurs, as an almost constant expression of the intoxication. It is uncommon, indeed, to find a marked toxæmia in which tissue loss does not occur; and hence the presence of a grave toxæmia associated with retention is the more interesting. Most of the amount that was retained was probably used in making leukæmic tissue. It, of course, occurs to one at once that the retention was due merely to poor excretion, but this possibility does not seem of much consequence when one considers that our second patient promptly almost doubled her excretion when *x*-rays were used, and that the patient with acute leukæmia, whose case was mentioned above, excreted enormous quantities of solids, in spite of the fact that he had extremely severe kidney lesions. The patients at present under discussion had no evidence of nephritis, and there is no reason why

they should have had marked incompetence of the excretory organs.

Another point seems to be clearly shown by the figures. The products of disintegration of leukæmic tissue do not appear to have any essential relation to the toxic symptoms that may occur in chronic leukæmia. Both our cases, while retaining nitrogen, were growing worse; one, immediately upon the beginning of very rapid tissue destruction, began to grow better; the other, having no increase of tissue destruction, continued to grow worse. Other cases that have improved largely upon the use of *x*-rays have almost certainly had tissue destruction similar to that which occurred in our successful case. The tissue that is destroyed in these cases is chiefly, if not entirely, the leukæmic tissue. Therefore we must, in this disease at least, restrict the idea that is so frequently expressed in connection with many nutritional disorders, that the toxic symptoms are chiefly due to the products of disintegration of tissue.

There are at times, however, symptoms of marked toxæmia in chronic leukæmia, especially in the later stages, and such symptoms were present in these cases, particularly in the first. It seems probable that these symptoms are produced either by products elaborated by leukæmic tissue in the ordinary course of metabolism, these products differing from those furnished by normal tissues of the same organs in being more toxic; or the symptoms may be due to poisonous substances elaborated in the course of the synthetic processes that go on during the actual building up of the leukæmic tissue. The former seems in many ways the readiest explanation of the symptoms, but the latter thought cannot be wholly dismissed, particularly when we consider that active increase in the splenic enlargement and in the number of leukocytes, is often coincident with signs of increasing toxæmia; while, on the other hand, if the disease is not progressing rapidly, there may be little or no evidence of intoxication, in spite of the presence, perhaps, of very extensive leukæmic deposits,

and in spite, therefore, of the fact that these leukæmic deposits are playing a large role in the individual's metabolism. The first-mentioned conditions occurred in our cases before *x*-ray treatment, and both patients were then constructing tissue. When, in our second case, tissue destruction became largely in excess of construction, the toxic symptoms disappeared; but in the other case there was no increase of tissue destruction, construction apparently continued, and probably increased, and the toxic symptoms grew worse.

The condition of phosphorus metabolism is of interest because there was so marked a retention. A similar condition has been previously observed by Moraczewski, while some other authors have found a balance or a phosphorus loss. Taylor considers a phosphorus retention very surprising in the light of our knowledge of leukæmia. It does not appear to us to be so remarkable. Leukæmics whose disease is progressing constantly construct tissues that are rich in phosphorus, and naturally, if their tissue construction is largely exceeding the loss—and the condition of nitrogen metabolism shows that this was clearly the case in the second of our patients—there will be a retention of phosphorus in the construction of phosphorus-containing tissue; and, since leukæmic tissues are of the class that contain a large amount of phosphorus, the phosphorus retention is likely to be relatively large.

There are, to be sure, large deposits of leukæmic tissue in persons with leukæmia, and, since this tissue contains large amounts of nucleins, the excretion of products of disintegration of nucleins (uric acid, purin bases, phosphates) is likely to be high; and, as a matter of fact, these substances are, as is well known, usually found in large amounts in the urine of leukæmics. This large excretion does not mean, however, that retention of the constituents of nuclein-containing tissue cannot occur in these cases. It is apparently merely a question as to whether the construction or the destruction of these tissues is more active at the time of observation.

To turn to the effects of the *x*-ray, reference to the figures in the second case—the one that rapidly improved—shows a transformation upon the use of this treatment that was most remarkable in its extent, and particularly in the rapidity with which it occurred. The changes in the average daily excretion in the urine were as follows: The nitrogen rose from 8.7456 gm. to 14.7933 gm.; the uric acid from 1.0545 gm. to 1.6243 gm.; the purin bases from 0.0441 gm. to 0.1513 gm.; the phosphates from 1.3323 gm. to 3.0793 gm. The average increase was therefore as follows: nitrogen, 6.0477 gm.; uric acid, 0.5698 gm.; purin bases, 0.1072 gm.; phosphates, 1.7469 gm. The increase put in the form of percentage of the amount previously excreted was, in round numbers: nitrogen, about 70 per cent., uric acid about 60 per cent., purin bases about 260 per cent., phosphates about 200 per cent. The diet remained practically the same during this time. The monotonous food had, to be sure, become somewhat repulsive to the patient, and she refused to take quite as much as before; but consideration of this fact makes the result more striking, not less so, for normally reduction of the intake within reasonable limits is, of course, almost at once followed by decrease of the outgo, while in this instance there was greatly increased excretion, in spite of somewhat reduced intake. The change in the diet was, however, of little consequence, and the amount of food remained sufficient to have maintained a distinct nitrogen retention had the excretion remained the same, but, as a matter of fact, the excretion became suddenly so largely increased that a previous decided nitrogen retention immediately became a very marked nitrogen loss. The break down of nitrogenous tissue produced by the *x*-ray was at least equivalent to the difference in the excretion in the urine before and during *x*-ray treatment, for, beyond the use of *x*-rays in the second period, there was no factor that was changed to any appreciable degree. As was stated, this difference in the nitrogen excretion was 6.0477 gm.; that s, about 70 per cent. of the previous excretion. Tissue

break down was, however, almost certainly increased much more than 70 per cent., because much of the nitrogen excreted in the preliminary period was derived from the food, while all the increase in the *x*-ray period came from the tissues, since there was no increase of the food in this period. The last statement is true, also, of the uric acid, purin bases, and phosphates; the uric acid increase was about 60 per cent., that of the purin bases about 260 per cent., of the phosphates about 200 per cent.; but even these figures do not indicate the whole of the increased break down of tissues of the kind that yield these substances, for a large part of the excretion in the preliminary period was unquestionably derived from the food, particularly a large part of the phosphates. It may safely be said that the tissue break down in general was increased more than 100 per cent. in the three days immediately following the institution of *x*-ray treatment, and most of this increase occurred immediately. This statement, indeed, seems very conservative when one observes not only the figures for the urine, but more especially those for the balance.

After this time the intake of nitrogen and phosphorus could not be accurately determined; the subsequent figures are, therefore, less valuable, though they show clearly a marked further increase in uric acid excretion. Nevertheless, as far as it was possible to calculate them in the varied diet that the patient got after this period, the nitrogen and phosphorus in the food were found to be for some time, until the patient's appetite improved, decidedly below what they were when she was on rigid diet. Hence, there is little doubt that she actually had, for some days, at least, after we ceased determining the balance, an even more marked tissue destruction than she had during the time that the balance was known. However, the change that can be seen in the three days during which the balance was determined is sufficiently amazing.

It is a somewhat surprising fact that, although the phos-

phorus excretion showed an even more remarkable increase than did the excretion of nitrogen and uric acid, the phosphorus balance still showed that there was a retention even after *x*-ray treatment was begun. It is not possible to explain this definitely. The suggestions that most readily occur to one are that the patient, though breaking down nucleoprotein, was building up other tissues that contain substances, such as lecithin, that are rich in phosphorus; or that the products of the phosphorus-containing portion of the destroyed nucleoprotein were excreted slowly as compared with the nitrogen. The latter seems more probable. Nucleoprotein, in the course of ordinary digestion experiments, quickly breaks up (Umber) into albumin and nucleic acid. Albumin very rapidly undergoes further disintegration, while this apparently occurs more deliberately with nucleic acid; therefore most of the nitrogen from nucleoprotein would appear quickly, and purin bodies and phosphates more slowly. Evidence that this was probably the course of events in this case is seen in the fact that the uric acid excretion reached its height only after several days, while the nitrogen excretion rose at once to about the level that it maintained subsequently. Furthermore, after the patient was allowed her choice of food the intake was, as was stated, reduced much below the previous point, and at this period a rough calculation of the intake indicated a phosphorus loss. The phosphorus excretion represents the effects of the *x*-ray much more definitely than does the phosphorus balance in this short period.

As we have already stated, results as striking as those we have mentioned are, so far as we know, not produced by any other therapeutic agent unless the dose used is such as to give rise to acute toxic effects. In this leukæmic not only was the effect of *x*-rays not damaging; it was profoundly benign. There was a rapid tissue loss such as is seen in severe intoxications caused by infections and by many direct chemical poisons, and occasionally in nutritional diseases; but, instead

of increasing the evidences of intoxication that were already present in this case, the process that produced the tissue destruction caused the appearances of intoxication to vanish rapidly, and the patient began quickly to regain symptomatic health. This condition of affairs is extremely striking in its contrast with common experience in other circumstances.

The results in the first case offer a remarkable comparison. They will be discussed somewhat further in considering the manner in which the *x*-ray acts, for they are of importance chiefly in that connection. At present it is of interest merely to refer to the fact that the figures show that *x*-ray treatment had no marked influence upon this man's metabolism. There was, apparently, a slight effort at increased metabolism, for the excretion of phosphates showed a noteworthy rise, and there was a slight loss of nitrogen, as shown by the nitrogen balance; but the phosphate excretion soon fell back in the period following the formal metabolism experiment, and, except for the fact that the uric acid excretion remained somewhat excessive, as it usually is in leukæmia, the excretion was persistently low; most strikingly low, indeed, for a man who was suffering from an intoxication so severe that it soon caused his death. This low excretion was, of course, largely due to a small intake of food, but this does not influence the fact that there was, at most, no noteworthy tissue loss.

As we have before remarked, our results in the successful case demonstrate in a very impressive way the profound power of the *x*-ray in influencing tissue processes. They show clearly that a very important effect, possibly the only important one, is an almost immediate increase in tissue destructive processes. This occurs not only in leukæmics, but in normal persons as well. Baermann and Linser have found an immediate, though less striking, increase in nitrogen metabolism in normal persons. They did not study the excretion of other substances, but Heile made some frag-

mentary and brief observations on the excretion of purin bases and uric acid in persons with various pathological conditions, and his results are in consonance with our own observations. Other studies made by one of us (Edsall, partly with Dr. Fife) in gout and in other conditions also show that the increase of metabolism is not confined to leukæmics, but they likewise indicate that it does not occur in all diseases.

There are certain conclusions that are of direct practical interest to be derived from the facts that have been discussed.

That acceleration of metabolism may be very useful in many obscure disorders of nutrition, in which there is apparently slow or imperfect disintegration of food or tissues, is a possibility that will be granted at once, and the effect of *x*-rays may properly be tried, with caution, in a considerable number of nutritional disorders, both because favorable clinical effects may perhaps be seen, and because a means of stimulating metabolism is something that has been much desired for purposes of investigation, and it may make it possible for the student of nutritional diseases to secure extremely useful knowledge concerning the nature and treatment of many of these diseases. There are already apparent, however, in previous clinical experience with *x*-rays, and in our own studies of metabolism, a number of facts which make it evident that the influence of the *x*-ray upon metabolism is likely to be limited in its clinical usefulness, and there are also facts which show that grave damage may result from the use of this treatment in some conditions, unless much caution is exercised. Some of these points relating to other disorders than leukæmia are not germane to the present discussion, and will therefore be referred to elsewhere; other points, however, and particularly those that relate to the dangers in the use of this agent, require some mention, since the emphasis that our study lays upon them and the new facts that it brings out

are of direct importance to the clinician. Our results appear to demonstrate, too, the manner in which some of these dangerous results are produced, and indicate the necessity for especial caution in the use of *x*-rays when certain diseases are present.

It is not necessary to insist that any method of treatment that may cause a patient to double his tissue break down requires care in its use, if dangerous results are to be avoided. It is true that the tissue destruction produced in leukæmies is probably rarely, if ever, equalled in normal persons, and only infrequently in persons with other diseases. It is likewise true that vast numbers of persons have been exposed to *x*-rays with such usual absence of apparent general effects that there has until recently been little fear of any bad results, excepting purely local ones. But it should, at the same time, be kept clearly in mind that an effect so profound and unfortunate as is sterility may apparently occur readily, and yet the evidence that it has occurred appears only when deliberate investigations are undertaken to demonstrate that it has resulted. This makes one at once consider the possibility that other similarly unfortunate effects that are at present obscure may result. Certainly one can scarcely doubt that the sudden necessity for completing the disintegration of as large an amount of tissue as our second patient destroyed daily and the excretion of the end products of these tissues may prove to be a severe tax upon many of the organs concerned in metabolism, and upon the excretory organs, the kidneys in especial. It is not surprising to learn that severe kidney lesions have been produced in leukæmia, and even in other disorders. If Heineke's observations are correct, these kidney lesions are not the result of direct action of *x*-rays; and, if this is the case, our observations seem to demonstrate the reason for their occurrence. The increased excretion that our second patient accomplished shows what is demanded of a leukæmic who is successfully responding to *x*-ray treatment; and while this demand may

safely be made temporarily of one whose organs are sound, there may be dangerous consequences with any patient, whatever his disease, if the labors of his exeretory organs are suddenly doubled, when they are, perhaps, already taxed nearly to their utmost capacity.

The remarkable tissue destruction that we observed furnishes also a probable explanation of the curious toxic symptoms that have occasionally been noted after the use of *x*-rays. A sudden flooding of the organism with products of tissue break down may readily be sufficient in itself to cause intoxication, and it may also readily overtax the katabolic and excretory functions of various organs, and render them unequal to even their previous tasks. The organism has such elasticity of function that harm probably results but rarely in persons whose powers are not already crippled, and evident harm has certainly not often been observed in any one. But the potentiality for harm certainly exists, and, while there is comparatively little knowledge as yet of such harmful effects, it must be remembered that the study of the dangerous general effects of *x*-rays has been arousing interest for but a short time, and, nevertheless, it has already proved surprisingly fruitful. Comparatively few conditions, too, have been studied in this connection, and broader investigation may develop further harmful effects, beyond those now known.

We would not be thought to desire to condemn offhand the use of *x*-rays. We believe, on the contrary, that the demonstration that *x*-rays may profoundly influence metabolism indicates the possibility of their good effects quite as forcibly as it shows the possibilities of bad results from them; and clinical experience has already clearly shown their great value in some conditions. We would, however, insist that the extent and importance of their effects upon tissue processes are just beginning to be appreciated, and that the power to produce such effects carries with it the power to produce great harm at times, unless the general manner of action is

appreciated and the danger is carefully avoided. We are convinced that there has been too great freedom in the use of *x*-rays. Not that the sphere of their usefulness is likely to be narrowed; it will, on the contrary, probably be widened, but it should be widened by tentative trial of the effects in individual cases, and with careful watching for the evil results that are known to occur, and for others that are not yet recognized. So far as has been shown by studies of metabolism, by changes in morphology, or by clinical observation, bad general results are not likely to occur if the exposure is brief and the dose not severe; and the point of chief importance in avoiding danger seems at present to be the use of a very small dose and a brief exposure until, in individual cases, it is determined that harm does not result, the dose being subsequently increased slowly if desired. It is of equal importance, however, to watch alertly at the same time for evidences in the urine or elsewhere of resulting damage. It has not been a sufficiently general custom to follow such a plan, the chief point customarily observed having been the avoidance of burns. The determination of the dose and the exposure should not be left wholly to the *x*-ray expert, but should be largely reached through the attending physician's general knowledge of the individual patient; the evil custom that is so prevalent of merely sending a patient to an *x*-ray expert with a statement of the condition to be treated should cease, and both physician and *x*-ray expert should regularly consider the possible general effects, as well as the local, in the individual who is to be cared for. It seems not improbable that studies of the effect of *x*-rays upon excretion in various diseases, and, particularly, studies in individual cases that arouse apprehension, will prove a help in determining which diseases and which individuals may be treated with considerable impunity, which require very careful and deliberate progress, and which should not be treated at all by this agent. Certainly, however, there can be no doubt at present that the existence of nephritis

should make one very cautious in using *x*-rays, and a good deal of care should also be exercised when there is already any form of toxæmia.

There is one point that has been dwelt upon chiefly by morphologists, and has caused a good deal of apprehension, that seems to us to be less an indication of danger than it is now generally thought to be. This is the widespread occurrence of necrosis in the lymphatic tissues in leukæmics and others who have been treated with *x*-rays. This is often considered evidence of the dangerous effects of *x*-rays, but its occurrence in leukæmia and in other diseases involving the lymphatic tissues appears to be actually evidence that the *x*-rays are accomplishing the purpose for which they are being used. Such changes show the necessity for caution, but instead of growing frightened about them one should probably consider them evidence of improvement in some diseases. The same effect is observed in the lymphatic tissues of normal persons, however, and in such persons, as well as in many diseases, it cannot be useful. How far extensive destruction of lymphatic tissue is a source of immediate danger to the normal organism is, as yet, unknown, but it is a striking fact that Heineke, in his animal experiments, saw no noteworthy symptoms that were evidently due to the destruction of lymphatic tissue, while later, when extensive bone-marrow changes occurred as a result of prolonged exposures, he did see very severe symptoms that resulted in death.

In concluding, we may refer to the manner in which *x*-rays act. It is not possible from clinical observation, or from studies of the morphological changes alone, to determine whether the effects are due to some physical or other direct influence of the *x*-ray, or to some peculiar response of the individual to stimulation of functions that lie within himself. It is, of course, known that some cases improve while other cases of the same diseases do not improve; and also that the individual leukæmic, for example, may at one time grow

vastly better, and later show no effect; but such observations do not demonstrate the existence of reaction or lack of reaction of the individual, for they may be explained on the supposition that in any of these instances the *x*-ray is exerting a direct influence that is peculiar to itself, but the disease, in unfavorable cases, is progressing so persistently and rapidly that it keeps ahead, so to speak, of the effect of the *x*-ray.

Our studies, however, have shown clearly, we think, that the influence is not direct, but is due to the power of the individual to respond to stimulation. This is of much interest from a practical standpoint, as well as a theoretical.

To make this point clear we would again refer to the fact that the one leukæmic who improved showed a striking effect upon metabolism during this improvement; while in the other case lack of improvement was associated not merely with evidence that the effect of the *x*-ray did not keep pace with the disease, but actually with evidence that there was practically no influence upon metabolism. Furthermore, Baermann and Linser, as was noted, have shown that the nitrogen metabolism of normal persons is decidedly increased by *x*-rays, and we have demonstrated the same fact, as well as a large increase of uric acid excretion, in a person whose metabolism was practically normal. In addition to this, we would mention with some emphasis the cases of gout previously referred to, in which nitrogen and phosphorus metabolism and uric acid and purin-base excretion were determined. It is an extremely striking fact that neither of these cases showed any distinct effect of *x*-rays upon metabolism. It is well known that patients with gout tend, as a rule, to have a very low excretion in the interval, while the excretion shows an apparently toxic increase with the attack. In each of our cases of gout, when metabolism was being studied in relation to the *x*-ray, the excretion was decreasing after an acute attack. It showed absolutely no increase, but actually continued to

decrease when *x*-ray treatment was started, and this was repeatedly observed afterward. The changes that are usually seen in metabolism in gout continued to be present in these cases, therefore, and the course was apparently undisturbed by exposure to *x*-rays.

The facts that have just been mentioned demonstrate, we think, that the effect is not a direct one, but one that requires response on the part of the individual. It might certainly be anticipated that, if any destructive action is exerted directly by the *x*-ray, this action is more likely to occur with the tissues of a dying patient than with the tissues of one who is improving, but the patient that improved showed tissue destruction strikingly, while the patient that died showed none. This apparently cannot be explained in any way excepting upon the assumption that the patient that died was incapable of doing something that the other patient could do. The same explanation must be given for the fact that normal persons and leukæmics who are improving show increase of nuclein metabolism and general nitrogen metabolism, while our two patients with gout showed no effect. Only peculiarities in individuals can explain such results. This dependence of the favorable effect of *x*-rays upon individual reaction helps largely to explain the difference in the results in different cases. These differences are apparently not due so much to mere stubborn progress of the disease as they are to lack of that power in the individual which makes him capable of controlling the disease by responding to the stimulating action of the *x*-ray.

To be more specific concerning the processes that are stimulated and accelerated by the *x*-ray, we consider that it is highly probable that the action is chiefly upon autolysis. A considerable number of physiological and pathological body processes have, with great probability, been shown to be due to autolysis; that is, to activities that have the characters of ferment-like processes, and that produce in their course the same classes of substances as

those found in the various stages of digestion. The view is now widely accepted that the exudate in pneumonia undergoes resolution as a result of sudden autodigestion, carried out not through bacterial influence, but through the activities of the tissues; the result in this case being due to a reaction that overcomes the effect of disease. In acute yellow atrophy and in phosphorus poisoning the liver, in particular, undergoes autodigestion, this being here apparently an important part of the progress of the disease. In involution of the puerperal uterus the excess of tissue is removed, in this instance for purely physiological purposes, by the same sort of autodigestion. These are conspicuous examples of fairly firmly established facts, illustrating the physiological and pathological importance of autolytic functions. Analogy with these and with many other similar facts that have been determined has led to the belief that katabolism in general is a ferment-like or digestive process.

Following, then, the general trend of thought, and the direction in which the results of recent experimental work pretty generally point, the most natural explanation of an increase in tissue destruction, when this increase is dependent upon individual body reaction, is that it is due to acceleration of autodigestive or autolytic processes. The remarkable suddenness and intensity with which the action of the *x*-ray begins, immediately after exposure, is more direct evidence in favor of the view that autolysis is influenced. This rapidity and intensity of action constitutes the most striking feature of the effect of *x*-rays upon metabolism. In our second leukæmic case, and in our normal subject, nitrogen and uric acid excretions were immediately greatly increased as a result of only five to eight minutes' exposure to *x*-rays. Baermann and Linser also saw an immediate influence upon nitrogen metabolism, and Heile observed the same effect upon purin bases and uric acid. Heile seems not to have controlled the diet and other factors, but this probably does not affect his results to any important degree. This extreme

rapidity of action is a common feature with agents that influence ferments. It is also a most conspicuous feature in the resolution of pneumonia, in which disease the potential capacity to digest the exudate is apparently usually present, but is latent until some unknown factor causes it ordinarily to become suddenly active, and then, within a brief time, a large mass of exudate is dissolved and disappears. In the suddenness and intensity of the change that occurs the effect of *x*-rays is closely analogous to the resolution of pneumonia; immediately after a brief exposure metabolism may proceed at double its previous pace, or, perhaps, even more rapidly.

Finally the analogy between the effect of radium and that of *x*-rays is so close that the probability that *x*-rays accelerate autolysis becomes nearly a certainty when one considers that Neuberg has demonstrated, *in vitro*, that radium has this influence.

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A CASE OF ACUTE LEUKÆMIA, WITH SOME STRIKING CLINICAL FEATURES. OBSERVATIONS ON METABOLISM IN THIS CASE, AND IN A CASE OF SEVERE PURPURA HEMORRHAGICA.[1]

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My chief purpose in this report is to discuss certain disturbances of metabolism in leukæmia and purpura hemorrhagica that are of much clinical and pathological importance, and to inquire somewhat into the nature of these disturbances, particularly their relation to the hemorrhage that occurs in both these diseases. I shall, however, first mention briefly some striking clinical features in the case of acute leukæmia, which are of interest from an etiological, and particularly from a diagnostic, standpoint.

There was an apparent connection of the beginning of the symptoms with the extraction of a tooth, and therefore with the opportunity for infection, a point that is of some interest in relation to the etiology of the condition; and the clinical resemblance of the case to diphtheria and angina Ludovici has serious diagnostic importance. In this instance the possibility that the disease had originated from mouth infection set up through the extraction of a tooth must, however, be dismissed as extremely improbable. The very early appearance of severe stomatitis in many cases of acute leukæmia has led to the repeated suggestion that the disease itself, or at least the rapidity of its progress, is caused by infection, particularly through the diseased mouth; and in a number of instances, as in my case, the extraction of a tooth was apparently directly followed by rapidly progressing acute leukæmia. In the instance that I am describing, however, the actual conditions were almost certainly the reverse of this; that is, the disease itself, in its incipient stage, evidently produced the symptoms that led to the extraction of the tooth.

As to the appearances suggesting diphtheria and angina Ludovici, there is, I think, in systematic writings dealing with acute leu-

[1] Read at the meeting of the Association of American Physicians, Washington, D. C., May 16 and 17, 1905.

kæmia, or in more fragmentary papers, little, if any, discussion of the possibility of mistaking this disease for diphtheria, and there is no sufficient consideration of the possibility of mistaking the disease for simple angina Ludovici without other general disorder. Late in the course of this case it would have been wholly impossible without bacteriological investigation to have stated that it was not diphtheria; and, on the other hand, angina Ludovici seemed, when I first saw the man, to be probably the main condition present until the blood examination, that was made immediately afterward, showed at once that he had acute leukæmia. In the classes in pathological anatomy in the General Hospital at Vienna, specimens from several cases of acute leukæmia have, I am told, been exhibited in recent years with the statement that they had been mistaken for some time for angina Ludovici. This mistake is a natural one, and could scarcely be avoided in some instances until the blood condition became distinctive. Indeed, there is every opportunity for patients with acute leukæmia to develop actual Ludwig's angina, the condition of the mouth that is so common in this disease giving ready opportunity for infection of the tissues of the neck.

Without giving extensive details of the clinical side of the case of acute leukæmia, I would refer to the following points: The patient, a man aged thirty-six years, was seen with Dr. Cryer on January 15, 1901. He gave a good family history, and a personal history that was of no interest until about three weeks before I saw him. For some months previous to this time he had been under severe business and emotional strain, but no results of any consequence had been noted. Late in December, 1900, the first symptoms of importance appeared. He then had swelling of the gum about the upper posterior molar tooth on the right side, together with much pain, and his dentist extracted the tooth. The fact of interest at this point is that the trouble with the tooth was almost certainly due to leukæmic infiltration of the tissues about it. The history first obtained from the patient apparently indicated the contrary—that the disease in the mouth and elsewhere had followed the extraction of the tooth, for subsequent to its extraction he had local ulceration of the gum, of unhealthy appearance and with necrotic pseudomembrane over its surface, and this ulceration advanced until it involved a large part of the surface of the gums of the left side of the mouth. At this period, too, the man noticed the first disturbance in his general health. The tooth, however, was healthy, and there was at that time no disease of the surrounding tissues, the necrosis having followed the extraction merely because of the disease that had already begun. It seems probable that had this point been ascertainable, it could have been shown in at least a considerable portion of the other similar cases in the literature that the initial symptoms of leukæmic infiltration actually preceded the development of the local opportunities for infection.

Because of the dental condition the patient was seen in consultation by Dr. Cryer a week after the tooth was extracted, and ten days later, after a telephonic communication, Dr. Cryer had him admitted to the private ward of the University Hospital for examination, thinking that the condition of the mouth might be due to an impacted tooth. It was, however, at once apparent that he had serious general disease, and at Dr. Cryer's request I took charge of him. In the period intervening between this time and his previous visit to Dr. Cryer he stated that there had been marked and rapid loss of strength, with a good deal of emaciation and mental depression; and he had also had decided disturbance of vision and hearing, having had difficulty in reading even the large print of a newspaper, and at times in recognizing the members of his family, and having become so deaf as to be uncertain about ordinary conversation. For some days before entering the hospital he had had much pain on attempting to masticate or swallow, and had had a slight, thin, bloody discharge from the nose; he had also become extremely hoarse, and had had difficulty in inspiration. There had been no other noteworthy symptoms. At the first glance the immediate suggestion was that he had a severe diphtherial infection. He was evidently much prostrated; the pulse was rapid and weak; he had marked inspiratory stridor, and his voice was a hoarse whisper; there was a thin, blood-tinged discharge from the nose; a little pseudomembrane was at once visible in the nose, and he evidently had distress upon swallowing. His temperature was 101.2°. General examination at once made the possibility of diphtheria very questionable; it showed the following conditions: He was weak and seemed emaciated; there were small ulcers, with hemorrhagic bases on the lips and about the nostrils; there was a narrow line of ulceration of the mucous membrane of the upper jaw, most marked posteriorly, but extending to the incisors; there were similar patches of ulceration on the lower jaw, though less extensive, and there were small ulcers beneath the tongue and on the dorsum of the tongue. All these ulcers had hemorrhagic bases, but were not bleeding. Their surfaces were covered with a dirty looking, yellowish-gray pseudomembrane-like necrotic deposit. The gums were swollen and congested, but did not bleed upon manipulation; the tongue was somewhat swollen. The pillars of the pharynx and the walls of the pharynx itself were very much swollen, and the tonsils were so large that there was a space of only half an inch between them. The lumen of the pharynx also seemed very small, as a result of the swelling of the tissues. There was, however, no redness, pseudomembrane formation, or ulceration back of the tongue. The nose was nearly blocked on both sides, the mucous membrane swollen and somewhat congested, and there were small ulcerated areas which showed a pseudomembranous deposit.

The man's neck appeared to be much swollen, particularly on

the left side, and the tissues, on the left side especially, felt dense and infiltrated half-way down to the clavicle. Part of this was evidently due to glandular enlargement, one gland, about one and one-half inches in length, being readily felt, as well as a number that were smaller; but the swelling of the neck was so conspicuous as to be evident at the first glance, and it appeared to be due to a considerable extent to diffuse infiltration of the tissues, and not simply to glandular enlargement.

The glands elsewhere could be everywhere felt, and in the axilla several were about an inch in diameter; the spleen could not be palpated, but the dulness was enlarged. Examination elsewhere showed nothing of diagnostic importance. The lungs were decidedly congested at the bases; the heart was a little dilated, the sounds weak, the action rapid. The man had difficulty in reading even the head lines of a newspaper, and he could hear a watch at but six inches distance with the left ear; three inches with the right.

A culture was taken at once, and proved negative for diphtheria bacilli. The resident physician's blood count, which was immediately confirmed by Dr. C. Y. White, showed 466,640 leukocytes; 1,820,000 red cells. The hæmoglobin estimations at this time and subsequently were unreliable because of the immediate clouding that took place.

The examination of stained specimens showed a very definite but somewhat peculiar picture of acute lymphatic leukæmia. I shall not discuss the morphology of the blood, as I have asked Dr. White to include the study of this blood in discussing a series of cases that he is collecting.

The conditions that I have mentioned show that there was a strong suggestion of diphtheria and also of angina Ludovici in the case. Twenty-four hours after I first saw him diphtheria could certainly not have been excluded without negative cultures; even the definite determination that acute leukæmia was present would scarcely have finally excluded diphtheria, for at that time he had pseudomembrane on both tonsils, and he had the nasal and laryngeal symptoms that are so common in diphtheria.

The further progress of the case was one of increasing prostration, with death two days and a half after I first saw him, from cardiac failure, œdema of the lungs, and sudden collapse. The course was interesting in only two particulars: In the first place, the obstruction of his larynx grew more and more severe, and finally became so marked that the possible necessity for tracheotomy was kept anxiously in view, though this measure would have been most reluctantly undertaken because of the hemorrhagic tendency. So far as I know, marked laryngeal obstruction has not been described in acute leukæmia, though it has repeatedly been seen in chronic lymphatic leukæmia. The laryngeal symptoms were, as was expected, found to be due to extensive infiltration

of the larynx, with marked swelling and slight ulceration of both the false and the true vocal cords.

The other point of interest was the hemorrhage. The man exhibited no hemorrhagic tendency, excepting as a result of the second puncture made for study of his blood. This minute wound was followed by oozing of blood in almost a continuous stream for the greater part of an hour; all measures used to stop it were ineffectual, and the amount of blood lost was certainly as much as a pint. This feature is interesting chiefly in relation to the manner in which the hemorrhage was produced. Grave hemorrhage from the same cause has previously been described in rare instances.

A few hours after his admission, when the diagnosis of acute leukæmia had been made, a metabolism experiment was begun. This, unfortunately, could be continued for but one period of twenty-four hours, because it became impossible after this to save his urine, owing to his profound prostration and mental obscurity. In this time, however, sufficiently characteristic conditions were observed.

He took during this period only milk and broth. The nitrogen content and the amount of P_2O_5 in these were determined. I also determined the nitrogen and P_2O_5 in the urine: estimations of the uric acid and purin bases were begun, but, unfortunately, were lost through the mistake of a laboratory servant.

The man's food contained 7.25 gm. of nitrogen, 1.84 gm. of P_2O_5. The urine during the same period contained 29.534 gm. of nitrogen and 3.056 gm. of P_2O_5. While I lost the estimations of uric acid and purin bases, I think I am safe in saying, from the large precipitate produced by ammoniacal silver nitrate, that the uric acid was greatly increased; it was probably above 2 gm., at any rate. The feces could not be accurately collected, and hence the nitrogen and phosphates in the feces were not determined; there was probably more than a gram of nitrogen in the feces, however. In addition to this, the man lost during this period, as I have stated, a large amount of blood, and this must have contained 4 gm. or more of nitrogen. The balance between the intake of nitrogen and the outgo in the urine alone shows a loss of 22.28 gm., and with the loss from other sources he must in all have had a negative nitrogen balance during this twenty-four hours of as much as 27 gm. The loss of phosphorus, while decided, was not so remarkable as the loss of nitrogen. It was probably over 2 gm.

Such tremendous tissue destruction is a condition that is comparatively rare in other diseases, but it seems to be very common in acute leukæmia, as far as the very few chemical investigations of this disease that are on record indicate. It appears, therefore, to be a very important element in the pathology of the condition. Magnus-Levy, in particular, directed attention to this very remarkable disturbance of metabolism, reporting his own results in three cases, in one of which he determined the nitrogen of the

urine, and in the other two the actual balance between the intake and the outgo. In the first of his cases there was a loss in forty hours by the urine alone of 24.8 gm. more than the patient had taken in his food. In addition to that, he lost 3 gm. in the feces and about 17 gm. by hemorrhage, so that in all this patient showed in a period of forty hours a negative balance of nearly 45 gm. of nitrogen. In the second case 85.4 gm. of nitrogen were lost in seven days, and on the last day there was a negative balance of 20.8 gm. In the third case, with a very low food intake, the urinary nitrogen averaged 21 gm. during the last seven days, and on one day the nitrogen excretion in the urine rose to 27 gm.

A similarly marked loss was evidently present in Ebstein's case, in which over 62 gm. of urea were found in the twenty-four hours' urine, and a number of other authors have seen much the same state of affairs. It is of interest that in Wey's case of chronic leukæmia, with a terminal very acute stage, the patient passed per day as much as 29 gm. of nitrogen in the urine. This violent disturbance is apparently not an essential part of the pathology of acute leukæmia, as there are one or two reliable cases on record that showed no marked loss; nevertheless, it appears from the observations that have been made to be a very pronounced and common feature.

Since leukæmia is a disease chiefly of the lymphatic glands and bone-marrow, it is but natural that the metabolism of the nucleins should show most striking evidence of disturbance. The excretion of uric acid and phosphates has been found very excessive in most cases, and some of the figures obtained by Magnus-Lævy were exceedingly remarkable. One of his cases showed a loss of about 15 gm. of P_2O_5 in fifteen hours, a most astonishing figure; and in the same case the uric acid excretion reached 12.22 gm., which, considering this patient's low food intake, was certainly twenty times the normal amount, while the purin bases were 0.321 gm. Similar, though less striking, losses have been observed by others. Wende, for example, reported a case in which the uric acid excretion reached nearly 5 gm. There are, however, a few cases on record in which the uric acid excretion was very slightly, if at all, increased.

It is a matter of great clinical interest, as well as pathological, to attempt to determine the cause of this profound disturbance of metabolism. Magnus-Lævy, because of his own observations on nitrogen metabolism in hemorrhagic disorders, particularly in a case of purpura hemorrhagica, and because of a few observations of other investigators on the relation of hemorrhage to destructive changes in metabolism, reaches the conclusion that a large part, at any rate, of the tissue destruction in acute leukæmia is probably dependent upon the hemorrhages that occur in this disease. This seems to me to be very questionable. Magnus-Levy's work, and that to which he refers, has shown to be sure that hemorrhagic con-

ditions are often associated with a marked nitrogen loss, and it is not improbable that a small amount of tissue destruction is dependent upon the hemorrhage itself. The experimental work of Hawk and Gies, for example, in which the only abnormality present was loss of blood, shows that mere hemorrhage does produce some tissue destruction. But in such experimental work, in which other abnormalities are not present, hemorrhage seems to cause but slight disorder of general metabolism, and hence it would appear to be an insufficient explanation of the extremely unusual conditions found in acute leukæmia. Furthermore, there are many cases of extensive purpura in which, even in the absence of accurate chemical investigations, the clinical appearances are such as to indicate pretty clearly that there cannot be in all cases a marked tissue loss. Therefore, since very severe abnormalities, besides the hemorrhage, are present in acute leukæmia, it seems to me that hemorrhage offers a very incomplete explanation of the metabolic disturbance in this disease. Violent acute disturbance of metabolism is usually due to some form of toxæmia, and it would appear more rational to look to such a cause in acute leukæmia than to attribute the major portion of the disturbance to hemorrhage; in other words, I should be prepared to learn that the hemorrhage and the disorder of metabolism were due to a common cause, probably a toxæmia.

The conditions in the case of purpura hemorrhagica that I shall at once mention indicate very strongly, I think, that while some tissue destruction occurred in this case also, hemorrhage was not the cause of it; and hence I believe that this case goes far to remove the basis of Magnus-Levy's hypothesis that hemorrhage is the main cause of the tissue destruction in acute leukæmia.

This patient was a boy aged sixteen years; he was admitted to the University Hospital on Dr. Musser's service December 15, 1904. Admission No. 3531. His trouble had begun eleven days before, with moderate joint pains, which had continued, but had not been severe at any time. There had been little swelling of the joints. Nine days before he was admitted to the hospital hemorrhagic spots had appeared in his skin; these had rapidly increased two days before his admission, and he had also had nausea and vomiting and cramping abdominal pain. The symptoms had become still worse on the following day. When admitted he looked very ill. He had nausea, frequent vomiting, and bloody bowel movements, and showed extensive subcutaneous hemorrhages, particularly on the arms and back. The symptoms continued severe, and on the 20th he was greatly prostrated and delirious, and his hemorrhages had increased to a most striking extent. I have never seen more widespread subcutaneous hemorrhages; they involved almost all the surface of the back, the arms, and much of the forearms; there were large extravasations in the skin over the front of the chest and abdomen, many large patches on the legs and a number on the

face. There were also small hemorrhages into the conjunctiva; he had hemorrhages from the mouth and nose; he vomited some blood, and he also passed blood from the bowel and with the urine. I began with this day (*i. e.*, urine of 20th and 21st, marked 21st in table) observations of his excretion of nitrogen, phosphates, and uric acid. The excretion on the first two days represents total loss, as the patient was taking no food at this time; he was, indeed, losing more than is indicated by the urine, as he was vomiting almost constantly. It was also impossible on the 27th and 28th to estimate the intake accurately, as he had severe vomiting much of the time.

It should be noted that on December 21st he was still having hemorrhages, was vomiting violently, and was generally prostrated; on the 22d he was still very ill, but his gastric symptoms had, temporarily, largely subsided, and hemorrhage had, so far as could be determined, stopped entirely; on the 23d nearly all marked symptoms had ceased, and on the 24th he felt so well that I temporarily stopped my observations, as his attack seemed to be over. The point of chief interest is, however, that on the evening of the 24th he had a return of his gastric symptoms, and on the 26th the joint pains, abdominal pain, gastric symptoms, and prostration returned, but he had no discoverable return of hemorrhage. Observations of metabolism were again begun on this day. These symptoms lasted two days, and then decreased. Subsequently, though he had the signs of an acute nephritis, he improved with great rapidity in his general condition, and gained eleven pounds in a week. The figures for January 3d and 4th, therefore, represent his condition during convalescence. At this time he was getting between 11 and 12 gm. of nitrogen in his food. In the preceding periods, when he took food at all, he was probably getting at most 3 or 4 gm. of nitrogen.

Date.	Urine.	Nitrogen.	Uric acid.	P_2O_5.
December 21	1800	22.478	0.196	6.192
" 22	1700	23.738	Lost	4.012
" 23	1350	18.295	0.178	2.484
" 24	870	14.323	0.158	1.531
Return of symptoms, but no hemorrhage:				
December 27	1560	22.579	.....	2.280
" 28	1470	20.580	.....	1.705
Convalescent:				
January 3	880	6.718	.....	0.950
" 4	1275	6.642	.....	0.918

For the first two days these figures show, as far as the nitrogen and P_2O_5 are concerned, conditions that are very similar to those in my case of acute leukæmia, and in the majority of the other cases in which metabolism has been observed, namely, a profound

loss. The next day, when there was no hemorrhage and the symptoms were all disappearing, there was a very marked decrease in the nitrogen and P_2O_5 loss; while on the fourth day the conditions were approaching the normal. The first four days, therefore, apparently support Magnus-Lævy's view that the hemorrhage may be responsible for much of the metabolic disturbance. The conditions on the 27th and 28th, however, indicate directly the contrary. At this period hemorrhage was absent, but the renewed metabolic disturbance was only slightly less severe than that at the time when hemorrhage was occurring in wide areas, from the mucous membranes and into the skin. The conditions on January 3d and 4th are those to be expected in a convalescent; the man was, as his weight indicated, showing a marked retention, and he was evidently using this in building up tissue.

One case does not, of course, prove or disprove an hypothesis. Nevertheless, the conditions in this case; the fact that extensive hemorrhage often occurs without the clinical appearance of tissue loss; the knowledge that hemorrhage does not neeessarily occur in acute leukæmia; and the fact that, besides the hemorrhages, evidences of grave disorders of other kinds are present in acute leukæmia and in many other hemorrhagic cases: all these unite, I think, to make it appear extremely improbable that the tissue loss should be attributed in considerable extent to the hemorrhage, and indicate, on the contrary, that the cause of both hemorrhage and tissue loss must be sought together in the nature of the disturbance that produces the disease.

At the time that I observed my case of acute leukæmia I suggested that it is probable that the tremendous tissue loss is due to some pathological disturbance of autolytic processes. This suggestion was at that time almost a pure hypothesis, but the hypothesis was based upon the fact that similar metabolic conditions are seen in pneumonia at the time of the crisis, and in acute yellow atrophy of the liver; and in these diseases sudden and very extensive autolytic tissue destruction occurs; in the lung exudate in the one case, in the liver in the other. Since that time further experiment has led physiologists and pathologists to a general acceptance of the importance of autolysis in a great number of physiological and pathological conditions, and the suggestion that the metabolic disturbance in acute leukæmia is a disturbance of autolysis is on general grounds now better justified.

More direct evidence in favor of this view is found, I think, in observations that I have recently made on the influence of the *x*-ray on metabolism in chronic leukæmia.[1] In a case successfully treated there was, immediately upon the use of the *x*-ray, a most

[1] Reported, with Dr. Musser, in the University of Pennsylvania Medical Bulletin, September, 1905.

astonishing increase in the excretion of nitrogen, uric acid, purin bases, and P_2O_5. The excretion was, on the whole, fully doubled and that of uric acid, purin bases, and P_2O_5 was ultimately much more than doubled. On the other hand, a case of chronic leukæmia that was unsuccessfully treated with the *x*-ray showed almost no change in metabolism as a result of this treatment, and soon died, with constantly decreasing excretion. The fact that normal persons respond to *x*-rays by increase of metabolism, and that the leukæmic successfully treated showed even more striking response, while, on the other hand, the leukæmic unsuccessfully treated, and also two persons with gout had no noteworthy alterations in metabolism as a result of *x*-ray exposures, led to the conclusion that the changes in metabolism that occurred as a result of exposure to *x*-rays are due to some response in the individual and not to any direct physical or other effect of the *x*-ray upon the tissues. The great rapidity of action of the *x*-ray upon metabolic processes, together with the other facts already mentioned, makes it seem highly probable that *x*-rays act in some way in increasing the ferment-like metabolic processes that are normal in the body; in other words, in stimulating autolysis. This becomes almost a definite fact when one considers that Neuberg has shown experimentally that radium increases autolysis *in vitro*.

The conditions in the case of chronic leukæmia that was successfully treated with *x*-rays bore a striking resemblance to the conditions in acute leukæmia, though they were not so extremely pronounced. The fact that autolytic processes can apparently be thus—*i. e.*, under the influence of the *x*-ray—changed from their normal state to one in which there is very unduly rapid tissue destruction suggests strongly, I think, that the conditions in acute leukæmia are actually due to some cause that similarly, though more markedly, excites an increase of autolytic tissue destruction.

Until the observations on the influence of the *x*-ray on metabolism in leukæmia were made I was naturally inclined to believe that the conditions in acute leukæmia are a part of the malignancy of the disease. The effect of the *x*-ray on chronic leukæmia, however, suggests strongly that the tissue destruction in acute leukæmia may be not an essentially malignant process, but one that is of benign purpose. In chronic leukæmia *x*-ray exposures produce, in cases successfully treated, a remarkably rapid tissue destruction that is evidently, from the clinical course of these cases, benign in its influence upon the organism. It seems wholly possible, therefore, that the destruction that occurs in acute leukæmia is a response of the organism to the leukæmic tissue hyperplasia, and is an attempt to control this and to destroy the leukæmic tissue. It is not improbable, however, that if this is the case metabolic processes run amuck in the destruction of leukæmic tissue, and carry the destruction so

far that other tissues are involved to a dangerous degree; and, too, death is probably often hastened by the intoxication that results from the products of the rapid tissue destruction.

The fact that tissue destruction has not been found greatly increased in all cases of acute leukæmia, but is so in most instances, tends rather to emphasize than to disprove this suggestion that the tissue destruction is an attempt at reaction on the part of the diseased individual, and that the purpose of the reaction is the destruction of diseased tissue. The fact that it is not constant indicates that the severity of the disease is not chiefly dependent upon the tissue destruction, and this latter point may readily be brought in harmony with the view that the tissue destruction is a part of the fight of the organism against the disease. Considering, again, the analogy between acute leukæmia and chronic leukæmia, when the latter is being treated by *x*-rays, the above suggestion concerning the purpose of the tissue destruction in acute leukæmia becomes more emphatic when we remember that the tissue destruction in chronic leukæmia that results from *x*-ray treatment is limited almost entirely, perhaps entirely, to the lymphatic tissues and bone-marrow—that is, to the diseased tissues.

In conclusion, I would refer to the curiously low excretion of uric acid in the case of purpura hemorrhagica, which is of interest when contrasted with the large loss of nitrogen, and particularly with the extremely large amount of P_2O_5 lost. As will be noticed, on the day when hemorrhage was continuing the P_2O_5 excretion was above 6 gm., and on the next day it was still about 4 gm.; amounts that are very excessive at best, and that are particularly so in this instance, because there was no intake of P_2O_5. Indeed, a noteworthy amount more than this was probably excreted through his vomit. On the other hand, the uric acid figures are about normal for a person who is temporarily taking no food; in fact, they are even rather low for such circumstances. The sources of the P_2O_5 are chiefly bone, nucleins, and other parts of tissues, such as lecithin, that contain much phosphorus. That it came in this instance largely from the bones is, of course, very improbable at best, and is practically ruled out by the fact that the general nitrogen excretion was so great that it indicates marked destruction of nitrogenous tissue. It is, of course, possible that lecithin destruction, which, like bone destruction, would yield no uric acid, was responsible for the excessive P_2O_5 excretion, but it is very difficult to conceive of a process that would cause such an extensive destruction of lecithin and of nitrogenous tissues in general and leave the nucleins uninvolved. It seems far more probable that, as is usually the case, it came from nuclein, and that uric acid had been produced; but that, owing to some peculiarity in the disease or the individual, in this case the uric acid had been destroyed and was probably excreted as urea; while in most of

the acute leukæmia cases that have been studied the uric acid was not further changed, but was excreted as such. The observations of Magnus-Levy and others on hemorrhagic diseases did not include estimations of the uric acid and P_2O_5, so that I cannot state whether the conditions that I found are frequent in purpura and other hemorrhagic conditions, or were merely peculiarities of this individual case. It would be of interest to determine whether this is a common feature in purpura hemorrhagica as contrasted with other hemorrhagic conditions. If so, it would show that the metabolic disturbances of acute leukæmia and purpura hemorrhagica, though they may closely resemble each other in a gross manner, may exhibit some striking differences in details. It would then be further evidence of the fact that has long been so evident, both clinically and pathologically, that hemorrhagic conditions of various sorts are very different in their natures, though the superficial resemblance provided by the hemorrhages leads, in a clinical discussion, to the inclusion of a number of those that are least understood under one general heading.

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AUTOCHTHONOUS SINUS THROMBOSIS OF THE CEREBRAL DURA.

WITH A REPORT OF THREE CASES.*

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While secondary thrombosis, such as follows middle-ear disease, has elicited great interest and been carefully studied in recent years, especially on account of its surgical treatment; the primary form, the autochthonous sinus thrombosis, because of its indefinite symptomatology, its uncertain treatment and its comparative rarity, has received much less attention.

Since the year 1899 there have come under our observation three cases of autochthonous sinus thrombosis.

The first case, reported by Drs. Wadsworth and Spiller,[1] is as follows:

CASE 1.—The patient, a boy, aged 7 years, according to his mother's account, had always been in good health and had been bright at school. On March 3, 1900, at 1:30 p. m., he complained of headache and vomited, at 3 p. m. he became uncon-

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1. Proceed. of the Path. Soc. of Philadelphia, Oct., 1900, p. 267.

scious, and at 9:20 p. m. he was taken to the hospital. At that time he was still unconscious, the veins of his face were engorged, the pupils dilated and immobile, the pulse weak and rapid, and the respirations slow and irregular (Cheyne-Stokes type). The temperature varied from 99.4 to 100 degrees Fahrenheit. Cyanosis was not present. He reacted to irritation with a pin. Death occurred at 12:30 p. m. the following day, March 4.

Autopsy.—At an autopsy held on the same day nearly a pint of clot and fluid was found in the ventricles of the brain, and a clot was found partially occluding the jugular foramen on the left side. Further examination showed that a clot had formed in the united veins of Galen at their union with the straight sinus. The thrombus was oval in shape, about three-quarters of an inch long by one-half inch wide, and consisted, as shown by the microscope, of recently clotted blood.

The superior longitudinal sinus was entirely occluded and calcified in its middle portion. This occlusion was probably the result of a previous thrombosis. The blood from the anterior portion of the superior longitudinal sinus had formed a new passageway between the layers of the falx cerebri. This passageway was not lined by endothelial cells, and conveyed some of the blood from the superior longitudinal sinus to the straight sinus at its junction with the inferior longitudinal sinus, and some of the torcular Herophili. The thrombus formed in the united veins of Galen had evidently caused the hemorrhage into the lateral ventricles and death.

The second case was reported by Dr. S. McC. Hamill,[2] and is included here because Dr. Hamill gave the brain to us for microscopic study. His clinical notes abbreviated are as follows:

Case 2.—No history of syphilis in the mother was obtained. The patient was born normally and was not asphyxiated. The temperature was slightly elevated from the second day after birth. On the seventh day after birth a papular eruption developed on the face and the temperature rose to 104 degrees. There was no gastrointestinal disturbance. On the fourteenth day marked twitching of the muscles of the right eye and constant lateral rotation of the head were observed. General con-

2. Archives of Pediatrics, 1903, p. 264.

vulsions did not occur. The child was somewhat cyanosed and nursed poorly, but did not cry. The next day the child was somewhat better, but on the sixteenth day the temperature rose to 106.8 degrees and he vomited a large quantity of altered blood and passed several tarry stools. The face became much cyanosed. Death occurred on the same day.

Autopsy.—At the autopsy, twenty hours later, several thrombi were found in the umbilical arteries. The liver was abnormally large. The brain showed a large mass of clotted blood overlying the left hemisphere, more marked anteriorly. This extended into the substance of the brain, causing some destruction of tissue. Overlying the left hemisphere was a less marked hemorrhage.

The superior longitudinal, the left lateral, the straight sinus and the veins of Galen contained firmly organized thrombi. The veins of the brain were distended with blood and some of the superior cerebral veins, on the left side, contained thrombi. Both lateral ventricles were dilated and contained considerable blood, especially the left.

Microscopic Examination.—There was no round-celled infiltration of the pia mater, of the medulla oblongata or cortex, and the walls of the blood vessels were not thickened. The pia about the medulla oblongata was infiltrated by a great number of red blood corpuscles, as was also the optic chiasm. The optic chiasm did not stain well by the Weigert hematoxylin method, probably because it had been kept in formalin. There was no cellular infiltration about the blood vessels of the cortex. Sections taken from portions of the cortex showed numerous minute hemorrhages and intense congestion of the capillaries of the tissue. The extensive hemorrhage had destroyed the upper part of the cerebral hemispheres, including the paracentral lobules, so that the Betz cells could not be studied.

A third case is a recent observation. The clinical notes obtained from the case-book of the Pennsylvania Training School for Feeble-Minded Children, of which institution the child was an inmate, are as follows:

Case 3.—S. M., female, 15 years of age at the time of her death. Seven years previously it was noted that her gait was peculiar and was described "as if she were walking on eggs." This probably means that the child was spastic. There was

unilateral exaggeration of the knee jerk. Mentality was low and vision was imperfect. Epileptic attacks occurred and usually began in the arms and face, finally involving the entire body.

Aside from her mental condition, which steadily deteriorated, there was no change noted until four months before her death, when it was observed that while not unable to walk, she disliked to do so and kept her chair as much as possible. Her sight had become still more defective and co-ordinate movements were impaired, although the grade of imbecility prevented accurate tests. No areas of anesthesia were found. The child was peevish and prone to cry without cause.

Her condition gradually became worse until locomotion was impossible. In bed, her thighs were flexed on her abdomen and her legs on her thighs. During the last three weeks of life great swelling of the feet with a tendency to the formation of blebs was observed. Speech was impossible for three weeks prior to her death, and for the last five days lifting her chin and so permitting fluids to gravitate to the stomach was the method of feeding her. Rise in temperature did not occur until the day before her death. Her heart action, pulse and respirations were regular and normal.

A record of the number of epileptic attacks shows that in 1901 she averaged eight per month, the highest number in any month was eighteen and the lowest was three; in 1902 she averaged the same, but the highest in one month was sixty-five and the lowest was two; in 1903 she had forty-three attacks in January, eight in February, three in March and nineteen in April. She died May 18, 1903.

Autopsy.—At the necropsy made May 19, the brain was found to be very edematous. The superior longitudinal sinus, one lateral sinus and the veins of Galen were thrombotic. Many of the blood vessels on the superior surface of the brain were occluded and a small collection of purulent matter was found about one of the blood vessels of the parietal lobe. The brain weighed 1,000 grams.

There were no signs of the thymus gland.

The right lung was not especially congested. It was crepitant. No distinct tubercles were found. It weighed 170 grams. The left lung was much more congested and appeared to be in a

state of red hepatization. The upper lobe was congested, but not so much as the lower. A piece of the lower lobe sank when placed in water. The left lung weighed 280 grams.

The heart was not especially fatty. A chicken fat clot was found in the right ventricle and one also in the left auricle. The valves were normal. The weight of the heart was 145 grams.

The liver was not enlarged, but moderately congested.

The kidneys and spleen were normal.

The lower limbs were somewhat atrophied. The spinal cord, examined macroscopically, appeared normal.

The brain and cord with their membranes were removed and preserved for microscopic study.

Sections from the paracentral lobule from each side showed considerable round-celled infiltration of the pia, with the blood vessels greatly congested and their walls thickened. The capillaries of the cortex, especially on the left side, were unusually prominent and a moderate round-celled infiltration was found about them. The Betz cells were apparently normal.

Within a blood vessel taken from the cortex was found a large mass consisting chiefly of multinuclear cells; about this blood vessel there was a slight round-celled infiltration. Another blood vessel showed a marked cellular infiltration about it. The cells here were multinuclear and had probably migrated from the blood vessel. A blood vessel from the choroid plexus was surrounded by a very intense cellular infiltration, the cells being chiefly multinuclear. The blood vessel in this section was occluded by a dense mass consisting apparently of fibrin. A section from the left lateral sinus showed the sinus filled with a partially organized thrombus; no endothelial lining was found. The optic chiasm was not degenerated, but a moderate round cell infiltration was found in the pia about the chiasm.

The right and left third cranial nerves were normal.

A moderate amount of round cell infiltration was found in the pia mater of the medulla oblongata and the walls of the blood vessels here were much thickened. The anterior pyramids were fairly well stained by the Weigert hematoxylin method.

Sections through the cervical enlargement showed no distinct round cell infiltration of the pia, and the nerve cells of

the anterior horns appeared normal. The crossed pyramidal tracts were very distinctly, but not intensely, degenerated. The direct pyramidal tracts, by the Weigert hematoxylin method, were not affected.

The mid-thoracic region showed the same degree of degeneration of the crossed pyramidal tracts as was seen in the cervical region. Cellular infiltration was slight throughout the spinal eord.

The degeneration of the crossed pyramidal tracts extended down into the lumbar region, and disappeared upward in the medulla oblongata. The microscopic examination showed the presence of lesions like those of cerebrospinal syphilis. The disease was probably hereditary in this case, and in all probability had caused the thrombosis of the dural sinuses.

These three cases belong distinctly to that class in which the thrombosis is due to a general bodily condition. Primary sinus thrombosis, or that form which is not due to direct extension of disease processes of the face or head, has excited a certain amount of interest during many years.

Th. v. Dusch[3] collected 58 cases of sinus thrombosis, of which 32 were due to gangrenous, erysipelatous or suppurative inflammation of parts of the body whose vessels are in close connection with the sinuses. In 4 the thrombosis appeared to result from tumors, etc., causing pressure on the sinuses or internal jugular veins. Fifteen cases were supposedly caused by lessened circulation from debilitating diseases, especially in those already in feeble health, as in children or the aged. In 6 cases no cause could be ascertained. One case he added as a supplement to his paper.

Comprehensive papers on the subject of sinus thrombosis have also been written by Lancial[4] and by J. A. Lidell,[5] the latter author having collected a number of cases. Lancial collected 7 cases from the literature, which he considered as cachectic in origin, i. e., as pro-

3. The New Sydenham Soc., vol. xi, p. 81.
4. "De la thrombose des sinus de la dure-mère," Paris, 1888.
5. Amer. Jour. of the Med. Sci., January and July, 1874.

duced by a debilitated condition of the organism. The cases that he collected were those reported by Tuckwell,[6] Corazza,[7] Wiglesworth,[8] Rotch[9] and Grancher.[10] Rilliet and Barthez[11] reported 18 cases, and Bouchut[12] 35 cases of cachectic thrombosis.

In addition to the cases referred to above, we have studied cases reported by Fisher,[13] Trevithick,[14] Hölscher,[15] Nonne,[16] Meigs,[17] Good,[18] Voss,[19] Ehrendorfer,[20] Richardson,[21] Hoffman,[22] Reinhold[23] and Phear.[24]

Primary sinus thrombosis is regarded by some as especially a disease of childhood and old age, the two extremes of life when the animal organism is least prepared to stand the strain of debilitating influences. The predisposing causes are variously given. Von Monakow[26] gives as the causes long-continued diarrhea, especially in children, great loss of blood, long-continued suppuration, carcinoma, tuberculosis, chlorosis and anemia.

According to Oppenheim,[26] primary sinus thrombosis is, as a rule, a result of cardiac weakness; it is, therefore, called marasmic. He also states that in children it is generally due to exhausting diarrhea, and in adults may develop in the terminal stage of exhausting diseases—tuberculosis or carcinoma; more rarely in the course of the acute infectious diseases. He mentions

6. St. Bartholomew's Hosp. Reports, 1874, p. 35.
7. Schmidt's Jahrbuch, 1866, p. 324.
8. Jour. of Mental Science, 1885, vol. iii, p. 371.
9. Boston Med., 1883, p. 174.
10. Grancher, unpublished, cited by Lancial (l. c.).
11. Cited by v. Dusch.
12. Cited by Lancial.
13. British Medical Journal, 1900, vol. ii, p. 9.
14. British Medical Journal, 1897, p. 1166.
15. Weiner klin. Rundschau, 1902, p. 561.
16. Mitthellungen aus den Hamburg Staatskrankenanstalten.
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18. Neurologisches Centralblatt, 1902, No. 8, p. 340.
19. Deut. Zeit. fur Nervenheilkunde, vol. xv, p. 297.
20. Weiner Med. Presse, 1892.
21. Jour. of Nervous and Mental Dis., 1897, p. 404.
22. Zeit. für Ohrenheilkunde, vol. xxx.
23. Cited by Voss.
24. Ibid.
25. Gehirnpathologie, Nothnagel's Sys. of Spec. Path. and Therap., vol. ix.
26. Lehrbuch der Nervenheilkunde, 3d edition, p. 763.

Bollinger as having established the fact that chlorosis often produces a sinus thrombosis.

Bouchut,[12] in his statistics of cases occurring in children, gives the following table of causes:

Chronic enteritis	5 cases.
Measles and catarrhal pneumonia	2 cases.
Chronic pneumonia	5 cases.
Phthisis	8 cases.
Anasarca without albuminuria	1 case.
Chronic albuminuria	3 cases.
Pertussis and pneumonia	7 cases.
Gangrene of the mouth	1 case.
Diphtheria	2 cases.
Scrofulous cachexia, tuberculosis of bones, lungs and intestines	1 case.

Bouchut calls attention to the fact that 23 out of the 35 cases he studied developed after pulmonary affections.

Fourteen of the cases that we have collected from the literature, including our own, were in children. The predisposing causes in these cases were pulmonary affections in 3 cases; long-continued suppuration in 2, and diarrhea, tubercular peritonitis and marasmus in one each. In the other 6 cases there was no history of any predisposing cause, the cerebral symptoms being the first sign of ill health. It is possible that in two of these six cases, namely, the case reported by Hölcher[5] and in our first case, where the blood from the superior longitudinal sinus had formed a new passageway between the layers of the falx cerebri, which was not lined by endothelium, that the abnormal circulation predisposed to thrombosis.

Murchison[27] is said to have been the first to call attention to the fact that sinus thrombosis is found at autopsy when death is due to syphilitic cachexia. He reported 2 cases, both of acquired syphilis; one in a woman, 27 years old, who had extensive syphilitic deposits on the dura and whose sinuses were full of "dark red coagulum." In the other, a gummatous deposit was found on the inner surface of the dura, extending about the left lateral sinus, the lumen of which was

27. Trans. Path. Soc. of Lond., vol. xiii, p. 250.

obliterated. Murchison himself does not attribute the thrombosis to syphilis *per se,* but mentions its presence only incidentally; as in both his cases there was extensive necrosis of the cranial bones and disease of the dura, it might be questioned whether these two cases could be considered as instances of primary sinus thrombosis.

In our third case there were signs of cerebral syphilis, and this disease was probably the cause of the sinus thrombosis. It seems as though *a priori,* syphilis whether hereditary or acquired, would be a likely cause of sinus thrombosis, though neither v. Monakow nor Oppenheim speaks of it.

The degeneration of the pyramidal tracts in our third case is very uncommon in sinus thrombosis.

Childbirth sometimes causes thrombosis of the sinuses, probably more often when there is copious hemorrhage; as in a case quoted by v. Dusch. In this case peritonitis was also present.

Chlorosis or anemia has been the cause in several cases, the anemia lasting from one to six months and followed by the sudden onset of cerebral symptoms and death.

In a case reported by Oglie, long-continued disease of the rectum was the only discoverable cause. A short time before the patient's death the power of speech was lost, but no other symptoms were observed. She died of asthenia, and at the autopsy thrombosis of the superior longitudinal and left lateral sinuses was found The inferior longitudinal sinus and the venæ Galeni were found partially obstructed.

Ogle[28] also reports a case of sinus thrombosis following pneumonia in a young man aged 26. He suddenly became unconscious and hemiplegic. At autopsy the superior longitudinal, left lateral and left petrosal sinuses were filled with a firm, reddish-brown and tightly adherent clot. The cerebral veins were all engorged. The brain substance was softened in places,

28. Trans. Path. Soc. of Lond., vol. vl, p. 30; also vol. x, p. 31.

and in the posterior and inferior part of the left middle lobe of the cerebral hemisphere was an abscess the size of a hazelnut.

A case mentioned by v. Dusch,[1] in a girl aged 12, who developed thrombosis of the superior longitudinal sinus during an attack of typhoid fever, probably belongs also to that class of cases where thrombosis of the cerebral sinuses occurs during the course, and usually near the termination of an acute infection. In the second case described in our paper, a baby two days old, the clinical history pointed to a general infection, which was followed by the sinus thrombosis.

In connection with those cases caused by anemia, a case reported by Nonne[16] is of interest. A woman had a large uterine myoma. Probably from the metrorrhagia caused by this, she became anemic. A little later she suddenly developed cerebral symptoms, and died in four days. The autopsy showed thrombosis of the superior longitudinal and lateral sinuses. The cortex was hyperemic, but there was no degeneration of the brain substance.

In a case reported by Wiglesworth,[8] dementia was present, and this condition, he thinks, may have caused the thrombosis, but the development of severe pulmonary symptoms before the appearance of the cerebral, and the presence of pulmonary lesions at the autopsy, make his conclusion doubtful. In another case, reported by the same author, the patient became insane for six days, and then died suddenly. At the autopsy a sinus thrombosis was found which, from its appearance, might have been several days old. A recent hemorrhage into the ventricle was also found. He thinks that in this case the acute insanity was a symptom of the thrombosis, and that death was due to the hemorrhage. The patient had previously been in good health, and there was no known cause for the thrombosis.

When it comes to a consideration of the immediate cause of the thrombus formation in the sinuses, we are

on a very uncertain footing. Various theories have been advanced, all of which lack definite proof. Von Monakow[25] thinks that sinus thrombosis gives a well-defined symptom-complex, and yet he speaks of its resemblance to meningitis. He makes two groups of sinus thrombosis—the marantic and that depending on inflammation of the cerebral veins or the pyemic form. He says that the slowing of the circulation in the brain, such as may occur in those afflicted with carcinoma, in emaciated children, in the aged, etc., has been supposed to cause thrombosis, especially if the cardiac action is weak. This view is at present far from proof.

Baumgarten has shown that blood in a vein tied at each end so that all circulation is prevented, may not coagulate even after weeks, provided the occlusion has been made aseptically and the sinus wall is healthy. The same blood, even after weeks, will coagulate if removed from the sinus, so that, as shown by Brücke, blood remains fluid if it is in contact with a living healthy vessel wall, even if the vessel is tied.

Von Monakow[25] says that there is no doubt that thrombosis of the cerebral sinuses and veins occurs after long-continued diarrhea in small children, after great loss of blood, in long-continued suppuration, in persons with carcinoma, tuberculosis, typhoid fever etc. The coagulation, however, does not depend on the feebleness of the circulation, nor the supposed thickening of the blood, but on changes in the walls of the vessels (loss of endothelial lining). Zahn has shown that the endothelium may be lost from chemical and thermic causes, that are active in marasmus. He thinks, also, that the death of certain elements of the blood, white blood corpuscles, or the blood plaques may cause sinus thrombosis, as in chlorosis. Virchow, years ago, showed that in a large number of cases the coagulation of the blood precedes phlebitis, and that phlebitis followed by coagulation rarely occurs.

Recent investigations in the coagulability of the blood

by Leo Leob[29] gave some important results that bear on this subject. This author found that the presence of certain bacteria or their toxins in blood plasma increased its coagulability in test-tubes, and also in the peritoneal cavity. There was a difference in this activity according to the bacteria used; for instance, the staphylococcus pyogenes aureus was more active than the bacillus coli. The absorption into the blood of tissue fluids increases the coagulability of the blood plasma. A piece of muscle put into fresh-blood plasma increases its coagulability. The same is true when a piece of blood vessel is placed in the plasma. This action is, to a certain extent, specific, tissues from the same kind of animal as the one from which the plasma was obtained being more effective.

It has not been proved that the endothelium exerts an inhibitory effect on the coagulation of the blood, but probably acts merely by preventing absorption of certain constituents from the tissues; and it also produces a smooth surface much in the same way as paraffin would, only much better. It seems most likely that in all these cases the coagulability of the blood is increased either by the presence of bacterial toxins or bacteria, or by tissue products.

Virchow pointed out that the most commonly observed seats of sinus thrombosis are the cranial sinuses and the veins of the lower extremities and of the true pelvis, and that the reasons therefor are anatomic. The fact that there are numerous fibrous bands crossing the cranial sinuses; that the sinuses are triangular in shape instead of circular, as are other blood vessels, thereby causing increased surface and so increasing resistance; that the tributary veins enter the superior longitudinal sinus at a right angle or sometimes even an obtuse angle to the course of the blood current; that in the cranium there is no muscular action to accelerate the current, and that the sinuses *in situ* are held open by their adhesions

29. Personal communication.

in spite of a diminished quantity of blood, are all factors that tend to produce a stasis in the blood current.

In connection with the etiology, it is well to say that there are many cases reported which might have been regarded as primary, except for the complete history or postmortem examination, such as those caused by a furuncle on the face, the removal of a nasal polyp, an abscess of the antrum of Highmore, etc.

In the primary form the superior longitudinal sinus is the most frequently affected. This is in great contrast to those cases that are secondary to otitis media, in which the lateral sinus is chiefly affected. Thrombosis, which is secondary to nasal or facial conditions, frequently occurs in the superior longitudinal sinus.

In the primary form, the superior longitudinal sinus is not the only one affected. The thrombosis may be very extensive, and involve all or nearly all the dural sinuses. The superficial veins are generally congested and may be thrombosed, and the same is true of the veins of the choroid plexus. In some of the cases extensive hemorrhage had occurred into the ventricles, and was the immediate cause of death; in other cases the ventricles were free, but cortical hemorrhages were found; in still other cases no hemorrhage was seen anywhere.

Abscess, or areas of softening, are rarely reported in primary thrombosis.

In the third case of our paper the endothelium of the superior longitudinal sinus was destroyed.

The appearance of the thrombus is very variable, according to its age. It may be a dark red coagulum, or it may be completely organized so that the sinus resembles a fibrous cord.

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PARAPLEGIA DOLOROSA CAUSED BY VERTEBRAL CARCINOMATA, SPINAL CARIES, AND MULTIPLE NEURITIS.[1]

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The term paraplegia as it is ordinarily used signifies a paralysis of both lower extremities, and it is not always recognized that by this term may be meant a paralysis of other parts of the body. Thus we may have a paralysis only of the upper extremities, a cervical, brachial, or a superior paraplegia; or a paralysis only of the lower extremities, an inferior paraplegia.

Cruveilhier[2] divided paralysis of the extremities into two clinical forms, distinguished by the presence or absence of pain, and these he named paraplégie douloureuse and paraplégie non douloureuse. The painful form of paraplegia, he thought, is caused by compression from a tumor growing in the subarachnoid cellular

[1] Read before the Philadelphia Neurological Society, February 23, 1904.

[2] Maladies de la moelle épinière, xxxv. livraison, p. 5. Anatomie pathologique du corps humain, 1835–1842, vol. ii.

tissue or outside of the dura. The non-painful form of paraplegia, he believed, is caused by a lesion of the cord substance. Paraplegia from compression, in his opinion, is accompanied by pain only when the compression develops slowly and there is irritation without implication of the cord itself. Paraplegia from fracture of the vertebral column, from a luxation in the cervical region, or from caries or softening of the vertebræ, is without pain.

Charcot[1] applied the term paraplegia dolorosa to metastatic carcinoma of the vertebræ, with which occur the shooting pains so characteristic of this disease, and since that time this term has been employed usually to designate the symptom-complex of spinal carcinoma.

It seems, perhaps, improbable at first thought that a mistake could be made in the diagnosis between vertebral carcinomatosis and multiple neuritis, but that such a mistake can readily occur will be shown in the history of one of the cases detailed in this paper. The motor symptoms of cancer of the vertebræ, which vary with the degree of involvement of the spinal cord, together with the sensory symptoms usually accompanying them, occur in other diseases, and we may have to diagnose between general sarcomatosis of the central nervous system, cerebrospinal meningitis, spinal caries, vertebral carcinomatosis, multiple neuritis, and other diseases.

The pains of paraplegia dolorosa, as usually described, are more or less constant, with paroxysms of greater suffering from time to time. The pains are sharp, lancinating, and are made worse by movement, and even the slightest touch causes intense discomfort. The distribution of the pain in the extremities and trunk depends upon the seat of the lesions.

The differential diagnosis of general sarcomatosis in most cases will cause no great difficulty. Besides the pains we usually have the accompanying symptoms of brain tumor, as headache, nausea, vomiting, optic neuritis; and we have also symptoms of cranial nerve palsies, depending upon the sites of the tumors.

Cerebrospinal meningitis can in most cases be diagnosed by the retraction of the head and the rigidity of the neck and spine,

[1] Oeuvres complètes, vol. ii. p. 116.

by the cerebral symptoms, and by the history of the case, although a differential diagnosis from a high cervical carcinomatous metastasis might be difficult.

The difficulty of diagnosis between spinal caries and vertebral carcinoma is well recognized There may be no spinal deformity whatever, as in one of the cases detailed in this paper, but the pains of spinal caries are hardly ever as severe as those of carcinoma. Schlesinger[1] mentions that in vertebral carcinoma there may not be any pain on pressure over the spinal processes or on sudden pressure upon the spinal column, but the pain may be caused by pressure along the back near the vertebral column so soon as an area near the diseased vertebræ is pressed upon.

As to the difficulty of differential diagnosis between vertebral carcinoma and multiple neuritis, Schlesinger remarks: "It is little known that in many cases of polyneuritis the diagnosis between vertebral tumors and multiple neuritis may be uncertain for a long time. I myself have seen two such cases in old people; in both, besides peripheral symptoms, there were spinal symptoms. These began with severe pains in one upper limb, stiffness of the neck, sensitiveness to pressure over the vertebræ, paresis of the corresponding extremity, with exaggeration of the reflexes, and later there was implication of the opposite side. The further course of the disease made the diagnosis certain. In one case the autopsy showed the integrity of the vertebral column and of the joints."

The three cases that we report show a remarkable resemblance to one another in their symptoms. The first was a case of carcinoma of the vertebræ; the second a case of caries of the vertebræ; and the third a case of multiple neuritis.

Case I.—M. R., female, aged forty-eight years, married, was admitted to the Philadelphia General Hospital, July 19, 1901, in the service of Dr. Spiller. The patient died three days after admission. The notes made by one of us (Dr. Spiller) are as follows:

The patient has had no children. She says that eight years ago

[1] Beiträge zur Klinik der Rückenmarks und Wirbeltumoren, 1898, Jena, Gustav & Fischer, pp. 127, 190.

she had an abscess of her right breast, which ruptured and discharged pus. Four years afterward she had pain across her back and around her waist, the pain being sharp in character. Lately she has had some pain in her lower limbs. She dates her disease from the beginning of these pains. Three weeks after they began she was obliged to take to her bed, and has been confined to her bed ever since. She has been constipated for the past four years, and has had incontinence of urine for about a month.

Present Condition. There is an extensive bed-sore over the left trochanter. The patient has a scar over her right breast. The lower limbs are very much atrophied, being hardly more than skin and bones, and are contractured at each knee. She has foot-drop on each side. The thighs in the median portion measure seven and one-half inches, and both legs in the median portion measure six inches. There are no fibrillary tremors in the muscles of the lower limbs.

The patellar jerks are absent on each side, but this may be due to the intense atrophy. Tapping the left patellar tendon causes slight adduction of the right thigh, but there is no movement on tapping the right patellar tendon. The Achilles jerk is absent on each side, and Babinski's reflex is not obtained, the toes not being moved. Tactile sensation cannot be tested, the patient not replying. Pain sensation seems much diminished. Pricking the lower limbs with a pin is perceived, but not correctly localized, and seems to cause intense pain. She complains of spontaneous pain in her left thigh. The feet are not contractured, but there is contracture at each hip. Voluntary movement of the toes is impossible.

Upper Limbs. The grip of each hand is almost nil. Both upper limbs are much wasted, especially the left, but there are no contractures. The movements are free, but weak. The thenar and hypothenar eminences on both sides are atrophied, but no more so than the rest of the upper limbs, which are not atrophied proportionally to the lower limbs. The biceps, triceps, and wrist jerks are exaggerated on each side. Testing the reflexes in either upper limb causes severe pain. The right upper arm in its middle portion measures six inches, the left five and one-half inches. Each forearm in its middle portion measures four and

one-half inches. Tactile sensation cannot be tested, but response to pin prick is quick.

The muscles of the face are extremely atrophied; the lips are very thin; the tongue is atrophied on each side and is protruded very slightly beyond the line of the teeth. There are no fibrillary tremors of the face and tongue. The fifth and seventh nerves are normal. There is corneal opacity of the right eye, and the right pupil is contracted. The left iris reacts to light, but it is difficult to determine the light reaction of the right iris. Pain sensation is sharply perceived in the face.

The patient was in the hospital only three days before death occurred, but the presence of a scar in her breast; the evidence of involvement of the spinal cord, as shown by the contractures; the atrophy and weakness of the extremities, the shooting pains and the tenderness to the slightest pressure gave the typical picture of paraplegia dolorosa, and the diagnosis of carcinoma of the vertebræ was made after the case was carefully considered.

The necropsy was performed by Dr. Simon Flexner. His notes are as follows: "The skull-cap contains two metastases, one the size of an almond, the other smaller. They project from the outer table of the skull. On removing the spinous processes and laminæ of the spinal column it is found that the bony structures are rendered soft by the growth of the tumor into them. The bodies of the vertebræ also contain masses of tumor throughout in the bony and in the cartilaginous intervertebral disks. These often project in the floor of the spinal canal. Two growths directly into the canal have taken place, one measuring 2 cm., the other 5½ cm. They are attached to the outer surface of the dura mater, and cannot be seen to penetrate the outer membranes. The cord is compressed by the growths. The smaller nodule is 8½ cm. from the medulla oblongata, the larger 10½ cm. They are firm, grayish-white masses, and were closely applied to the inner wall of the canal, from which they were separated in removing the spinal cord. The brain shows no metastases. The dura mater is adherent to the skull, but there are no metastases. There is a sclerotic carcinoma of the breast, and metastasis also in the sternum, ribs, liver, spleen, and kidney."

The microscopic examination is as follows:

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The carcinomatous tissue which is present on the outside of the dura does not penetrate very far into the dura, and distinct carcinomatous tissue is not seen within this membrane. The inner part of the dura in some places contains an accumulation of cells which are oval or elongated, mingled with much fibrous tissue, and do not assume the form of carcinoma masses. Some perivascular cellular infiltration is found within the cord where these carcinomatous masses are present on the outer side of the dura. The carcinomatous masses are chiefly on the posterior part of the spinal dura.

The crossed pyramidal tracts are much degenerated in the lumbar region, and there is some degeneration on one side at least in the area the posterior roots occupy in entering the cord. The nerve cells of the anterior horns of the lumbar region are considerably altered. In many the nucleus is displaced, the cell bodies swollen or else much atrophied, and in many there is an excess of pale yellow granular matter.

Cervical Region. The column of Goll and the lateral columns are considerably degenerated. Slight degeneration is found in the columns of Burdach. In the lateral columns the degeneration extends farther forward than the area of the crossed pyramidal tracts. The direct cerebellar tracts and Gowers' tracts are a little affected. The nerve cells of the anterior horns are in much the same condition as those in the lumbar region. The Marchi method shows considerable degeneration in each crossed pyramidal tract in the lumbar region and of the columns of Goll in the cervical region.

Case II.—M. B., female, aged twenty-eight years, single, was admitted to the Philadelphia General Hospital, June 11, 1902, in the service of one of us (Dr. Spiller). The notes made at that time (Dr. Spiller) are as follows: In February of this year the patient suffered with intense pain all over the back, and a little later the lower limbs became weak. Eight weeks ago her legs gave away, and she fell out of her chair, but she says her lower limbs were weak before the fall. There is no weakness of the upper limbs. Her family history and personal history are negative. Six or seven years ago she had numerous abscesses in front of the chest and abdomen, the scars of which can be seen.

Four years ago the patient was thrown down by a bicycle. She has been operated upon twice for necrosis of the bones of the knees. The present examination shows that the legs are flexed at the knees and the thighs upon the abdomen. The feet are contractured in extension, and the contractures at each knee are distinct, especially at the right knee. All the extremities are wasted, the lower especially. Trophic disturbances are present in the feet and soles. The loss of power in both lower extremities is almost complete, except that the patient can flex the right thigh slightly upon the hip. The patellar jerks are much exaggerated, especially this reflex on the left side. Ankle clonus is present on the left side, but not on the right. Both Achilles jerks are exaggerated. The Babinski reflex is obtained on each side. Sensation for touch and pain is irregularly absent over the dorsal surface of each foot. Any irritation of the limbs causes pain in the feet and back. It is probable that hyperalgesia exists in the lower limbs, as a slight pin-prick causes severe pain in the back and limbs. The upper limbs are normal, the reflexes and sensation not being disturbed. Bedsores are present over the sacrum.

At the autopsy the seventh, eighth, and ninth thoracic verterbæ were found soft and friable, and the meninges were thickened, but were not adherent to the cord. The meningeal vessels were dilated. Gross examination of the cord showed about the mid-thoracic region on the outer side of the dura, on its anterior and right side, a tuberculous mass about two and one-half inches long. Its upper portion reached to the mid-thoracic area.

Microscopic Examination. The secondary degeneration in the columns of Goll in the cervical region is slight, as is also the secondary degeneration in the crossed pyramidal tract of the lumbar region. Recent minute hemorrhages are found in the gray and white matter of the cervical region. The nerve cells of the anterior horns of the lumbar region appear to be normal, while those of the cervical region may be a little diseased. The anterior and posterior roots of the lumbar and cervical regions are normal.

Neither in the history of this case nor in the post-mortem record is there any mention made of a spinal deformity, and one

of us (Dr. Spiller) has a distinct recollection that there was no deformity of the vertebral column in this case. Absence of deformity is rather unusual in a case of spinal caries. Most authors admit that this may occur.

Case III.—E. P., female, aged forty-nine years, housewife, was admitted to the nervous wards of the Philadelphia General Hospital, April 18, 1903, service of Dr. Pearce. Her father died of tuberculosis. She has had the ordinary diseases of childhood, denies venereal history, and says she never drank. A daughter says that the patient had rheumatism of one or both ankles six years ago, occurring at irregular intervals, and later involving both knees. There was no weakness or stiffness of the lower limbs, and the wrists were not involved until two years ago, when the daughter says that the contractures of the lower extremities began. One year ago the patient began to act strangely, would declare she saw strange faces, had delusions of varying character, and at times became violent. She had at this time attacks of violent pain in her stomach and had vomiting spells. The physicians at that time made a diagnosis of cancer of the stomach.

The patient came into the service of Dr. Spiller, June, 1903. Notes made about one month after admission by one of us (Dr. Weisenburg) are as follows: The patient's mental condition is poor. Bed-sores are present over the buttocks, and there are sores over the malleoli of both ankles. There is incontinence of urine and feces. The lower limbs are flexed—the leg on the thigh, the thigh on the abdomen. The left leg is swollen, the right is not. Both knee-joints are decidedly swollen. Pressure over the patella does not show any fluid in the knee-joints, which are rigid. The patient complains of pain at the slightest pressure. On turning the patient over from side to side no movement of the knees is seen. It is impossible to test for the reflexes of the lower extremities on account of the pain. Plantar irritation produces no movement of the toes in either direction.

Resistance to passive movement of the upper extremities is poor, and the grip of each hand is almost nil. The distal and middle phalanges are in extension. Atrophy of the hands and forearms is marked on each side. The biceps jerks are present on each side, but diminished, while the triceps and wrist reflexes

are absent. One month ago Dr. Mann attempted to straighten the knee-joints under ether, and extension was applied to the lower extremities, but without satisfactory results.

The blood count at this time was as follows: Hæmoglobin, 58 per cent.; white corpuscles, 11,000; red corpuscles, 3,180,000. Differential count showed nothing. The urine was normal.

A further examination (by Dr. Spiller), June 2, 1903, gave the following results: The patient has had incontinence of urine and feces for the last three months. She seems to have difficulty in hearing. The deafness was not present when her daughter last saw her. Any handling of the patient causes her great pain. The face is much emaciated. The pupils are equally dilated, and respond equally and promptly to light. There is no paralysis of the facial nerve on either side. The masseter contracts on each side, but not forcibly. The tongue is protruded in the median line, and there is no tremor or atrophy. The upper limbs are much emaciated, especially the hands, and voluntary movement of the upper limbs is much restricted, especially at the shoulder and elbow. The patient never bends her fingers, and moves her hand with the fingers extended. The biceps, triceps, and wrist reflexes are absent on each side. Pin-prick is felt in each hand. Attempt to take any of the reflexes of the upper and lower limbs gives great pain. There is great tenderness to pressure along the spinal column. She cannot move the lower limbs at all, and these limbs seem to be completely paralyzed. The patient's mental condition is impaired, although she understands what is said to her, if said distinctly.

She died June 3, 1903.

The necropsy was performed by Dr. Yates. A few old foci of tuberculosis were found at the apex of each lung. Both knee-joints were filled with what was considered to be tuberculous pus, and the bones were eroded. The breasts were negative, as was also the stomach. There was no general glandular enlargement. There was also fatty degeneration of the liver and heart, and the kidneys were in a state of chronic parenchymatous nephritis.

The results of the microscopic examination are as follows:

The nerve cells of the anterior horns of the cervical and lumbar regions are intensely altered, as shown by the thionin

stain. Many of these nerve cells are much shrivelled and have lost their dendritic processes. Some are merely small masses of pale-yellow granular matter, with only a trace here and there of chromophilic elements. In some places the cells are so diseased that they appear as mere shadows. The alteration of the nerve cells of the anterior horns is as intense in the cervical region as in the lumbar.

There is no evidence of myelitis or meningitis. The blood-vessels of the cord and pia are not diseased, and there is no round-cell infiltration. The direct and crossed pyramidal tracts are not in the least degenerated. Notwithstanding the intense alteration in the cells of the anterior horns, the anterior roots appear to be very little affected, as shown by the acid fuchsin stain. No degeneration of the spinal cord is shown by the Marchi method. A piece of nerve removed from one of the limbs, and probably from the distal portion, as it has been customary to take a nerve from the distal portion of the limbs, shows considerable degeneration by the Weigert hæmatoxylin and acid fuchsin stains. A piece of muscle that was probably removed from one of the thenar eminences or the sole of the foot is intensely atrophied, and the small nerve fibres contained within these sections of muscle are much degenerated, as shown by the Weigert hæmatoxylin stain. A piece of the same muscle stained by the Marchi method shows no recent degeneration.

The clinical picture presented by this case—viz., the partial paralysis of the upper and the total paralysis of the lower extremities, the implication of the sphincters, the great emaciation, the contractures of the limbs, the great tenderness to pressure along the spinal column, the extreme pain and tenderness, even at the slightest pressure over any part of the limbs, and the history of possible cancer of the stomach—was typically that of paraplegia dolorosa, and the diagnosis of vertebral carcinoma was made.

The microscopic examination revealed the findings of a chronic multiple neuritis. We do not see how it would have been possible, even reviewing the case in the light of the pathological findings, to have made a correct diagnosis during the life of the patient with such a symptom-complex as that detailed.

A very interesting point in the history of Case I. was the bulbar involvement. The notes read: "The muscles of the face are extremely atrophied; the lips are very thin; the tongue is atrophied on each side and is protruded very slightly beyond the line of the teeth. There are no fibrillary tremors of the face or tongue. The fifth and seventh nerves are normal." There is no note made of the character of the speech or of the ability to swallow, but the patient was in such a serious condition that the examination could not be complete, and opportunity was not given to examine her a second time. It is probable that the atrophy of the face was part of the general extreme emaciation, but the involvement of the tongue was distinctly pathological.

Bruns[1] records a similar case of vertebral carcinomatosis where there were distinct bulbar symptoms. These consisted of a right-sided atrophy and paralysis of the tongue, right-sided paralysis of the soft palate, difficulty in swallowing, increase of the pulse rate, and occasional vomiting. The atrophy and paralysis of the tongue became bilateral. The macroscopic examination gave no explanation of the bulbar symptoms. We have been unable to find another similar case.

In 1897 Schlesinger[2] called attention to the fact that in diseases causing contraction of space in the uppermost part of the spinal canal, especially tumors, the clinical symptoms may be ushered in by bulbar phenomena. He reports a case in which the disease began with sudden bulbar manifestations, followed by spinal symptoms. At the autopsy a solitary tubercle in the uppermost cervical cord was found. A careful microscopic examination of the bulb revealed nothing to explain the condition, and Schlesinger therefore concludes that through circulatory disturbances in the neighborhood of the tumor, possibly through transitory œdema in the region of the nuclei, the bulbar symptoms might be explained.

Nonne[3] records a case of intramedullary ascending sarcoma in which, as soon as the lesion approached the cervical cord, bulbar symptoms became manifest. Microscopic examination did not

[1] Archiv f. Psych. u. Nerven., vol. xxxi. p. 162.
[2] Deutsche Zeitschr. f. klin. Med., vol. xxxii., sup. heft, p. 98.
[3] Archiv f. Psych. u. Nervenheil., 1900, vol. xxxiii. p. 410.

reveal anything explanatory of these symptoms. Nonne regards them as an expression of intoxication. He quotes cases reported by Gläser,[1] Oppenheim,[2] and Senator,[3] in support of this opinion. In Gläser's case there was a glioma of the medulla oblongata which extended downward as far as the sixth cervical segment. Basal symptoms were prominent. Oppenheims' case was one of lymphosarcoma of the anterior mediastinum, with the symptom-complex of polioencephalomyelitis. Bulbar symptoms were pronounced. The microscopic examination did not explain the symptoms, and Oppenheim thought the lymphosarcoma was the cause of the symptom-complex. Senator's case was one of multiple myelomata of the ribs, with nephritic complication. Here, too, the bulbar symptoms were prominent, and the findings did not satisfactorily explain the symptoms. The macroscopic examination of the medulla oblongata in our case revealed nothing, but in the microscopic examination some of the cells of the hypoglossus nuclei were found distinctly diseased. The nuclei of some of the cells were displaced toward the periphery, the chromophilic elements were disintegrated, and in some of the cells there was an excess of yellow pigment. We were not able to detect any implication of the hypoglossal nerves in a carcinomatous mass, and it is probable that the alteration of the hypoglossal nuclei was caused by some poisonous product of the numerous carcinomata.

[1] Deutsche med. Wochenschr., 1897, No. 52, p. 835.
[2] Deutsche Zeitschr. f. Nervenheilkunde, vol. xv. p. 1.
[3] Berliner klin. Wochenschr., 1899, No. 8.

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THE EARLIER CHANGES IN ARTERIOSCLEROSIS OF THE NERVOUS SYSTEM.*

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It is impossible to make a sharp distinction between the early and late manifestations of arteriosclerosis in the nervous system; there are, however, certain lesions that occur in cases of advanced arterial disease, and are known to every physician; these I shall refer to briefly. Under the late lesions I include areas of extensive softening, secondary degeneration, etc. As life advances, the bloodvessels, especially those at the base of the brain, become sclerotic and often atheromatous, and areas of softening in the basal ganglia, pons, or the white matter and cortex of the cerebrum are not uncommon, and are most frequently produced by thrombosis. Several areas of softening may occasionally be seen in the brains of persons who have passed beyond middle life. Lapinsky [1] has found that with rare exceptions the capillaries of the cerebral cortex are diseased when the large vessels at the base of the brain are sclerotic, and in such cases the lumina of some of the capillaries are much diminished or even occluded. We are therefore justified in concluding that intense alteration of basal vessels is indicative of alteration of the brain capillaries.

An area of softening in each lenticular nucleus or near the internal capsule of each side, even though small, may cause a symptom-complex known as pseudobulbar palsy; these areas of softening are usually the result of arteriosclerosis.

It is said sometimes that arteriosclerosis cannot be distinguished from syphilitic disease of the bloodvessels. This, I think, is a mistake. Syphilis is a frequent cause of arteriosclerosis, especially when the latter occurs in the young, and in some cases

* Read by invitation.

the arteriosclerosis may be a parasyphilitic affection, in the same manner in which tabes dorsalis is a parasyphilitic affection. This form probably cannot be distinguished from other forms of arteriosclerosis. I have seen the brain and cord from many pronounced cases of nervous syphilis, and occasionally have been unable to detect anything abnormal with the naked eye. This absence of macroscopic lesions is not true of every case of syphilis of the nervous system. In those cases in which little or nothing can be detected by the naked eye a microscopic examination probably will show, if the disease be syphilis, thickening of the pia, adhesion of the pia to the spinal cord or brain, round-cell infiltration of the pia or of the walls of the vessels, and possibly miliary gummata arising in the pia and extending into the cord. These are not the lesions of arteriosclerosis, and in this opinion I am supported by Sander,[2] Degenkolb,[3] and others. According to Degenkolb perivascular round-cell infiltration is not caused by arteriosclerosis, but only by infections and intoxications. This view I believe to be correct.

Since the investigations of Charcot and Bouchard, in 1868, miliary aneurysms of the brain have been regarded as the common cause of cerebral hemorrhage. These aneurysms are probably a result of arteriosclerosis. Von Monakow,[4] in speaking of them, refers to the writings of Vulpian, Eichler, Weiss, Zenker, Roth, Arndt, Ziegler, and Löwenfeld, and states that at the present time they are the most probable source of cerebral hemorrhage. Some seem to regard them as the only source of cerebral hemorrhage not traumatic in origin. L. W. Weber[5] reports a case that leads him to conclude that multiple spontaneous cerebral hemorrhage may occur in severe vascular disease without the formation of miliary aneurysms, and more recently Ferrand has published a thesis in which he ascribes to the lacunes, described by Marie, and mentioned farther on in my paper, a prominent part in the formation of cerebral hemorrhage. I have not been able to obtain his thesis, but in a review of it the statement is made that Ferrand[6] believes the miliary aneurysm is infinitely less common than is usually supposed, and that the common cause of hemorrhage in the brain is the lacune.

The blood pressure is increased in arteriosclerosis by the rigidity

of the walls of the vessels and by the contraction of the lumen; therefore any unusual exertion may cause rupture of a diseased cerebral vessel, and it is not necessary to assume that miliary aneurysms exist.

According to L. Jacobsohn[7] the two regions in which arteriosclerosis of the brain is most manifest are the large basal ganglia and the pons, with the medulla oblongata. The investigations of Heubner, Duret, and others have shown that the arteries of the cerebral cortex anastomose, whereas those of the basal ganglia and of the white matter are end arteries, as are also the arteries of the brain stem. The end arteries of the internal capsule and brain stem ascend almost perpendicularly as small vessels coming from much larger ones, and therefore the blood pressure in these small vessels is high. In the pons thrombosis is more common than hemorrhage.

Binswanger and Alzheimer[8] have studied the degeneration of the brain caused by arteriosclerosis. The weight of the brain is diminished, the perivascular spaces are enlarged, the ventricles are dilated, the nerve cells are pigmented, the vessels of the white matter and of the cortex are degenerated and tortuous, and fatty granular cells and blood pigment are found in the perivascular spaces; the glia about the vessels is thickened and spider cells are found, many nerve cells are degenerated, and the medullated fibers are fewer than normal.

In some cases they also found that the arteriosclerosis affects the vessels of the basal ganglia and the brain stem more than those of the cortex. These pathologic alterations cause pronounced symptoms such as headache, vertigo, loss of power of attention, failure of memory, and mental dulness. In pronounced cases the symptoms are more intense, and dementia may develop.

It seems to me not improbable that impairment of mental activity in advanced age may have some relation to the pigmentation of the nerve cells that increases so markedly after middle life is passed. It would be difficult to prove this, but theoretically we may hold that the large accumulations of pigment masses within the nerve cell must interfere with its function. The term pigmentary degeneration, employed for this process, is, therefore, wisely chosen.

The diagnosis of paretic dementia in the aged should be made with great care. A. W. Campbell [10] has shown that in some cases in which this diagnosis from the clinical side seemed positive the lesions of paretic dementia were not found, and those of senility were present. He was able to observe opacity and thickening of the membranes, increase of cerebrospinal fluid, extreme wasting of the brain and other changes common to both diseases, yet the microscopic features were distinctive, and in addition certain alterations were evident, such as marked chronic endarteritis, embolic and thrombotic softenings, and perivascular hemorrhages with destruction of the surrounding tissue in the basal nuclei and in the pons. These are common changes in senility, but rare in paretic dementia. The symptoms of paretic dementia caused by arteriosclerosis have been observed by others (Binswanger, Alzheimer).

Marie [11] first showed in his large service at the Bicêtre, where are many aged persons, that hemiplegia of the aged is not the result most frequently of cerebral hemorrhage or softening, but of a lacunar process. He expresses surprise that comparatively little attention has been given to this subject. These cavities are of irregular shape, and may vary from the size of a millet seed to that of a large pea, and rarely may be so large as a bean. There may be only one cavity in a cerebral hemisphere, or there may be ten or more in the two hemispheres. They are found most frequently in the external segment of the lenticular nucleus or in the optic thalamus, and not infrequently in the pons. Granular cells are found about these spaces when they are of recent formation. The condition has been described as microscopic softening. In brains in which these cavities are found the bloodvessels are sclerotic; the pia is moderately thickened; the convolutions, especially those of the frontal lobe, are atrophied; the ventricles are dilated; the choroid plexus is often cystic. The vessels of the spinal cord in these cases are sclerotic, and sometimes diffuse sclerosis is found in the posterior columns. It is not senility that causes these lesions, but senility with arteriosclerosis. The cavities are formed by the rupture or closure of small bloodvessels. The transient hemiplegia of the aged is probably caused by the formation of one or more of these small cavities, and this is a subject of great clinical importance.

The état criblé of Durand-Fardel, found in the brain of the aged, consists of many minute cavities in the white matter, of the size of the point or the head of a pin, that are formed by repeated congestion of the bloodvessels. Each cavity contains a bloodvessel, and is a perivascular dilatation.

It is uncertain to what extent senile dementia is caused by arteriosclerosis. Alzheimer says that some authors believe that senile dementia is caused by the atheromatous condition, whereas others think that an hereditary weakness of the central nervous system produces an early atrophy of the nerve cells in association with the malnutrition brought about by the diseased vessels. In a case of presenile dementia that Alzheimer studied, intense atrophic changes were found in the nerve cells, but the atheromatous alteration of the vessels was unimportant. It seems to him possible that the arteriosclerosis of other organs, for example, of the kidneys, may cause alteration of the blood, and in this way affect the nerve cells. This view is disputed.

According to Noetzli, cited by Alzheimer, there is a loss of about two hundred grams in the weight of the brain of the male or female in senile dementia.

Redlich[12] has described a condition in the brains of those who have had epilepsy and senile dementia that he has called miliary sclerosis. Numerous plaques of the size of a ganglion cell, or four to six times this size, were found in the cerebral cortex. They were especially numerous in the pyramidal cell layers. According to Redlich they were derived from neuroglia cells, and contain many fine fibers, although in some plaques the tissue was homogeneous and not fibrillar. Pronounced arteriosclerosis was present in each case. It is uncertain whether this miliary sclerosis is in any intimate relation with arteriosclerosis, but it seems probable that it is.

The explanation that Hirsch[13] gives for optic atrophy occurring with cerebral arteriosclerosis is interesting. Optic atrophy is not rare in this condition, and is caused mechanically by pressure. The optic nerve and the ophthalmic artery pass through the optic foramen in a common sheath. There are cases on record in which the necropsy showed a marked thickening of the artery at this place, in consequence of which the nerve was compressed and atrophied.

Arteriosclerosis produces distinct alteration of the spinal cord. E. Demange[14] has described perivascular sclerosis and minute hemorrhages occurring in the spinal cord in arteriosclerosis, and very recently Pic and Bonnamour[15] have mentioned the finding of similar sclerotic areas, but the lesions in their cases seem to have been slight.

The changes that occur in the spinal cord in arteriosclerosis, according to Sander,[16] are not caused by the contracted kidney, occurring with arteriosclerosis, as some have thought. In the early forms of arteriosclerosis the most intense degeneration may occur in the nervous system, although the general disease is slight. Arteriosclerosis in the kidneys causes changes in the nervous system only in proportion to the marasmus it produces.

In the cases of senility studied by Sander changes were found in the white and gray matter of the cord, and these consisted chiefly in a loss of nerve fibers, especially in the peripheral portions of the lateral columns, with proliferation of the neuroglia. The nerve cells had undergone pigmentary degeneration. The vessels were thickened, and some of them were thrombotic. Round-cell infiltration of the pia or of the walls of the vessels was unimportant.

It seems to me surprising that the changes described by Sander as presenile, and depending on arteriosclerosis, could in some cases be so intense as he pictures. The alteration of the cord, caused by senility according to him, may be the same as that caused by pernicious anemia. I find it difficult to believe that such pronounced alteration of the spinal cord is caused by arteriosclerosis alone, because I have never seen it in the many spinal cords I have studied.

Arteriosclerosis of the spinal cord has been studied in this country especially by Wm. Hirsch. According to him the cells of the anterior half of the cord are more likely to be affected than those of the posterior part, and this he attributes to the peculiarity of the blood supply of the cord. The anterior spinal arteries are less numerous than the posterior, and the anterior arteries anastomose so as to form one longitudinal vessel on the anterior surface of the cord. The posterior arteries are six in number, and run parallel from the upper part of the cord to the conus. We can

readily understand that disease of the anterior arterial supply is likely to be more serious than disease of the posterior supply.

The lower part of the cord, according to Hirsch, is more frequently affected than the upper, and this he explains by the more direct blood supply in the lower region of the cord, and the less protection thereby afforded to the arterioles of the anterior horns in the lumbar and sacral regions against an increased blood pressure.

Motor and trophic disturbances, therefore, are more common than sensory symptoms in arteriosclerosis of the spinal cord, and are more prominent in the lower limbs.

Hirsch[17] believes that arteriosclerosis occurring at the posterior half of the lower part of the cord may, by the proliferation of interstitial tissue, cause a degeneration of the posterior columns, and in this way produce conditions which even anatomically resemble tabes.

Arteriosclerosis is not confined to any one part of the body, but in some cases the spinal symptoms may predominate.

Redlich[18] has found in paralysis agitans in the posterior and lateral columns small islands of sclerosis that had their origin in the vessels, and were therefore perivascular. The small vessels within the white matter have a narrow lumen, because of the thickening of the vessel walls. The arteries of the spinal pia are also thickened. In some places the nerve fibers of the white matter of the spinal cord appear atrophied; in others they have disappeared. In the cervical region the columns of Goll are slightly sclerotic. The nerve cells of the anterior horns are deeply pigmented. Amyloid bodies are numerous. These lesions are regarded by certain investigators, with whom I must agree, as signs of senility, and Redlich also is inclined to regard some of them as of this character. He thinks that the sclerosis of the bloodvessels of the cord is probably a part of the endarteritis deformans of the larger vessels. The lesions he describes as occurring in paralysis agitans he acknowledges are found sometimes in aged persons who have not had paralysis agitans. He is able to refer to a number of authors who have reported lesions in paralysis agitans like those he has described; and I have seen them in quite a number of cases.

With a knowledge of the existence of these lesions in the spinal cords of certain aged people we can understand the causes of the contractures, especially of the lower limbs, the subjective disturbances of sensation, the changes in the tendon reflexes, etc., that occur in some old people, and that have been studied by Demange, Copin, Gowers, Redlich, and others.

A few words in regard to the changes produced by arteriosclerosis in the peripheral nerves. Some years ago I attempted to obtain evidence that degeneration of bloodvessels produces changes in the nerves of the same territory. I may refer to my remarks made at that time.[19]

Schlesinger[20] says that the primary nature of the vascular disease and the secondary nature of the neuritis are not recognized by all, but he thinks that the vascular alteration occurs first. He reports a case in which pain in the feet and livid discoloration of the feet and hands were followed after some months by gangrene of the left foot. The left foot was amputated, and the arteries and veins of the nerves within it were much thickened. The nerve fibers were normal in many bundles, but in most they were more or less altered and the connective tissue of the nerves was proliferated. He thinks that without doubt the vascular degeneration occurred before the degeneration of the nerve fibers in this case, and he seems to have based this opinion chiefly on the clinical signs, and yet the disease began with pain in the feet as well as with livid discoloration.

When closure of an artery occurs the degeneration of the nerves may be only in the part below the thrombus, as seen in cases studied by Lapinsky. It is not necessary to quote many examples of this. We can accept without dispute the statement that a nerve speedily degenerates when the blood supply is abruptly cut off. Lapinsky says that in cases of acute ischemia he found the changes of the nerve fibers more marked toward the distal ends, where the effects of closure of the arteries were most felt.

The nerve changes were not so perceptible in chronic vascular disease, and, according to Lapinsky, they have been seen in comparatively few cases. In some cases the changes of the nerve fibers were very slight and occurred only in certain areas; in other cases the nerve fibers were well preserved and the connective

tissue about them was proliferated; in still other cases the nerves were perfectly normal. Lapinsky has collected the reports of a number of cases from the records bearing on this subject. He observed eight cases of vascular disease; in seven of these the arteries of one lower extremity were affected, and in one the arteries of both extremities were diseased, and gangrene developed in the part imperfectly nourished. The connective tissue of the nerves was increased in all the cases, and this was especially true of the endoneurium.

He concludes, after a careful study of the subject, that chronic endarteritis or arteriosclerosis may cause degenerative changes in the nerves nourished by the diseased vessels; the nerve fibers are very resistant, but the connective tissue proliferates.[21]

Joffroy and Achard[22] seem to have been the first to describe neuritis of vascular origin. In a case of neuritis they found that the most pronounced lesions of the vessels were associated with the most pronounced lesions of the nerves, and from this they concluded that the degeneration of the nerves was due to the thickening and obliteration of their nourishing arteries. Neither this case nor the one published by Dutil and Lamy[23] establishes beyond question the vascular origin of neuritis, although such an origin seems very probable. Dutil and Lamy say that in their case the parallelism existing between the vascular and nervous lesions justifies attributing the degeneration of the nerves to the thickening and obliteration of their nourishing arteries.

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MULTIPLE SCLEROSIS, WITH A REPORT OF TWO ADDITIONAL CASES, WITH NECROPSY.[1]

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Multiple sclerosis has been attracting much attention recently on account of the statements made regarding its infrequency in America. The views held regarding this subject are well presented in a paper by E. W. Taylor and J. W. Myer[2] published in 1903, and statistics are given by them. In contrast with these statements we find that L. Bruns[3] says that during a period of twelve years he had made the diagnosis of multiple sclerosis 70 times in 5,500 cases of nervous disease, or in 1 1-3 per cent. Twenty-one of these patients (30 per cent.) had symptoms of optic nerve disease. The diagnosis of multiple sclerosis was positive in only 38 of the 70 cases, and the 20 cases (above he speaks of 21 cases) with optic nerve affection were included in these 38 cases, making 58 per cent. Redlich,[4] in a paper published in 1903, remarks that multiple sclerosis is one of the most frequent diseases of the central nervous system.

Two cases of multiple sclerosis with necropsy were reported by one of us (Spiller[5]) in January, 1903, and two additional

[1]Read before the Philadelphia Neurological Society, Dec. 22, 1903.
[2]Taylor and Myer. Boston Medical and Surgical Journal, April 9, 1903.
[3]Bruns and Stölting. Monatsschrift für Psychiatrie und Neurologie, Feb. and March, 1900.
[4]Redlich. Die Deutsche Klinik, 1903.
[5]Spiller. American Journal of the Med. Sciences, Jan., 1903

cases with necropsy have occurred in his services at the Polyclinic Hospital and the Philadelphia Hospital, and are reported in the present paper. These make six cases with necropsy reported in detail in America. The other two were reported by Burr and McCarthy[6] and by Hunt.[7] The frequency of multiple sclerosis in Europe is well known, and in 1898 attention was called by one of us (Spiller[8]) to the rarity of the diagnosis in America. At that time little or nothing had been said concerning this subject further than the remark in the edition of Dana's text-book published in 1892 and omitted in later editions.

The two additional cases with necropsy which we now report are as follows:

Case 1.—Miss M. C., twenty-eight years of age, a dressmaker by occupation, was referred to the Polyclinic Hospital, clinic of Dr. Spiller, August 19, 1903. The notes of the first examination made by Dr. Weisenburg are as follows:

Her father died from "consumption of the bowel." Her mother has rheumatism and is hysterical.

Miss C. began to menstruate when she was twelve years old, and has been very irregular. She began sewing when she was sixteen years of age. She has always been sickly and very nervous. Last September she noticed stiffness in her lower limbs when she got up in the morning, and she had difficulty in moving her lower limbs. She had also a numb sensation in these limbs and could not feel a pin prick at all. She never has had pain, although she has a sensation as of a tight band about the lower limbs. The sensation of stiffness has partially disappeared, but when she grows excited the paresthesia is increased. When she gets up in the morning she feels as though she were walking on rubber. She was confined to her bed for seven months. About last Christmas she noticed that she could not hold her urine so well as previously. She is obstinately constipated. Her memory is somewhat impaired, and the vision of the right eye seems diminished. The upper limbs have not been stiff. She says that at times she drags her left lower limb and may fall while walking.

She walks well with her eyes open, but is ataxic, although she does not fall, when her eyes are closed. She staggers when standing with eyes closed. The patellar reflex is exag-

[6]Burr and McCarthy. Journal of Nervous and Mental Disease, 1900.

[7]Hunt. American Journal of the Medical Sciences, Dec., 1903.

[8]Spiller. The Philadelphia Polyclinic, 1898, p. 147.

gerated on each side, but more so on the left, and patellar clonus is obtained on the left side. Ankle clonus is not present. Babinski's sign is obtained on each side. The upper limbs are not affected. She has inframammary and inguinal tenderness.

The pupils are equal and the irides respond to light and in accommodation and convergence. The tongue is normal. The fifth and seventh nerves are not affected.

Miss C. was admitted to the Polyclinic Hospital September 9, 1903, and was seen by one of us (Dr. Spiller), and the notes then made are as follows:

The patient shows no muscular atrophy. The lower limbs are not spastic. The patellar reflex is a little exaggerated on each side, and there is a tendency to patellar clonus on each side, but no true patellar clonus. The Achilles jerk is normal on each side; Babinski's reflex is present on each side, the big toe being moved distinctly upward. Tactile sensation is preserved all over the body, but the patient says she feels a touch more distinctly in the upper limbs than in the lower. Pain sensation seems to be normal everywhere. She has some inguinal tenderness on the left side. The grasp of the hands is normal. Resistance to passive movement in the upper limbs is normal. The biceps tendon, triceps tendon and wrist reflexes are normal on each side. The pupils are equal, or possibly the right is a little smaller than the left. The reaction of the iris to light and in accommodation is normal The tongue is protruded straight and shows no tremor and nc atrophy. The facial muscles are not implicated on eithei side. Constipation is obstinate. Speech is not affected. Nystagmus was not observed in this or in any examination. Speech was not peculiar. A diagnosis of diffuse lesions in the posterior and lateral columns was made.

On September 16 a note was recorded that the patient was delirious and talked irrationally, and had had involuntary micturition while asleep. The patient was found excited and anxious about her condition, and probably worried by something that had occurred in her past history, but she was rational.

On September 18 she was sitting quietly in the ward. She got up suddenly and jumped out of a third story window. She was not unconscious as a result of this fall, and her head did not appear to be injured. Both bones of the right forearm were broken at the lower third and a compound comminuted fracture of the left wrist was found. The back of the trunk was badly contused over the buttocks as high as the lower thoracic vertebræ, and a depression over the spinal column was found at the lumbo-thoracic junction. The lower limbs were paralyzed.

On September 19 the following notes were made: The pa-

tient talks freely and it is evident that she is worried by some private affair. The bowels and bladder are paralyzed. She has complete paralysis of the lower limbs and cannot even move the toes. The patellar reflex is lost on each side. There is no ankle clonus and Babinski's sign is not obtained. The level at which sensation for touch is preserved can not be accurately determined because of the patient's inability to fix her attention on the examination. A pin prick is not felt at all in the left lower limb, and very imperfectly in the right lower limb; but is felt over the whole of the abdomen. The head and upper limbs except where the fracture has occurred, are not affected.

An X-ray examination made September 22 seemed to show an injury of the second and third lumbar vertebræ.

The patient had fever about 101°, varying from 1½ to 2° daily, pulse 116 to 132, respiration 24 to 28. She became gradually weaker and died October 3.

The necropsy was made by Dr. Randolph. His notes abbreviated are as follows: Extravasation of blood is found over the lower anterior surface of the sternum, and especially over the anterior surface of the spinal column. A subdural hemorrhage is present over both occipital lobes, but the skull is not fractured. The first lumbar vertebra is fractured, and the body of this vertebra is displaced backward. At the seat of fracture the spinal cord is softened and disorganized, but above this level the cord appears to be normal.

The microscopical examination gives the following results: The spinal cord below the third lumbar segment is softened as a result of the fracture of the first lumbar vertebra. Sections from the lower part of the second lumbar segment or upper part of the third lumbar segment show several areas of sclerosis, and the area of the left crossed pyramidal tract contains fewer nerve fibers than in normal sections, and presents the appearance of secondary degeneration. Symmetrical areas of sclerosis are found in the anterior and posterior columns. In sections stained by hemalum and acid fuchsine a slight round cell infiltration is seen about some of the vessels in the spinal cord and in some parts of the pia. The nerve cells of the anterior horns stained by the acid fuchsine are much degenerated. They are swollen and their nuclei are eccentric. This alteration is probably the result of the fracture. The Nissl method could not be employed. Sections from about the same level stained by the Marchi method show much recent degeneration widely distributed. Numerous bundles of degenerated fibers coming from the posterior roots are seen entering the left posterior horn. Similar bundles are not found in the right posterior horn, because at this level the right posterior horn was implicated in a sclerotic

area and the medullary sheaths of many of the nerve fibers coming from the posterior roots have disappeared.

At the tenth thoracic segment the areas of sclerosis are numerous. Marchi sections from this level show much recent degeneration in the sclerotic areas, as well as some degeneration that is secondary and resulting from the fracture of the spinal column.

The areas of sclerosis are even more numerous at the eighth thoracic segment than at the tenth thoracic segment.

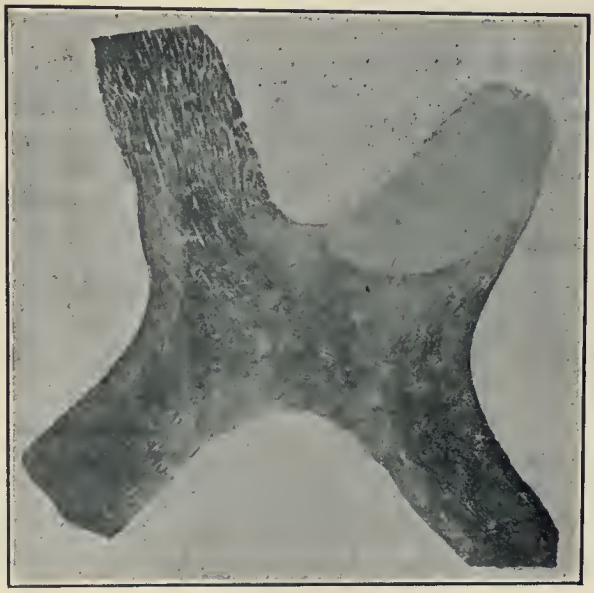

Fig. 1. Photograph of the optic chiasm and optic nerves from Case 1, showing the right optic nerve sclerotic as high as the chiasm and sharply defined from the normal tissue of the chiasm. The left optic nerve is well stained.

At the seventh thoracic segment the areas of sclerosis in the anterior columns are symmetrical.

Throughout the thoracic region some round cell infiltration is found about the blood vessels of the cord, but it is impossible to determine any direct connection between this infiltration and the sclerotic areas.

Sclerotic areas are found in the lower cervical region. The nerve cells of the anterior horns at this level are not much altered. The upper part of the cervical region was not obtained at the necropsy.

Sclerotic areas are not seen in the medulla oblongata or pons.

The right optic nerve is almost completely degenerated as far as the commissure, where the degenerated area is sharply marked off from the normal area. The left optic nerve is not degenerated.

Case 2.—P. B., a male, aged twenty-four years, came to the Polyclinic Hospital May 19, 1898, to the service of one of us (Dr. Spiller). He had been a collector, and in this occupation had walked much and been much exposed to wet and cold; later he had worked in a machine shop.

The family history is unimportant. The patient denies venereal disease but says he had masturbated freely. He has been losing power in his lower limbs for the past nine months, but has no loss of power in the upper limbs, and no pain anywhere, no headache and no involuntary seminal emissions. About five months previously he had difficulty in holding his urine, but only during a period of about two weeks. He has been constipated during the past two months. He has no girdle sensation. Sight has been poor during the past year. Six or seven months previously he frequently stubbed his toes in walking.

His gait is very ataxic. Romberg's sign is present. The patellar reflex is much exaggerated on each side, but ankle clonus is not obtained on either side. Achilles jerk is very prompt on each side. Sensation is normal everywhere. The upper limbs are distinctly ataxic. The irides react promptly to light and in accommodation, and the voluntary movements of the eyeballs is good. Slight nystagmus is present when the patient looks to the right and upward. Contraction of both visual fields is present, and is most marked in the temporal side. There are no gross changes in the eyegrounds.

The patient was lost sight of after he had been coming to the clinic for a long time, but in the early part of 1901 he was admitted to the Philadelphia Hospital and soon came into the service of Dr. Spiller. He had been confined to his bed about a year on account of weakness of the lower limbs. Atrophy had not developed.

Notes made April 9, 1901, are as follows: The patient is unable to walk at all. He can stand a few minutes with support, but his legs soon give away. Both upper and lower limbs are incoördinate, and the left lower limb more so than the right. The reaction of the iris to light and in accommodation is slow. Nystagmus is present. The extraocular muscles are not affected. Beginning optic atrophy is found in each eye. The facial muscles are not implicated, and the tongue is protruded straight.

September 10,1901.—The lower limbs are somewhat emaciated, but not excessively so. No contractures are observed anywhere. The lower limbs are spastic, and the spasticity is increased by passive movements. The patellar reflexes and the Achilles tendon reflexes are exaggerated, and ankle clonus is obtained. Sensation for touch and temperature is diminished in the lower limbs, but for pin prick is normal. Babinski's sign is present on each side. Both lower limbs are paralyzed, but the toes can be moved slightly. He is unable to raise himself in bed, and turns his body over with great difficulty. The voluntary movements of the upper limbs are good. Speech is weak and slow, but not scanning and not explosive.

July 31, 1903.—There is slight ptosis of each upper eyelid. Nystagmus is present when the patient looks directly in front of him. Speech is somewhat explosive but not scanning. The upper limbs are weak. The man is emaciated. Intention tremor is present and more marked in the left upper limb than in the right. Tactile sensation is lost in the portion of the body between the knees and a line two inches below the nipples, but sensation for pin prick is preserved everywhere. He has no incontinence of urine and feces.

An examination of the eyes made about this time showed that the temporal side of the disc in each eye was abnormally white, suggesting incipient atrophy.

The man died August 10, 1903, from phthisis and chronic nephritis.

A microscopical study of the spinal cord and brain from this case gives the following results:

The areas of sclerosis are very extensive throughout the spinal cord and medulla oblongata.

Sclerotic areas are found in the sacral region, and those in the posterior columns on both sides of the cord are symmetrical.

In the mid lumbar region the areas of sclerosis are remarkably symmetrical in the anterior, lateral and posterior columns. The areas in the lower, middle and upper thoracic regions are symmetrical.

The sclerosis in this case is somewhat different from that in many cases of multiple sclerosis, in that many of the degenerated areas are not sharply defined from the normal tissue, but shade off into it.

In the middle of the cervical swelling the sclerotic areas on the two sides of the cord are still nearly symmetrical.

Sclerotic areas are numerous in the medulla oblongata, and they are found also in the pons, cerebral peduncles, cerebral cortex and optic chiasm. Both the right and left optic nerves are almost completely degenerated except in certain parts of the periphery of each nerve.

The Marchi stain shows recent degeneration along the edges of some of the sclerotic areas. Perivascular round-cell infiltration in moderate intensity is found in the pia and within the spinal cord, but is pronounced in the pia of the optic chiasm and within the chiasm.

The nerve cells of the anterior horns in the lumbar and cervical regions stain well by the Nissl method. A brief abstract of each case is as follows:

Case 1.—The patient, a woman twenty-eight years old, had always been sickly and nervous. She noticed stiffness and weakness of the lower limbs in September, 1902. She complained of paresthesia in these limbs and had some disturbance of objective sensation. About Christmas, of 1902, she had difficulty

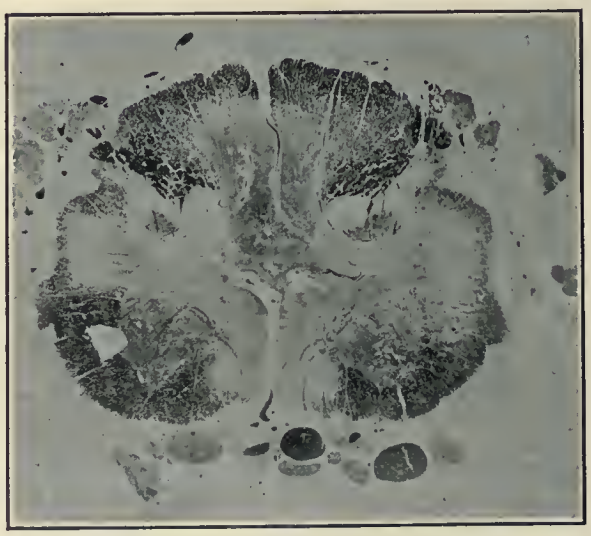

Fig. 2. Photograph of a section of the lumbar cord from Case 2, showing remarkable symmetry of the sclerotic areas in the anterior, lateral and posterior columns.

in holding the urine. Vision of the right eye appeared to be diminished. The gait was not striking when the eyes were open, but was ataxic when the eyes were closed. The patellar reflex was a little exaggerated on each side. Babinski's sign was present on each side. The upper limbs and head were not affected. Speech was not peculiar and nystagmus was not observed. The woman while in the hospital jumped from a third story window and died after an injury received

from the fall. She had a fracture of the first lumbar vertebra. Areas of sclerosis were found throughout the spinal cord, and the right optic nerve appeared almost completely degenerated.

Case 2.—This patient first came under the observation of one of us (Dr. Spiller) in 1898, and had been under his care much of the time since until the patient's death. In 1898 the man was twenty-four years old. He had been exposed to wet and cold. The notes made in 1898 state that he had been losing power in his lower limbs for nine months, but had no loss of power in

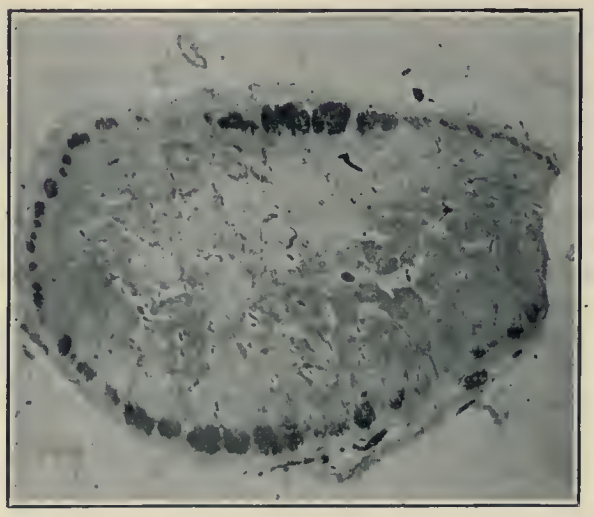

Fig. 3. Photograph of one of the optic nerves in Case 2, showing a sclerotic area implicating the transverse section of the nerve except at the periphery.

the upper limbs and no pain anywhere. He had had difficulty in holding the urine during a period of about two weeks. Sight was poor. Gait was ataxic. Romberg's sign was present. The patellar reflex was much exaggerated. Sensation was normal everywhere. The upper limbs were ataxic. Slight nystagmus was present.

In 1901 he was unable to walk at all. Beginning optic atrophy was found in each eye. Speech was slow but not scanning.

In July, 1903, intention tremor was observed in the upper limbs. He had incontinence of urine and feces. Tactile sensation was much impaired in the lower limbs and trunk. The temporal side of the disc in each eye was abnormally white, suggesting incipient atrophy.

Sclerotic areas were found throughout the cord, medulla oblongata, pons, cerebral peduncles, and in the white matter and cortex of the cerebrum. The areas in the spinal cord were remarkably symmetrical.

Flatau and Koelichen[9] say that the number of published cases in which multiple sclerosis caused the clinical appearance of transverse myelitis is not great. They refer to the cases of Pitres, Siemerling, and Nonne, and report a case in which the symptoms were flaccid paralysis of the lower limbs, incontinence of urine and feces, and decubitus; sensation was not disturbed. The upper limbs and cranial nerves were not implicated, and the patient did not have intention tremor, nystagmus, scanning speech or mental symptoms. An ophthalmoscopic examination was not made.

The first case that we report in this paper was suggestive of transverse myelitis, but it was supposed to be a case in which diffuse lesions were present in the lateral and posterior columns, and certain facts in the history suggested syphilis. The fall from a third story window during the time the case was being carefully studied caused symptoms that masked those originally present. An examination of the eyegrounds would probably have shown alteration of the right optic disc, and this examination would doubtless have been made if the accident referred to had not occurred soon after the patient entered the hospital.

The frequent implication of the optic nerves in multiple sclerosis was known to Charcot some thirty years ago. It has been mentioned repeatedly by Oppenheim, and more recently the subject has received attention from Bruns and Stölting and others. A person with sclerotic patches in the optic nerve may have little or no disturbance of vision, and the ophthalmoscopic examination may reveal an unsuspected condition, especially as the disease of the optic nerve may be

[9]Flatau and Koelichen. Deutsche Zeitschrift für Nervenheilkunde, Vol. 22, Nos. 3 and 4, p. 250.

among the first or even the first sign of the multiple sclerosis. Sclerotic patches may occur in any part of the visual tracts as far back as the cortex of the occipital lobe. According to Bruns and Stölting the chiasm is frequently the seat of sclerotic areas. The ophthalmoscopic change consists often of pallor of the temporal side of the disc; optic neuritis or optic atrophy also may be found.

In both the cases reported in this paper optic nerve degeneration was pronounced, and it was present also in the other two cases reported by one of us (Spiller), and also in the case of Burr and McCarthy. An examination of the eyegrounds is therefore of great importance in every case presenting symptoms that could be attributed to multiple sclerosis, because the disturbance of vision, as in both the cases reported in this paper may be slight as compared with the alteration of the optic nerves.

Bruns and Stölting[10] confirm the observations of Oppenheim regarding disturbances of the bladder and of sensation, at least in the later stages of the disease. Vesical symptoms and sensory disturbances were present in both of our cases.

The degeneration of the posterior root fibers of the mid lumbar segment on the left side in the first case was caused by the fracture of the first lumbar vertebræ and injury to the spinal roots. The degeneration of the medullary sheaths by the Marchi method was very distinct, and the degenerated fibers could be seen entering the posterior horn of the left side in large numbers. As the posterior roots within the cord on the right side at the same level were implicated in a sclerotic area, and the medullary substance of these fibers had disappeared, no degeneration of these roots by the Marchi method could be detected. This observation shows that the patellar reflex may be exaggerated, even though the medullary sheaths about the fibers concerned in the reflex have disappeared. It has been known that the function of nerve fibers within the spinal cord may be preserved after the medullary sheaths of these fibers have disappeared, and our case shows that the same is true of the fibers concerned in the tendon reflexes.

Flatau and Koelichen discuss the pathological findings of

[10] Bruns and Stölting. Monatsschrift für Psychiatrie und Neurologie, Feb. and March, 1900.

multiple sclerosis, whether they are inflammatory or not, and they make the statement that most of the recent investigators favor the inflammatory theory. They refer to Ribbert, Cramer, Bikeles, Goldscheider, Balint, and others. Redlich, however, does not accept the inflammatory theory. Flatau and Koelichen, from a study of their case of multiple sclerosis and from their investigations of the literature, conclude that multiple sclerosis should be classed with disseminated myelitis. Strümpell, in a note at the end of their paper, makes the criticism that it would be better to regard their case as one of acute disseminated myelitis, instead of multiple sclerosis, and he insists on making a sharp distinction between the two diseases.

It is exceedingly difficult to determine the relation of multiple sclerosis to multiple myelitis. In the latter disease we do not find usually the areas of sclerosis sharply defined, at least to the naked eye, from the surrounding normal tissue. In our second case many areas of sclerosis shade off into the normal tissue, and at some places perivascular cellular infiltration is found, and yet this is unquestionably a typical case of multiple sclerosis. In our first case the perivascular cellular infiltration is distinct at certain places but it is impossible to establish a close relation between these and the sclerotic areas. This should be a suitable case for this purpose, as death occurred less than a year after the first definite symptoms of multiple sclerosis were manifest, and from a cause independent of this disease.

Redlich has called attention to the symmetry sometimes found in the areas of the two sides of the cord in multiple sclerosis. The symmetry throughout the spinal cord in our second case is extraordinary, and suggests a vascular origin or a defect in the development of the cord. We have never seen in any case of multiple sclerosis such symmetry extending throughout the cord, and yet we have at our command sections from many cases of multiple sclerosis. Fig. 3 shows the symmetrical areas on the two sides of the cord in the lumbar region.

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A FURTHER STUDY ON THE SENSORY SEGMENTAL ZONE OF THE UMBILICUS.

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Read before the Philadelphia Neurological Society, April 26, 1904.

THE exact determination of the sensory zone in which the umbilicus lies is of great importance as regards the surgery of the spinal column. In a paper read by one of us (Spiller) before this Society, Dec. 23, 1901, and published in the *Philadelphia Medical Journal*, Feb. 8, 1902, the different views held by investigators of this subject were presented. It may be well to refer to these briefly, in order to show the doubt prevailing in regard to the sensory zone of the umbilicus.

Boettiger thinks it is uncertain whether the umbilicus lies in the distribution of the ninth or tenth thoracic segment; Walton places it in the distribution of the eleventh thoracic segment; Dejerine in the distribution of the tenth thoracic segment; Head regards the tenth thoracic sensory segment as in the subumbilical region and the upper border of this segment

as passing directly through the umbilicus; Wichmann believes that the umbilicus lies in the area of the tenth thoracic segment; Paterson places it between the tenth and eleventh thoracic segments; Kocher at the lower border of the tenth thoracic segment; and Seiffer draws a line from the umbilicus a little downward, and then upward and around the trunk, and regards this as the limit of the tenth thoracic segment.

From this review of the literature it will be seen that there is much to be said in favour of the situation of the umbilicus within the tenth thoracic sensory segment, but this is an opinion we are unable to accept.

In the paper by one of us (Spiller) referred to above, a case was reported which seemed to show that the umbilicus lies between the ninth and tenth thoracic sensory segments. The line defining the anæsthetic area passed directly through the umbilicus, and the tenth thoracic segment of the cord was much softened. The ninth thoracic segment was believed to be intact, but further study shows it is possible that the lower part of this segment was affected, so that instead of the umbilicus lying exactly on the border between the ninth and tenth thoracic sensory segmental areas, we may conclude from this case that it may lie in the lower part of the ninth thoracic sensory segmental zone. The correction is not very important.

We have had the opportunity to confirm the views formed from a study of this case. A man was struck in the back by the falling of a bank of earth, and was brought to the Polyclinic Hospital, Nov. 17, 1899. He had complete paralysis of both lower limbs, and loss of sensation below a line drawn around the abdomen about one inch below the umbilicus, resulting from fracture of the vertebræ. Operation was performed by Dr John B. Roberts, and the displaced fragments of bone were removed. The patient was transferred to the Philadelphia General Hospital, Oct. 8, 1900. He remained completely paralysed in his lower limbs until his death in the summer of 1903. The lower limbs were much atrophied, he had severe bedsores, the patellar and Achilles reflexes and skin reflexes of the lower limbs were lost, and no movement of the toes was produced by plantar irritation. He had incontinence of urine and fæces and a girdle sensation. Sensation in all forms was lost in both lower limbs and over the abdomen to a line drawn one inch below the umbilicus, even

until the examination made shortly before the patient's death. This line was sharply defined.

A careful microscopical examination of sections taken from the upper part of each segment of the spinal cord from the tenth thoracic to the upper part of the cervical enlargement showed that as high as the upper part of the tenth thoracic segment the cord was completely destroyed. Many normal fibres entered the cord in the posterior roots of the ninth thoracic segment.

This examination seems to show conclusively that the umbilicus, in this case at least, was not situated in the tenth thoracic sensory segmental zone, inasmuch as the tenth thoracic segment of the spinal cord was entirely destroyed, and the zone of anæsthesia ceased one inch below the umbilicus. The umbilicus therefore probably lies within the ninth thoracic sensory segmental zone, and this conclusion is in conformity with the findings of the previous case. The importance of this determination must be apparent on account of the prominence of the umbilicus as a surgical landmark.

In this case, as in the former case, the Babinski reflex was not obtained, and in both cases the sacral region of the cord was softened. The absence of this reflex in these cases of lesions of the central motor tracts may be explained by destruction of the reflex arc, and it would be well if more attention were paid to the condition of this reflex in complete transverse lesions of the cord above the lumbar region. It is possible that in this sign we may have a means of judging of the condition of the sacral region of the cord in cases of fracture of the vertebræ.

PHYSIOLOGIC EXTIRPATION OF THE GANGLION OF GASSER.

FURTHER REPORT ON DIVISION OF THE SENSORY ROOT FOR TIC DOULOUREUX, BASED ON THE OBSERVATIONS OF FOUR CASES.*

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REMARKS BY DR. FRAZIER.

In June, 1901, three years ago, I reported to the Section on Surgery of the American Medical Association then in session at St. Paul, the results of a series of experiments on dogs conducted by Dr. Spiller and myself, with a view toward determining the feasibility of dividing the sensory root of the gasserian ganglion for the relief of tic douloureux.

RESUME OF EXPERIMENTAL WORK.

These experiments consisted in carrying out this operation on a number of dogs and subjecting the structures removed several months later to a rigid histologic examination to determine whether regeneration of the

* Read at the Fifty-fifth Annual Session of the American Medical Association, in the Section on Surgery and Anatomy, and approved for publication by the Executive Committee: Drs. DeForest Willard, Charles A. Powers and J. E. Moore.

sensory root after simple division could occur. The results of these investigations admitted of but one interpretation, namely, that there was not the slightest evidence of regeneration within the central nervous system. More recently,[1] Dr. Spiller and myself pursued this line of investigation in a series of experiments on the sensory roots of the spinal ganglia with equally positive results.

Having established by experimentation in lower animals beyond a peradventure of doubt the inability of the sensory root to regenerate at least within the central nervous system, it only remained to obtain equally positive results in the human subject before any substantial claims for the operation as a rational, practical and "tried-out" procedure could be made. These we present to-day as a result of our experiments with four cases; all have remained free from recurrence.

ADVANTAGES OF THIS OVER OTHER PROCEDURES.

Extraction of the ganglion. Certain theoretical claims were advanced in favor of the operation, and these have been substantiated by our clinical experience.

1. *Control of Hemorrhage.*—It minimizes the amount of hemorrhage. No one can speak the truth and say that hemorrhage is not a troublesome feature. Hemorrhage from the middle meningeal artery is of little or no moment, and it can be controlled easily whether the vessel be injured as it courses along the temporal bone or at the foramen spinosum. On the contrary, hemorrhage from emissary veins is distinctly troublesome. The greater the number and firmness of dural attachments, the greater will be the hemorrhage from this source, and the nearer we approach the ganglion the firmer the adherence and the freer the bleeding. Inasmuch as the ganglion receives its greatest blood supply from below, surgeons are advised to put off elevation of the ganglion to the last. To divide the sen-

1. University of Pennsylvania Med. Bul., June, 1903, p. 126.

sory root the base of the ganglion is left undisturbed and this cause of free and persistent bleeding avoided.

The only other source of hemorrhage worthy of consideration is the cavernous sinus. Injury to this sinus has caused hemorrhage, if not serious and alarming, at least necessitating suspension of the operation for a day or more. This vascular channel being in intimate relation with the internal aspect of the ganglion, is exposed to danger once the operator begins to free it from the ganglion. Confining, as we do in practicing division of the sensory root, our manipulations to the root itself and to the posterior aspect of the ganglion, we work at the point of greatest safety, insofar as the sinus is concerned, and need never give it a thought.

2. *Simple Technic.*—Its execution is comparatively simple. It goes without saying that the exposure of the ganglion is by far less difficult than its extraction. Once the ganglion is exposed, we have made all the preparations necessary for the division of the sensory root; thus this operation is complete before the difficulties common to the extraction of the ganglion have been approached.

3. *Avoidance of Injury to Adjacent Structures.*—The cavernous sinus is not exposed to injury. The abducens is in such intimate relation with the ophthalmic branch that division of one is almost impossible without division of the other. In the extirpation of the ganglion it is a matter of great difficulty to preserve this cranial nerve intact. The motor root is always destroyed in extraction of the ganglion; whereas, in division of the sensory root, the motor root may be preserved intact.

4. *Reduction in the Rate of Mortality.*—If the troublesome difficult features attending operation for the extraction of the ganglion are, to a great extent, eliminated, there should be an appreciable reduction in the time required to complete the operation, and it is only reasonable to predict that the operation, which is more

economical as to time and attended with considerably less hemorrhage, will be attended with a lower mortality.

TECHNIC.

This phase of the subject has been treated fully in previous papers.[2] The approach to the ganglion by the usual Hartley-Krause method, the temporary or permanent resection of the zygomatic process, the exposure of the foramina ovale and rotundum as guides to the ganglion; an incision in the dura propria from one foramen to the other; the reflection of dura propria from the superior and posterior aspect of the ganglion revealing the sensory root; picking up of the root on blunt tenaculum and division of same completes the operation.[3]

DIFFICULTIES ATTENDING THE OPERATION.

An objection has been made to the operation we advise for the relief of tic douloureux, viz., that the sensory root can not always be exposed, and that in such a case resection of this root would be impossible. Dr. Spiller thinks it is extremely probable that resection of the posterior part of the gasserian ganglion would have the same effect as resection of the sensory root. The object we strive for is the division of the central nerve

2. University of Pennsylvania Med. Bul., December, 1901; Philadelphia Med. Jour., Oct. 25, 1902.

3. Considerable importance has been attached to what has been called the intra-arterial route and the difficulties attached to injury to the middle meningeal artery grossly exaggerated. One familiar with the great variation in the course of the middle meningeal artery and its relation to the temporal and frontal bone realizes at once the futility of attempting to establish a point below which one can operate always with the assurance that the vessel will not be injured. The danger of injuring the middle meningeal vesael in opening the skull is due to the fact that the vessel sometimes runs in a bony canal, sometimes in a deep channel. When the fragment of bone is removed the vessel is lacerated. Sometimes there is no canal at all, usually the canal begins sufficiently high to escape injury; exceptionally, however, the canal begins so far down that it would be impossible to make an opening large enough to enable one to carry out the necessary manipulations on the ganglion by the so-called infra-arterial route. Common sense prompts one to make the opening as near the base of the skull as possible, not especially to avoid the artery, but in order to reduce to a minimum the distance from the margin of the skull to the ganglion and to make the opening only as large as the manipulation may require. No other directions to the operator are necessary; he avoids injuring the artery if he can, and if he can not, it is a matter of no difficulty to control the hemorrhage.

processes which arise in the cells of the gasserian ganglion. Many of the cells that send processes into the sensory root are cut off from this root by a resection of the posterior part of the ganglion, and the effect in the permanent relief from pain would probably be the same as though the sensory root were divided. If, therefore, there is any difficulty in exposing or recognizing the sensory root Spiller recommends a resection of the posterior part of the ganglion, believing that it would be as effective as a resection of the sensory root.

PHYSIOLOGIC EXTIRPATION OF THE GASSERIAN GANGLION.

Up to this time the claims which have been made for division of the sensory root have been based altogether on the results of our own experimental and clinical evidence. It might be well at this juncture to introduce the evidence of an impartial critic whose judgment and opinions in matters pertaining to the physiology, pathology and anatomy of the nervous system are held in great respect. Van Gehuchten has published recently a most instructive and interesting paper on the surgical treatment of trifacial neuralgia,[4] and in this article he discusses somewhat at length the effects of division of the sensory root. Owing to the fact that he believes this operation to be as radical in effect as extirpation of the ganglion, he has styled the former not inappropriately the "physiologic extirpation of the ganglion," and regards it as both less dangerous and more complete than the operation of Krause.

His observations and conclusions on the question of regeneration or degeneration of the sensory root confirm absolutely our own. Every fiber of the central nervous system, he says, attacked by secondary degeneration is a fiber inevitably lost. "The nerve fibers of the central nervous system interrupted at any part never regenerate. The section of the large root of the tri-

4. Le Nevraxe, vol. v, and University of Pennsylvania Med. Bul., April, 1904.

geminal nerve is equivalent, then, at least as regards its effects on the bulbo-spinal root, to the destruction or extirpation of the gasserian ganglion itself. Whether the cause of the trifacial neuralgia resides in the semilunar ganglion, or in one or the other of the three peripheral nerves, at the moment we interrupt completely all communication between the ganglion and cerebrospinal axis, we destroy inevitably the route by which painful impressions are conveyed to consciousness.

"The section of the large root of the trigeminal nerve, even though it does not constitute an anatomic extirpation of the semilunar ganglion, is equivalent, then, to a true physiologic extirpation, and is the only one which is of importance in point of view of treatment of trifacial neuralgia.

"This physiologic extirpation is not only more complete and easier to accomplish than the tearing out of the ganglion recommended by surgeons, but it has an advantage over this mode of operation which is not to be despised. It leaves intact the connections of the ganglion with the peripheral organs."

That the operation on the root is much more simple than the extirpation of the ganglion might be inferred from the fact that many surgeons, among them Poirier, Horsley and Lauwers, recommend tearing out the root as a preliminary measure to extirpating the ganglion. If the exposure of the root were a matter of any great difficulty, this step of the operation naturally would have been postponed until the last when the ganglion was entirely freed from its attachments.

It has been said that the suggestion made by Dr. Spiller, in 1898, of treating tic douloureux by division of the sensory root was not original; that there was on record one instance in which, prior to 1898, the operator had deliberately torn out the root. This is quite true, but it should be borne in mind that the surgeon did not perform this as an operation of choice, but did it because he was unable to remove the ganglion. His

patient died within a few hours, and he never repeated the operation nor recommended it to others. For the conception of the idea that division of the root was equivalent to physiologic extirpation of the ganglion credit is due to Spiller alone. Furthermore, those who have taken exception to the claim of originality ought to have known that there is a very distinct difference between avulsion of and division or resection of the root. Avulsion of the root is not only unnecessary, but what is still more important, may be distinctly harmful. Simple division of the root suffices to cause complete and persistent degeneration of the bulbospinal root of the trigeminal nerve, and the possibility of recurrence of the symptoms is therefore *nil*. Avulsion may expose even the pons to concomitant lesions (Van Gehuchten), and for this reason alone the procedure should be rejected.

AVOIDANCE OF OCULAR DISTURBANCES.

Noteworthy in our experience is the absence of any ocular disturbances. Attention has already been called to the frequency with which the structures on its inner aspect, including the third, fourth and sixth nerves, have been injured in extirpation of the ganglion, and to their escape from injury in division of the sensory root. The most serious ocular disturbances of extirpation of the ganglion is corneal ulceration. Although no especial pains have been taken to guard against it, our cases have been entirely free from this complication. Spiller says it is probable that sympathetic fibers pass to the eye after entering the trigeminal nerve through the gasserian ganglion, and as in division of the sensory root these fibers are not injured, the danger of ocular disturbance by this operation is lessened. The trophic influence of the gasserian ganglion on the eye may possibly depend on the integrity of these sympathetic fibers, but it is probable that these fibers are not so numerous in man as in the lower animals. (The literature bearing

on this subject has been carefully studied by Kreuzfuchs.) Of this phase of the subject, Van Gehuchten writes: "The persistence of the anatomic connections between the peripheral organs and the gasserian ganglion, separated from the nervous axis, without doubt, prevents the grave ocular complications mentioned by Kraus and Lauwers." The experimental investigations of Van Gehuchten himself and of Lugars and Bonne have shown that while degeneration of the fibers of the central stump follows division of the sensory root, the ganglion itself does not undergo any marked modification. This is equally true of the posterior roots of the spinal cord and their ganglia as of the cranial nerves and their ganglia.

METHODS OF ABBE AND VAN GEHUCHTEN.

Recognizing from his wide experience the difficulties and dangers that attend extirpation of the ganglion, Abbe recommended another operative procedure, because it was very much safer and, in his opinion, equally efficacious. This consists in division of the second and third divisions at their exits to their respective foramina and the subdural interposition of tissue. Two objections to this method of treatment at once suggest themselves: The first that the operation is applicable only to those cases in which the pain is distributed only to the second and third divisions; the second that there is a possibility of the rubber tissue acting in the rôle of a foreign body setting up a reaction in the tissues, which would terminate in abscess formation and necessitate the removal of the foreign material.

Abbe says: "It is certainly past dispute that there is no need for the removal of the first branch of the fifth pair in any case of grave tic douloureux unless the origin is to be found in a tumor of the gasserian ganglion or behind it." This may apply to the majority of cases, but it certainly is not a rule without exception. In fact, in two of the four cases which constitute this series,

the pain was most intense in the distribution of the first division.

It might also be said of Abbe's operation that it offers no assurance against subsequent involvement of the first division, and so far as the mortality is concerned, it should be no less than that following division of the sensory root, since both are intracranial operations, the only difference being that in one two peripheral branches are divided, while in the other the central root of the ganglion.

Van Gehuchten, in his recent contribution to the treatment of trifacial neuralgia, recommends the tearing out of the peripheral branches, a procedure which, he says, is simpler and much more easily executed than intracranial resection. This recommendation is based on the following phenomena: Simple division of a cranial nerve nearer to or further from the base of the cranium is followed by degeneration of all the cells of origin, but with complete integrity of all or almost all of the fibers of the central end. This degeneration is only temporary, however, and is soon followed by reparation of the nerve and restoration of the function. Tearing out of the nerve, on the other hand, produces reactional phenomena much more intense; the degeneration that follows soon becomes an achromatosis, and this, in turn, is followed by atrophy and disappearance of all the injured cells. These phenomena have been observed only in motor nerves, and to prove whether sensory nerves would be affected in a similar manner, experiments were conducted on rabbits; the three peripheral branches were seized with a hemostatic forceps at their exits from the supraorbital, infraorbital and mental foramina and torn away. The results were positive; not only was there atrophy of the cells of the ganglion, but Wallerian degeneration of its bulbospinal root.

As regards the technic of the operation, the nerve should be freed as far as possible from all its connec-

tions and seized as near as possible to the base of the cranium, in order to make the resulting traumatism more intense. In reviewing the literature of the subject, Van Gehuchten found that this operation had been recommended and practiced by Blum in 1881, and later by Doyen. There seems to have been some apprehension on the part of surgeons that there was danger in employing the force necessary to tear the nerve, of inflicting some serious injury to the brain centers. In any other cranial nerve this complication might occur, but the gasserian ganglion is so firmly attached to the base of the skull that this accident could not be considered possible.

These observations of Van Gehuchten are certainly worthy of the surgeon's consideration. If avulsion of the nerve will result in such degenerative changes of the ganglionic cells and the bulbospinal root that restoration of function is impossible, this operation should be practiced as a substitute for the intracranial operations. Whether or no surgeons at large would be willing to practice in those cases in which a so-called central operation is indicated, it should at least be given a trial, when circumstances call for a peripheral operation; that is to say, instead of resecting a portion of the inferior dental or infraorbital nerve, the nerve should be forcibly torn away. If Van Gehuchten's observations are correct, it is reasonable to assume that there would be less chance of recurrence in the case of the latter than of the former operation. Not, of course, until this operative procedure has been proven successful in its application on the human subject can it claim the support of the surgical profession. Therefore, with the exception of a few isolated cases, it is supported only by the results of experimentation on rabbits.[5] Davis, in 1898, operated on a case in which this idea of Van Gehuchten's was put into practice, but with unfavorable results. The superior maxillary nerve was

5. University of Pennsylvania Med. Bull., April, 1904.

exposed as it ran from the gasserian ganglion. The nerve, as it entered the bone, was grasped with a hemostatic forceps and pulled upward; with another forceps the nerve was grasped closer to the ganglion and twisted loose from it. The relief which followed the operation was only temporary, the pain gradually returned and became so severe as to require a more radical operation. In commenting on the case, Davis says the explanation of the return of pain is left to the experts. The operation was practiced in the manner prescribed by Van Gehuchten; it might be claimed that the twisting out of the nerve was not sufficiently violent or brusque, but this view is hardly acceptable.

REMARKS BY DR. SPILLER.[6]

In studies of the nervous system of dogs,[7] in which the sensory root had been cut, I found that when only the external part of this root was divided the degeneration in the spinal root of the trigeminal nerve of the pons and medulla oblongata by the Marchi method was only in the dorsal part of the root. This is well shown by photographs in the article referred to. I believed from these investigations, published in December, 1901, that I was justified in concluding that the fibers of the lateral portion of the sensory root at its entrance into the pons, in their further course, occupy the dorsal part of the descending spinal root. From this it follows that the fibers of the inner portion of the sensory root occupy the ventral portion of the descending spinal root.

The investigations of Van Gehuchten on the changes occurring in the sensory root of the trigeminal nerve, after tearing out peripheral branches of this nerve, are important. He says, in relation to this subject: "This

6. The following observations on the relative position of the fibers belonging to the three peripheral branches of the trigeminal nerve in the gasserian ganglion and the sensory root and their continuation in the spinal root are by Dr. Spiller, including an explanation for the limited area of anesthesia of the face occurring after partial division of the sensory root.

7. Spiller and Frazier: University of Pennsylvania Med. Bul., December, 1901.

degeneration of the fibers of the bulbospinal root, after a tearing out of the peripheral nerves, is so constant that we have encouraged one of our students, Dr. Bochenek, to employ this method in determining the situations in the bulbospinal root of the fibers belonging to each of the three branches. The results of his investigations have shown that after a tearing out of the frontal nerve the degeneration is localized exclusively to the ventral portion of the bulbospinal root; after a tearing out of the mental nerve, it occupies the dorsal portion of the same root. The tearing out of the infraorbital nerve is followed by a degeneration of a certain number of fibers in the middle region.

"Our own recent investigations are in support of these findings. They show, further, that the number of fibers in degeneration of the bulbospinal root is in direct relation to the number of peripheral fibers that have been ruptured. Bochenek, in his investigations, was content to tear out only one of the branches of the ophthalmic nerve of Willis, the frontal nerve; he obtained distinct degeneration involving a small number of nerve fibers at the ventral extremity of the bulbospinal root. In our own investigations we have torn out the three branches of the ophthalmic nerve, emptying completely the orbital cavity. After a survival of forty-five days we have obtained a much more extensive degeneration of the ventral portion of the bulbospinal root.

"This degeneration of the fibers of the bulbospinal root can be understood, in our opinion, only by admitting that rapid atrophy occurs in a certain number of cells in the semilunar ganglion, an atrophy following the tearing out of the peripheral branch. We desired to determine the existence of this atrophy by the examination of the gasserian ganglion, but our investigations have not been successful. After the tearing out of one or the other of the three branches of the trigeminal nerve, chromolysis of the cells in the ganglion is found after about ten days, but if the animal is allowed to live fifty or sixty

or eighty days it is impossible to determine whether the number of nerve cells has diminished in the ganglion on the operated side, even after a tearing out of all three nerves, frontal, infraorbital and mental. These results should cause no surprise; the gasserian ganglion is difficult to remove; it has, further, a very complex structure; its constituent cells, instead of being placed one close

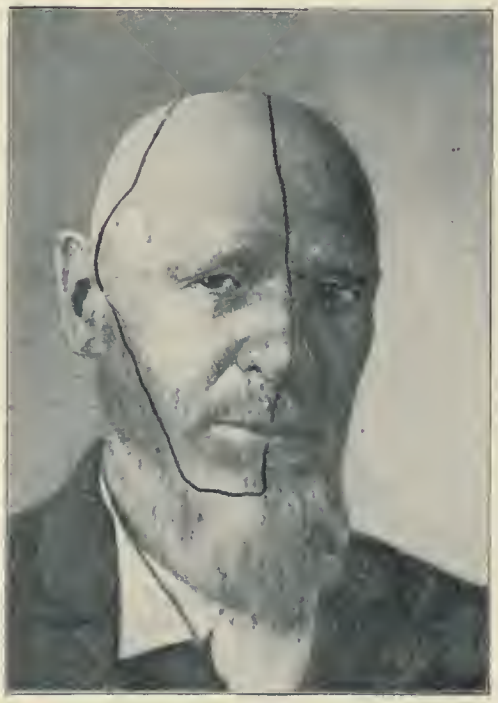

Fig. 1.—Showing the area of anesthesia one week and thirty-two months after division of the sensory root.

against the other, are usually situated in long bands, like islands, between the fasciculi of nerve fibers, which they accompany in a certain part of the nerve. It is, furthermore, very difficult, if not impossible, to make comparable serial sections of the two semilunar ganglia of the same animal.

"Having in mind the Wallerian degeneration of the fibers of the bulbospinal root after a tearing out of the branches of the trigeminal nerve, and the cellular phenomena which occur in the cells of origin of the peripheral nerves after the tearing out, we believe that we may conclude that the tearing out of one or the other branches of the trigeminal nerve is followed by rapid atrophy of the corresponding cells of the gasserian ganglion, an atrophy which causes in its turn Wallerian degeneration of the central fibers. It is, therefore, proper to propose the tearing out of the nerve as a rational surgical treatment of trifacial neuralgia."[5]

Comparing Van Gehuchten's results with those obtained by me, it will be seen that the fibers of the ophthalmic nerve are represented in the ventral portion of the descending spinal root of the trigeminal nerve (Bochenek, Van Gehuchten), and that the fibers of the inner portion of the extrapontile sensory root are represented in the ventral portion of the descending sensory root (Spiller); therefore, these fibers do not mix with those belonging to the other peripheral branches of the trigeminal nerve; likewise that the fibers of the third division are represented in the dorsal part of the descending spinal root (Bochenek, Van Gehuchten), and that the fibers of the external portion of the extrapontile sensory root are represented in the dorsal portion of the descending spinal root (Spiller), and, therefore, these fibers do not mix with those belonging to the other peripheral divisions of the trigeminal nerve.

This is an important conclusion, because if only the outer portion of the sensory root of the trigeminal nerve is cut loss of sensation should be expected only in the third division of the nerve, and we may conclude when loss of sensation is found also in the distribution of the second division that at least half the sensory root is cut through. This explains why sensation of the face is only partially lost when only a portion of the sensory root is cut, and in such cases it will probably be

found that the anesthesia is in the third division of the trigeminal nerve, because the external fibers of the sensory root are more likely to be divided than the inner.

Recent anatomic studies in the territory innervated by the sensory root of the trigeminal nerve, show that this territory is less extensive than formerly supposed. The sensory area of the trigeminal nerve as shown by Otto Grosser does not extend to the chin.[8] In the diagram of Frohse, the cervical nerves supply the sensation to a considerable area of the face above the chin. According to Zander, the area of the cervical nerves extends almost to the corner of the mouth, and is only about a finger-breadth from the bony orbital border. It is very important that these facts should be borne in mind when the extent of the anesthetic area caused by resection of the sensory root is tested.

SYMPATHETIC FIBERS IN THE GANGLION OF GASSER.

The effect on the sympathetic fibers of the eye from operations on the trigeminus is worthy of attention. Kreuzfuchs has collected considerable proof of the existence of sympathetic fibers in this nerve.

Budge cut the trigeminus in animals, in some cases through the trunk, in others peripherally to the ganglion, and found that after either operation contraction of the pupil occurred. After central division of the fifth nerve the pupil did not contract so greatly nor persistently as after peripheral division of the nerve. Budge assumed that the trigeminus receives in the gasserian ganglion those sympathetic fibers which innervate the dilator pupillæ, and this opinion has been held by all subsequent investigators who have studied the motor tract for the dilatation of the pupil. These fibers pass from the gasserian ganglion to the eye through the first division of the trigeminus, and therefore contraction of the pupil occurs after division of the trigeminus.

8. Grosser: Centralblatt für die Grenzgebiete der Medizin u. Chirurgie, Feb. 23, 1904.

Schiff also found that dividing the trigeminus causes contraction of the pupil, and that there is a difference when the division is made behind or in front of the gasserian ganglion.

Claud Bernard found that the pupil contracts after division of the trigeminus and after a certain time dilates but never attains the same size as the pupil on the other side. These phenomena occur after central as well as after peripheral division of the fifth nerve, but these changes are much more striking and are associated with disease of the cornea when the division is peripheral.

Balogh concluded that all pupillary dilator fibers pass through the gasserian ganglion and the first division of the trigeminus.

Similar opinions were held by Oehl and Gutmann, although the latter believed that no pupillary dilator fibers arise in the medulla oblongata, as Balogh had assumed, and that the division of the trigeminus stem has no effect on the pupil. This view has been shown to be incorrect by Claud Bernard and by Kreuzfuchs.

Budge having believed that the trigeminus contains motor dilator fibers, later investigators have tried to determine whether these fibers are a part of this nerve or merely received from the sympathetic. From the investigations of Schpilow and Braunstein, it seems to be decided, at least for many animals, that the trigeminus receives the dilator fibers of the pupil through the gasserian ganglion.

Kreuzfuchs has cut the trigeminus in rabbits near the base of the brain. The pupil was smaller immediately after the operation than it was later. In these animals exposure and irritation of the cervical sympathetic on the operated side caused maximal dilatation of the pupil on the same side, so that the dilator fibers could not have been cut.

Examination of cases in which the gasserian ganglion has been removed in man seems to show that removal

of this ganglion does not cause contraction of the pupil, so that Kreuzfuchs doubts whether what is true of the lower animals is true also of man, viz., that all dilator fibers of the pupils pass through the gasserian ganglion, and he is inclined to accept the view that in man the dilator fibers act through the abducens. He says, however, that after removal of the gasserian ganglion in man, the pupils are of equal size in the light, but in shadow the pupil on the unoperated side is larger.[9]

It seems probable from these observations that even in man a certain number of sympathetic fibers enter the gasserian ganglion, but in a case of division of the sensory root reported in 1901 by Dr. Frazier and myself no difference in the size of the pupils in shadow can now (May 21, 1904) be determined. After several years a readjustment of the pupillary mechanism is to be expected.

RESUME OF FOUR CASES.

CASE 1.—J. L., age 68. Duration of affection, five years. Previous treatment, four peripheral operations. The first division alone was involved.

Operation.—October 12, 1901. Two years and eight months ago.

Result.—No recurrence.

CASE 2.—S. R., age 79. Duration of affection, three years. Preliminary treatment, course of hypodermic injections of strychnia with only temporary relief. Third and second divisions involved in the order named.

Operation.—October 21, 1902. One year seven and one-half months ago.

Result.—No recurrence.

CASE 3.—A. W., age 54. Duration of affection, nine years. Treatment, nil. Second and third divisions involved in the order named.

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9. Kreuzfuchs: Oberstelner's Arbeiten, vol. x, p. 275.

Operation.—March 31, 1903. One year and two months ago.

Result.—No recurrence.

CASE 4.—F. S., aged 54. Duration of affection, 14 months. Previous treatment, nil. First and second divisions involved.

Operation.—March 17, 1904.

Result.—No recurrence.

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SPONDYLOSE RHIZOMYELIQUE; A STUDY OF THE RELATIVE FREQUENCY OF SPINAL INVOLVEMENT IN RHEUMATOID ARTHRITIS, WITH AUTOPSY FINDINGS.*

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Rigidity of the spine has in the last few years attracted considerable attention from clinicians. References to this condition are found scattered through the literature of the last century, but little attention was paid to it as a separate pathological condition until v. Bechterew published his paper, in 1893. This was followed by papers by Marie, Strümpell, and Bäumler, and in the last two years a large number of cases have been placed on record. It is very evident from a study of these cases that several different diseases, with local manifestations referred to the spinal column, have been classed under the same general heading. It will be my aim in this paper to consider rigidity of the spinal column occurring as a separate and distinct clinical and pathological entity and rigidity of the spine as a local manifestation of rheumatoid arthritis.

The disease described by v. Bechterew is localized in the spinal column without involvement of other joints. It may affect a part or the entire spine. In the latter case there is a kyphosis affecting the upper dorsal and lower cervical ver-

* From the William Pepper Clinical Laboratory, Phœbe A. Hearst Foundation.

tebræ. There is an absence of the anterior curve of the spine in the lumbar region. The result of this rigidity of the upper spine together with the kyphosis gives the patient an appearance as if the head was pushed down into the shoulders and at the same time a forward extension of the neck. The rigidity of the lumbar spine, with the absence of the normal curve in this region, produces a peculiar attitude and gait. He stands with the legs partly flexed at the hips and knees and with the feet and legs rotated decidedly outwards. In all movements of the trunk the spine acts as a single bone, remaining in all attitudes perfectly fixed.

To these symptoms, all of which are due to the fixation of the spinal column, there is added in many cases a group of sensory symptoms referred by v. Bechterew to the spinal roots.

Subjective disturbances of sensation are present in the extremities, especially the upper extremities, such as pain and paræsthesia. Pain referred to the abdomen is not infrequent. Increase of reflexes occurs in the lower extremities associated with cramps in the legs. Impairment of sensation is found in the lower cervical and upper dorsal distribution, and also some atrophic wasting of the muscle groups in this region. The electrical examination shows no other change than a slight quantitative diminution. As ætiological factors, trauma, probably with concussion (Erschütterung) of the spinal column and heredity have been suggested. The following case belongs to this type of disease, and I report it here to contrast it with the cases of rheumatoid arthritis in which the spinal column is involved:

Case I.—C. W., aged 34 years, white, weaver by occupation (but in early adult life an acrobat), was referred to me in September, 1899, for persistent pain in the abdomen and rigidity of the spinal column. His grandfather and uncle had had paralysis for several years before they died. He had two healthy children; his wife

had had two miscarriages; otherwise his family history contained nothing of importance. As a child he had the usual diseases of childhood; acute articular rheumatism with a cardiac complication at 12 years, and gonorrhœa at 20 years. He had Texas fever, with a "bloody flux," from which he recovered and remained in good health until eight years previously. At that time while descending a small flight of stairs he missed his footing and fell some distance, landing on his feet. At that time he felt considerable pain in the right hip. This disappeared in a short time and he had no further trouble until over a year later. Pain reappeared in the right hip and for the past six years he had had more or less pain in both the right and left hips and at times over the lumbar and lower dorsal spine. This pain was a dull ache; much worse after several hours' work at his trade of weaver, which necessitated more or less forward and backward movement while in an upright position. At night he stated that he could hardly straighten up. His main complaint for the previous two years had been that of a constant pain referred to the pit of the stomach; he stated that "it felt as if there was a brick in the abdomen and as if the anterior wall of the abdomen was stuck fast to the spine." For the past two years he had had frequent nocturnal seminal emissions with night sweats. His memory had been failing for the past year. He was a sparely built man with the typical flexed attitude at the hips and knees; a sunken, forward position of the head; and a rigid, awkward gait, with the toes adducted and the legs separated and flexed. The dorsal and lumbar spine was rigid and there was present only very slight forward movement in the cervical region. There was no ankylosis or other involvement of other joints. The erector spinæ group of muscles were hard and boardlike and somewhat wasted. The scapular groups were also wasted and hugged closely the underlying structures. He swayed more with the eyes closed than would a normal person. The knee jerks were present only on reinforcement. All the reflexes of the lower extremities were diminished. The reflexes of the upper extremities were normal.

Sensation over the extremities, normal; over the trunk there was hyperæsthesia in areas, more marked over the lower part of the abdomen. He was not sensitive to pressure over the nerve

trunks. The hips were freely movable and not painful on motion or to direct pressure. Percussion over the dorsal and lumbar spine produced pain.

Visceral examination revealed an old mitral regurgitant lesion with an associated enlargement of the heart in full compensation; a moderate grade of atrophic emphysema with very impaired respiratory excursion and respiration mainly abdominal in type.

We had therefore in this case symptoms almost if not entirely confined to the spinal column and its supporting muscles and to the nerve roots. There was no trace of disturbance in the extraspinal articulations and the symptoms referred to the spine developed insidiously and were progressive in character. The diminution of the leg reflexes, associated with the early subjective symptoms referred to the lower extremities, might be explained by the fact that the spinal process in this case was ascending in type and whatever damage to the roots may have taken place would more likely be further advanced in the legs than in the upper spinal distribution. The most interesting thing about this case was the long duration of what was evidently a chronic joint affection remaining limited to the spinal column. The abdominal pain and the pain in the extremities in the absence of any other lesion must be referred to the spinal roots.

If the other symptoms recorded did not occur in typical cases of rheumatoid arthritis I should have been disposed, on account of the course of the disease (extending over eight years), and its strict limitation to the spine, to class this case as a distinct clinical entity apart from rheumatoid arthritis. The following case is of considerable interest in this connection:

Case II.—J. R., male, aged 11 years, was admitted April, 1901, suffering with acutely swollen painful joints. He had had measles at the age of 5 years, but had otherwise been healthy. The present trouble started in March, 1900, with swelling of the feet and knees, with pain and tenderness. In July the hands were affected in the same way. On admission the wrists were markedly swollen, but were not painful to ordinary pressure. Fluctuation was present in both wrist joints. Grating was likewise observed. The joints of all the fingers were similarly affected.

The metatarsal articulations of both great toes were enlarged and tender. The blood count at this time showed R. B. C., 6,000,000; W. B. C., 14,000; Hg., 60 per cent. There was a systolic murmur over the aortic cartilage transmitted into the vessels of the neck. At my last examination during the past spring all the joints of the extremities were more or less ankylosed. The spine appeared to be involved throughout its entire course. In the cervical region there was little motion left, but not complete ankylosis. The ankylosis was much more extensive in the dorsal spine and to a lesser degree in the lumbar region. There were distinct symptoms of root involvement. Wasting about the shoulder girdle and in the extremities, zonal hyperæsthesia on the trunk, and an atrophic condition of the skin in the area of the affected joints were noted.

This case was of considerable interest on account of the early age at which it developed and the sensory and reflex symptoms indicative of root and spinal involvement.

The following cases will give some idea of the frequency and extent of spinal involvement in rheumatoid arthritis:

Case III.—J. S., male, white, aged 34 years. Occupation, fireman. All the joints were ankylosed, the patient being rigid; the entire spine was rigid and immovable. It was necessary to feed with liquid or semiliquid food.

Case IV.—D. M., male, 35 years old; song and dance artist. The disease began with an acute attack of pain and fever ten years previously; this was followed after a year's quiescence by a progressive involvement of all the joints, beginning in the right upper extremity and extending to all the joints of the body. The maxillary joints were but little affected. The spine was rigid with marked tenderness throughout its entire extent, there was some movement present in the cervical region. A marked kyphosis affected the dorsocervical area.

Case V.—K. M., female, aged 53 years; housewife. An acute attack of pain and swelling began in the hands twenty-six years before, and extended to all the joints of the extremities, which

later became ankylosed. The spine was almost rigid in the dorsal and lumbar areas, but quite movable in the cervical area; no curvature or tenderness.

Case VI.—M. W., 49 years old; housewife. The disease began with an acute attack twenty-one years before, and gradually affected all four extremities, the dorsal and cervical vertebræ; lumbar spine not affected; some slight kyphosis in the upper dorsal area; cervical area and all the affected joints very tender.

Case VII.—T. C., male, aged 31 years, occupation, brick maker. The acute attack began fourteen years before with severe pain in lower extremities. Some time after this he fell and injured his spine and has not since been able to walk. Symptoms referable to the spine became much more marked after the injury. The disease progressed in the other joints until at the present time there is practically complete ankylosis of all the joints, including the jaw joints. There is some kyphosis with tenderness and pain referred to the cervical region; marked arterial sclerosis with a systolic murmur over the apex of the heart.

Case VIII.—M. E., male, aged 33 years, farmer. Acute attack occurred seventeen years previously, affecting ankles and knees; joints of lower extremities markedly involved and to a lesser degree those of the upper extremities; jaws also involved; complete rigidity of the entire spine; considerable pain present with tenderness; slight lateral curvature in cervicodorsal area.

Case IX.—M. S., female, 68 years old, housewife. Acute attack began thirty-two years before in the right shoulder and wrist; since that time all the joints had become more or less involved; vertebræ were all involved with some tenderness in the lumbar region and some slight lateral curvatures in the cervicodorsal; process most intense in the cervical area.

Case X.—F. R., male, aged 36 years, soap worker. Acute attack began thirty-five years before with involvement of the hands; history of injury in the hand and arm first affected; main involvement found in the upper extremity; some crepitus with pain in the joints of the lower extremity; recent involvement of the cervical area

of the spine; dorsal and lumbar areas completely ankylosed; an area of zonal anæsthesia corresponding to the scapula of the right side; some tenderness with a slight kyphotic curvature in the cervicodorsal area.

Case XI.—M. W., female, aged 64 years, housewife. Acute attack occurred twelve years before after an attack of grippe. The lower extremities were at first affected. This was followed by rigidity of the spine and later of the lower extremities. The affection of the spine was confined to the cervical and upper dorsal areas. The lumbar spine was little if at all affected. There was some anæsthesia of the trunk in the middorsal distribution of the right side.

Case XII.—M. T., male, aged 63 years, carpenter. Acute attack began fourteen years before, following grippe. The ankles were at first affected, later the joints of the lower extremity. He had had "lumbago" ever since the beginning of the disease. The main involvement of the spine was confined to the dorsolumbar area; there was considerable crepitus with comparatively little limitation of movement in the cervical area. There was an area of anæsthesia of the trunk corresponding in distribution from the sixth to the tenth dorsal spinal segments with a zone of hyperæsthesia above this area.

Case XIII.—M. W., female, aged 49 years, housewife. The acute attack began twenty-one years before, after the birth of a stillborn baby. There was an acute painful swelling of the joints with fever affecting both upper and lower extremities. There was very marked atrophy of the muscles and also of the skin; marked deformity in all four extremities; spinal involvement confined to the cervical and upper dorsal areas, associated with distinct scoliosis and some kyphosis in the same area.

Case XIV.—This patient had been under my care at the Home for Incurables, and was later admitted at the University Hospital, where he died and where the autopsy was performed. I am indebted to Dr. Stengel for his notes of the case and for the autopsy material.

D. M., aged 32 years, white, admitted to University Hospital January 17, 1902, service of Dr. Stengel; electrician; occupation necessitated use

of right hand a great deal; used alcohol moderately; father died of pleurisy; mother and one sister living and well; no history of injury; never had any sickness except present trouble. Eight years before, patient began to have pain and stiffness in the right wrist. The fingers of the right hand were involved in a few weeks, and successively the wrist of the left hand (not as marked as the right); this was followed by an involvement of the ankles, feet, knees, hips, and spine. He had been at the Home for Incurables for the previous two and a half years. Until admission to the hospital he was able to walk with the aid of a cane, and to sit in a semierect position in a high chair.

Physical Examination: Lay in bed on back, semirecumbent, legs and thighs flexed; he asked frequently to be lifted higher on pillows; could sit on side of bed with hips partially flexed; apparent age forty-five years; gait not noted; facies, expressive of tremendous emaciation. Bony structure that of a man of moderate size and development. Skin dry, glazed, and shiny, especially over ribs; on abdomen showed superficial scaling. Brownish pigmented patches on ring and small finger of right hand, and ring finger of the left hand; slight on forehead; œdema marked in feet. No abnormal pulsations or eruptions. Temperature: local not elevated; general, 98.2° F.; superficial arteries slightly sclerosed; no lymphatic enlargement; muscles markedly wasted; strength very poor; muscles appeared to have been of moderate development; tremors slight; no contractures; nails show marked linear striation.

Joints: Right thumb and middle finger subluxated; little finger fixed; right wrist joint fixed; left wrist movable. Elbow motion good. Shoulder motion limited, could not raise arms to horizontal position; anteroposterior motion also limited; neck very rigid; spine showed impaired motion. Great toes fixed in hammer toe position; second toes fixed, remaining toes showed impaired motion. Limitation of motion in articulations of tarsus. On right side reversal of anteroposterior arch of foot, convexity downward. Right knee spindle shaped, enlarged, motion limited. Left knee, moderate motion; left hip, motion good; right hip, fixed. Head, angular in shape, size proportionate to body. Hair dry. Face showed signs of wasting, sunken eyes, hol-

low cheeks and temporal fossæ, prominent molars, chin, and nose, thin lips. Color, slight pigmentation on forehead; pallid. Eyes, dark brown; size normal, pupils reacted to light and accommodation; conjunctivæ slightly congested; sclera, pale. Ears, large, no abnormity in shape; mastoids prominent; hearing good. Jaws showed some impairment of motion; lips thin, dry, and pale. Mouth and nose, mucous membrane pale; breath, fœtid; teeth, few and carious; gums pale; tongue dry whitish coating, movements good, marked tremor. Palate, tonsils, and pharynx slightly congested; voice, slightly hoarse; vocal cords not examined; neck thin, motion restricted; carotid pulsations not marked; no thyreoid enlargement; lymphatic glands not enlarged. Thorax: All normal depressions very marked from emaciation. Respiratory movements limited, breathing largely abdominal from lack of mobility of costal and spinal articulations. Apex beat fifth interspace one and one half inch within nipple line; pulsation visible in fourth interspace; no thrills; fremitus marked on both sides. Lungs: Percussion showed apex to be level with clavicle; base at sixth rib on left side; very slight descent with inspiration; percussion note not appreciably impaired. Heart: Upper border at lower edge of third rib; right border, slightly within right border of sternum; apex, one and one half inch within nipple line, fifth interspace. Auscultation sounds clear, but weak; no murmurs; cardiac action irregular. Abdomen: No thorough examination; walls very rigid. Liver enlarged, one inch below costal margin. Gastric area extends as low as umbilicus. Spleen not palpable. Nervous system: Gait not noted; coordination impaired from condition of joints, and weakness; slight tremor, largely volitional. Muscular strength impaired, equally decreased on the two sides. Reflexes: Patella, biceps, and triceps increased. Sensation: Tactile not appreciably impaired; sight, hearing, and speech normal; some mental impairment and irritability.

Blood: Hæmoglobin 38 per cent.; R. B. C., 5,130,000; W. B. C., 21,200.

Uranalysis: Urine slightly cloudy, pale yellow. neutral, no precipitates; sp. gr., 1013; albumin, distinct ring with HNO_3; sugar, negative; indican, distinct. Cystoscope showed urates, epithelial cells, a few leucocytes, and hyaline and granular casts.

Pathological Examination.—No gross changes were observed in the central nervous system. Microscopical examination of the brain showed a moderate grade of arteriosclerosis. The large cortical pyramidal cells of the motor cortex were the seat of senile changes, i. e., they were of somewhat smaller size with a diminution in the number of dendrites, a lessened quantity of chromatin, and a deposition of yellow pigment at one extremity of the cell. This deposition of pigment in some of the cells occupied a greater portion of the cell area. In such cases the nucleus took a somewhat eccentric position. These changes are normal to old age, and occurring at an earlier period of life in cases of marked arteriosclerosis are simply indicative of presenility. These changes occasionally occur in conditions of intense intoxication. I have observed them in a case of diabetic coma.

A microscopical examination of the spinal cord showed the same cellular changes as observed in the cortex. There was also a condition of arterial sclerosis of the vessels of the cord, with miliary aneurysms. Two miliary aneurysms, one in the area of the crossed pyramidal tract of the cervical area of the cord, the other in the anterolateral tract of the upper dorsal area, were observed. Small areas of perivascular sclerosis obtained here and there throughout the cord. The areas were not uniform around all vessels and occurred only around certain vessels, and like the miliary aneurysm formation, were in the distribution of the pial vessels, i. e., not in the distribution of the anterior spinal artery and its branches. There were small black granules scattered here and there over the entire area of cross section of the cord by the Marchi method. Inasmuch as a few sparse black granules may occur in normal conditions as a manifestation of nutritive changes within a normal limit an increase in the number of these fat granules is, I take it, merely the accentuation of the same nutritive changes in the myelin, due to the arteriosclerosis. The same condition obtained in the nerves. In the longitudinal section of the nerves these black granules were present, but not sufficiently frequent to constitute degeneration, i. e., the myelin formed a continuous entity between the nodes of Ranvier and the minute black granules which were occasionally present, never oc-

curred as a continuous row of black dots, such as would necessarily be present if the nutritive changes in the myelin were sufficiently intense to constitute a pathological process. While, therefore, I consider the presence of those conditions both in the spinal cord and peripheral nerves as within the normal pale, it is only so here described within such limits. When the arterial changes are taken into consideration I should not consider them entirely normal in a man thirty-two years of age, but abnormal only in the sense of deficient nutrition due to arteriosclerosis.

In a cervical and lumbar enlargement of the cord, the ganglion cells of the anterior horns were diminished in number and the seat of the following changes: The yellow pigment occupied a large part of the cell area with an eccentric position of the nucleus and diminution in the number of dendrites. The nuclei of most of these cells were of much smaller size and stained very deeply with the nuclear stain. The nucleus with the hæmalaun-eosin took a pale violet tinge, in which the filaments of chromatin could be seen under a high power. In the cells under consideration the nucleus was reduced to one half or even one third of the normal size, took a deep purple stain, in the midst of which the nucleolus was hardly perceptible. In a few of the cells the nuclear area was so reduced as to form a very slight ring around the nucleolus. The other ganglion cells, both in the cervical and lumbar enlargements, were fewer in number than in normal cords.

The anterior and posterior roots were normal by the Van Gieson, hæmalaun-eosin, and Weigert stains. By the Marchi method, the posterior roots showed a number of small black granules, both in transverse and long section, but not sufficient to constitute unquestionable degeneration. This was borne out by the fact that secondary degeneration was not seen by the Weigert method, other than as a slight perivascular sclerosis, in the posterior column. In such a chronic process this would undoubtedly be present had this degeneration gone beyond the limits of a functional and restorable process.

The changes in the spinal intervertebral ganglia, other than the marked arteriosclerosis of the vessels, were confined to the ganglion cells. The normal ganglion cells should be spherical with a large vesicular nucleus, staining a very pale violet with hæmalaun, with the cell sub-

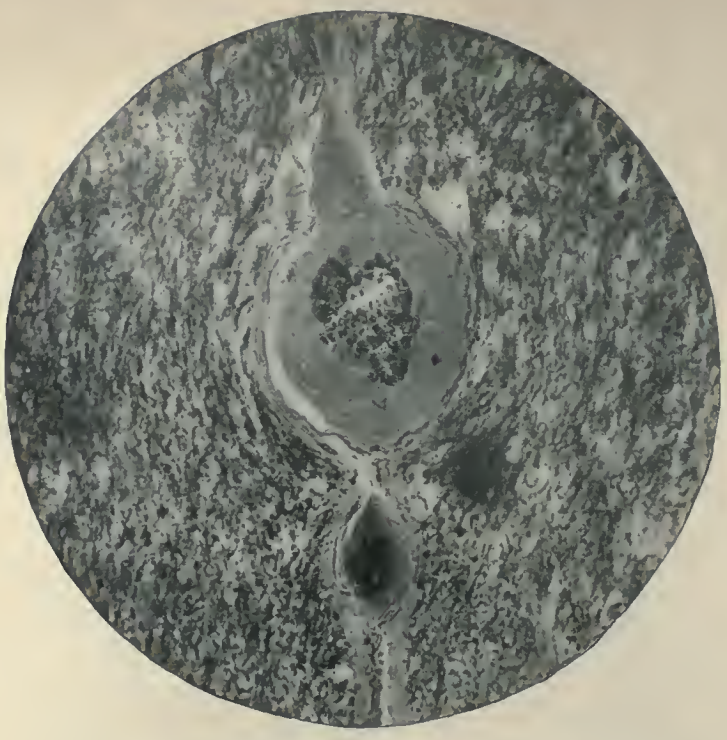

FIG. 1.—Miliary aneurysm in the anterolateral tract of the spinal cord of Case 13. This aneurysm involves one of the pial arteries. Rarefaction and an area of sclerosis are seen around the aneurysm.

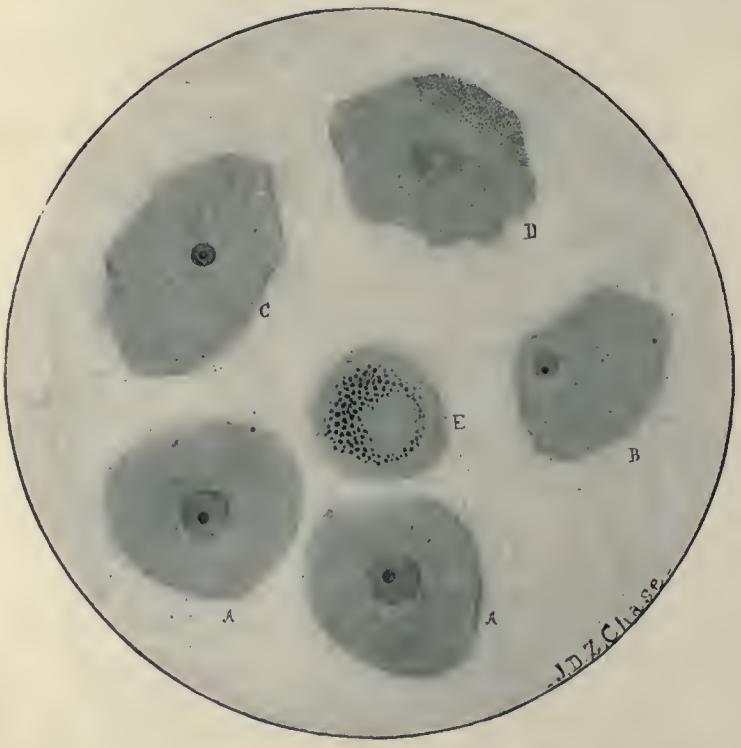

FIG. 2.—Section with the exception of "E" stained by "Hæmalaun-carbolic-eosin" stain. A A, Normal cells. B, Eccentric position of nucleus, with diminution of its size. C, Marked diminution in size of nucleus. The nucleus has taken very deep stain. D, Atrophy, with pigmentation of the cell and with shadow nucleus. E, Perinuclear pigmentation, as shown by Marchi method.

stance staining a light purple. The chromophilic bodies of Nissl were distinctly stained and were in these cells finely granular and absent at the periphery of the normal cells. In the ganglia of this case, it is exceptional to find a cell approaching the normal. The yellow pigment described was present in these cells in large quantities. In some of the cells it appeared as a dark yellow homogeneous mass, whereas in others it occurred as very fine granules, giving a pale yellow tinge to the cell protoplasm. The arrangement of the pigment in the spinal ganglion cells was somewhat different from that observed in the cells of the spinal column. The usual arrangement of the pigment in the spinal cells is toward one end of the cell. In the spinal ganglia the deposition of pigment as a rule is around the nucleus in the centre of the cell. This is brought out very distinctly in sections by the Marchi method. The granular pigment in this case, both in the cells of the spinal cord and of the spinal ganglia, gave a black stain by the Marchi method and a purplish black stain by the Weigert sheath stain. The same character of pigmentation with more advanced changes in the nuclei and other evidence of senile degeneration of the cells, both of the spinal cord and intervertebral ganglia and the Gasserian ganglion, were present in a case of migraine with extensive arteriosclerosis of the central nervous system. In some of the cells, instead of a deeply stained contracted nucleus, the nuclei were very pale without nucleoli and without the chromatin filaments of the normal nucleus. The chromophilic elements of the cell protoplasm stained less intensely in these cells, especially towards the periphery of the cell. The outline was somewhat irregular in shape. In more advanced stages of degeneration the cell outline is very irregular, the cell protoplasm taking a homogeneous pale violet stain with a deposition of large quantities of yellow pigment at one side and sometimes taking up the entire cell area; the nucleus is either entirely absent, or if present has an eccentric position at the edge of the cell and at times appears as a vacuolar area in the midst of a mass of pigment, but taking no stain and appearing as a clear, stainless area.

All these cell changes have been noted as occurring in the intervertebral spinal ganglia, and are also present in the Gasserian ganglion.

An examination was made of the sciatic nerve

and two similar nerves sent to the laboratory unlabeled. The examination of the sciatic nerve by the Marchi method showed no distinct, well defined degeneration, merely the presence of small black granules here and there as described. The examination by the Weigert sheath method showed distinct degeneration in small groups of fibres. This degeneration was not that of individual fibres, but of a number of contiguous fibres running parallel in the same area of the nerve. This was best seen in microscopic sections cut in the long axis. The muscles were not submitted for examination.

The pathological lesions described in this case, i. e., the cell degeneration of arteriosclerosis and the changes in the peripheral nerves, have been found in other conditions. I have noted before the same cell degeneration in a case of migraine with arteriosclerosis of the nervous system and have also seen it in other cases of arteriosclerosis. The same group of lesions identical with all those described are present in a case of paralysis agitans with joint deformity.

The similarity of certain cases of paralysis agitans to the ankylotic form of rheumatoid arthritis is very striking. Spiller has recently called attention to this same condition. I have been impressed of this similarity for a long time, and Dr. Carncross, in an investigation of my cases at the Home for Incurables, both of rheumatoid arthritis and paralysis agitans, has noted in a number of cases a distinct identity of joint and sensory symptoms. The lesions of the sensory ganglia (the spinal and Gasserian) are of especial interest in their relation of chronic trophic disturbances. The association of disturbance of the sensory system to both acute and chronic trophic disturbance, has not received the proper attention. I have called attention to it in hydrophobia, for my attention had first been directed in this direction by Dr. Burr's observation at the Philadelphia Hospital of the rarity of trophic necrosis without sensory derangement. The atrophy arrangement in the muscles and other tissues in direct association with diseased joints, so called Charcot reflex atrophy, is simi-

lar, although not so extensive as the trophic disturbance in the same structures in rheumatoid arthritis. It is probable in cases of reflex atrophy following a joint injury, that a functional or organic disturbance of the sensory neurone, such as is described in this case, may be the explanation of the condition. The findings in these cases, if they teach anything, support the theory of an affection of the central nervous system for the cause of rheumatoid arthritis; that these lesions, however, may be secondary to the joint changes should not be lost sight of, especially as we see an identical symptom complex developing in the course of tuberculosis which may more easily explain the theory of a local pathological process in the joints.

In drawing conclusions from the cases here reported, it must be remembered that all of these cases, with the exception of Case I, are of long standing and exhibit an advanced state of the disease. Notwithstanding this fact the frequency of the spinal involvement is striking. There is, however, no special reason why the spinal articulations should not be affected with the same frequency as the other joints. The fact remains that these joints are rarely involved in acute articular rheumatism. In Case I during the period of the initial acute stage, symptoms referable to the spine were not present, or at least were not spoken of by the patient, and yet within two years well defined and apparently advanced rigidity of the spine was presented on examination. The presence of root symptoms in this case, flattening of the chest, etc., gives us a clinical picture if the other joints are left out of consideration, almost if not exactly identical with that in the group of cases described by v. Bechterew.

The history of the case of isolated spinal rigidity (C. W.) deserves careful comparison with those here tabulated. In all the cases of rheumatoid arthritis there is a well defined history of acute manifestations in the joints followed at varying intervals by the progressive joint changes and at times with acute exacerbations

of the chronic symptoms. In all the cases here reported of rheumatoid arthritis in which the spine is entirely involved, there is an extensive involvement of nearly all the other articulations, even the jaw joints in some of the cases being affected. In the case of C. W. the onset was insidious, without acute symptoms, and followed some time after a shock to the spine. The initial symptoms in this case were referred to the legs and in all probability were of root origin. The immunity of the other joints after ten years of progressive stiffening of the spine is noteworthy.

In spite of the similarity of the joint symptoms in some of the cases of rheumatoid arthritis to the disease described by v. Bechterew, we are not at all positive that the latter disease is in all cases or even in the case here under consideration to be considered as being a local manifestation of rheumatoid arthritis. One should be careful about arriving at positive conclusions in such a matter, inasmuch as it is highly probable that a group of ætiologically distinct joint affections are classified clinically under the term rheumatoid arthritis. From a study of the cases at our disposal we are justified in drawing the following conclusions:

(1) That ankylosis and rigidity of the spinal column is a frequent manifestation of advanced rheumatoid arthritis.

(2) That it may develop early in the course of the disease and be associated with irritative root symptoms.

(3) That if the disease described by v. Bechterew is to be considered as a distinct clinical entity separate from rheumatoid arthritis, it should only be diagnosticated as such after the disease has progressed over a considerable period of time without involving joints other than those of the spinal column.

(4) That we are not able at present to differentiate from rheumatoid arthritis that large group of cases, reported by Marie and others, where the rigidity of the spine is associated with changes in the hip and other joints.

A CYSTIC PAPILLOMATOUS EPENDYMOMA OF THE CHOROID PLEXUS OF THE LATERAL CEREBRAL VENTRICLE. A CONTRIBUTION TO THE CLASSIFICATION OF GLIOMATA.

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(From the William Pepper Clinical Laboratory (Phoebe A. Hearst Foundation) and the Laboratory of the State Live-stock Sanitary Board.)

There is, perhaps, no class of tumors which has given rise to more discussion as to their essential nature than those originating in or mainly composed of neurogliar tissue. This is in part, if not entirely, due to the peculiar relation of the neuroglia to the rest of the brain structure. In the other organs of the body the skeletal or supporting tissue is composed of connective tissue derived from the mesoderm. In the central nervous system the supporting tissue is composed of neuroglia, has its origin in the ectodermic layer of the embryo, and is therefore essentially epithelial in its nature. Notwithstanding this fact, the typical glioma follows the type of the sarcomata of other organs, derived from connective tissue. In its growth and clinical manifestations it also follows more closely the sarcomata than the epithelial tumors. For these reasons the gliomata have been at times classified as a subdivision of the sarcomata or mesoblastic tumor group.

One important fact is overlooked in considering this matter, and that is, that the neuroglia acts only in part as the structural framework of the central nervous system, and that true connective tissue from the walls of the bloodvessels and extensions of the covering membranes of the brain and cord play an impor-

tant role. This is especially true in the spinal cord. From this connective tissue true sarcomata can and often do develop.

The structure of the fully developed glioma, as stated above, follows the type of the small round-cell sarcoma. It is composed of delicate neuroglia fibres and small round nuclei closely placed together; it is without interstitial enveloping tissue, is richly supplied with bloodvessels, and infiltrates the surrounding healthy tissue. As we approach the central ventricles a type of

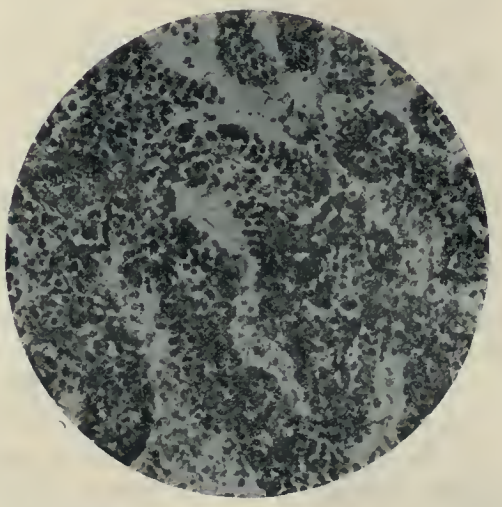

FIG. 1.—Alveolar arrangement of cells is shown. Melanin pigment is seen at the left margin of the photograph.

glioma is met with differing somewhat in structure from this form. The nuclei are larger, with a visible cell protoplasm about the nuclei, and not infrequently star-shaped or cubical cells are seen. According to Streube and others this type of tumor is the development of "rests" of the ependymal cells, the mother-cells of the neuroglia, which have been isolated in the brain substance, or from pockets which still remain in connection with the ventricles, and from which the glioma develops. In the immediate neighborhood of the ventricle, and growing directly from the layer of ependymal cell lining the

ventricles, a tumor form is met with composed of the cubical type of ependymal cell, more or less transformed by the resistance of the surrounding tissues and the rapidity of growth. To this special form of tumor formation the name ependymoma has been given. The tumor about to be described differs in its essential characters from any which I have been able to find in the literature, in that, while developing from the ependymal

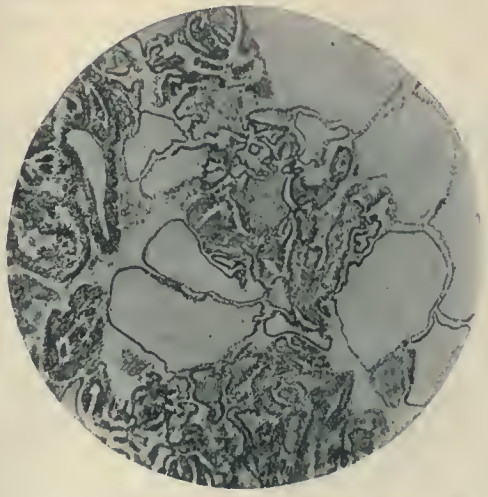

FIG. 2.—The distended acini filled with a gelatinous exudate are seen in the centre of the picture. The lower segment of the field shows the acinous arrangement of the tumor mass, as shown in Fig. 1 under a higher power.

cells, it follows the structure of an adenoma, or, more correctly, a cystic adenoma.

The specimen was from a horse which showed symptoms of progressive and marked intracranial pressure. Gross examination showed a large mass, 7 x 4 x 4 cm., of a soft consistence, dark red in color, with here and there areas of black and very dark red. Scattered through the mass were sago-like masses of soft, gelatinous material.

The Microscopic Examination. Sections removed from the neighborhood of the choroid plexus—*i. e.*, the original site of the plexus—showed nothing of the normal arrangement, but a picture

revealing the general build of the papillomatous growth, or, more correctly, an adenomatous arrangement of a racemose gland. The structural work is composed of connective tissue growing from that surrounding the bloodvessls. The connective tissue is present only in very small amount between the acini. The cells of the acini are the cubical cell, with small, round, deeply staining nuclei, following the type of the ependymal cell.

Here and there the acini are filled with a hyaline material. In other sections large areas of this hyaline material, surrounded by a thin layer of the same type of cell as that described above,

Fig. 3.

and giving the appearance of a section from the thyroid gland, are seen. The hyaline material is not colloid and gives none of the staining reactions for colloid. With the Van Gieson stain it does not stain at all. With Pianese stain, No. 3, it gives a salmon color. It reacts the same as the gelatinous exudate met with in other pathological conditions of the ependymal lining of the ventricles.

In some of the acini large, round, multilocular, vesicular cells are seen, with a very small eccentric nucleus, situated deep in the hyaline exudate.

In many of the acini the proliferation of the cells has extended through the basement tissue, and form nests of cells here and there, leaving no doubt as to the malignant nature of the tumor.

In considering the ectodermic origin of the cell type, the arrangement of the tumor, the secretion of the hyaline material into the acini, it was decided to place this tumor in the class of carcinomata, and a diagnosis of ependymomal adenocarcinoma was given. As will readily be seen from the photograph (Fig. 3), the structural formation follows that seen in papillomata, or, more strictly, a cystic papilloma, such as is seen in ovarian tumors. Inasmuch, however, as the cell type is not that of the true papillomata and the evident malignant nature of the tumor, both as to gross and microscopic findings, lead us to place this tumor under the head of the carcinomata.

The development of a tumor giving all of the morphological characteristics of a compound racemose type of gland, and composed of cells originating from ependymal cells, is of extreme importance in determining the nature of ependymomata and gliomata. The ependymal cell, as the "mother" type of cell of the neuroglia cell, determines its character. If, therefore, a glandular type of tumor can develop from the ependyma cell, it necessarily follows that the gliomata, whether of the small round-cell type or those composed of larger and more irregular cells, belong to the same class of tumors found elsewhere in the body growing from the ectoderm.

I am indebted to Dr. C. Y. White, pathologist to the State Live-stock Sanitary Board, and to Dr. Harger for the material on which this paper is based.

CHOLESTEATOMA VASCULOSA OF THE CHOROID PLEXUS OF THE LATERAL CEREBRAL VENTRICLE.

By D. J. McCarthy, M.D.,
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(From the William Pepper Clinical Laboratory (Phoebe A. Hearst Foundation) and the Laboratory of the State Live-stock Sanitary Board.)

The deposition of cholesterin crystals in nervous tissues undergoing various pathological processes is well recognized by neuropathologists. The presence of cholesterin crystals in the choroid plexus is, however, a comparatively rare occurrence. I have yet to see a primary deposition in the choroid plexus of a human being. In the horse it is of not infrequent occurrence, and is always associated with some pathological process in the parenchyma or interstitial tissue of the plexus.

A very interesting form of cholesterin formation in the choroid plexus is seen in the "cholesteatoma vasculosa telæ choroidea et ventriculorum cerebri" described by Kitt.[1] The case coming under my observation gave rise to some difficulty in diagnosis on account of the peculiar structure and situation of the tumor mass. The horse presented nothing in the clinical picture to suggest a brain tumor other than a certain amount of stupidity and confusion—the so-called "dummy." At the autopsy a body the size of an English walnut was found almost free in the left lateral ventricle. It was of a soft, almost fluid consistence in the centre, surrounded by a tough, fibrous capsule, and attached by a small band of tissue to the choroid.

[1] Pathologische Anatomie des Hausthiere, v. ii., S. 581.

The microscopic appearance led at first to a diagnosis of endothelioma by the pathologist, on account of certain peculiarities in structure, but the appearance is typical of the cholesteatoma vasculosa.

The capsule is composed of fibrous tissue derived from the bloodvessels of the choroid, and in this case contained a large quantity of elastic fibres. In the meshes of the fibrous tissue large numbers of cells, the size of a polynuclear leukocyte, but mononuclear in type, are seen. The nucleus is, however, irregular in shape, and not infrequently appears to be made up of several globular masses of chromatin. Irregular spindle cells with a pale, newly formed nucleus are also present. As the centre of the tumor is approached the reticulum of connective tissue becomes looser, giving much the appearance of lymphoid tissue. The greater part of the area of section is taken up by the accumulation of round cells. The majority of these are the size of a polyuuclear leukocyte, but do not give the staining reaction of leukocytes. The nuclei are sometimes round, but more often of the same irregular type as is seen in the meshes of the capsule. The irregularity of the shape of nuclei is often very marked, but true polynuclear cells are not seen. A large, round, mononuclear, vesicular type of cell is also seen. The nucleus is round or irregularly oval, and stains a pale blue with hæmatoxylin. A peculiar type of cell is seen here and there throughout the section. This is a multilocular cell, three to four times the size of a polynuclear leukocyte. The nucleus is small and eccentrically situated. The cell body is divided up by septa of chromatin, giving the appearance of a beehive arrangement. A type of cell similar to this, but not identical with it, is found as a normal structure in the Raynaud bodies in the peripheral nerves.

A large part of the area of section is taken up by the crystalline masses above described. These are more or less limited by capsules of connective tissue. In some areas the crystalline substance is the only substance present. In others, and these are the more numerous, rows of cells, some round, some spindle type, fit in the areas between the crystalline deposit. The nuclei of

the spindle cells are large and pale; those of the round type of cell are very irregular. The arrangement of the cells in rows gives a picture at first glance not unlike that of an endothelioma.

The tumor tissue is everywhere richly supplied with blood-vessels. The presence of melanin pigment in considerable

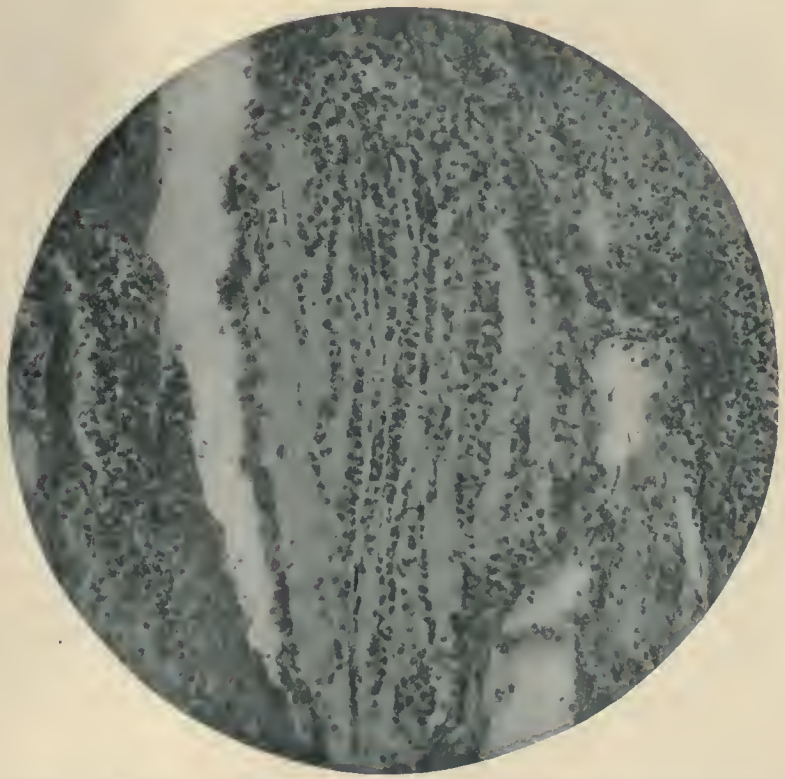


FIG. 1.—A section of the central area of the tumor formation, showing the capsule of a cholesterin area, with rows of large cells arranged in columns through the centre of it. Magnified 350 times.

quantities is probably the result of previous hemorrhage. No recent hemorrhage was present in the sections examined.

It will be seen from a study of the picture (Fig. 1) that the structure of the tumor under consideration does not at all correspond to the cholesteatoma met with in the human being. In

the latter the pearls are composed of flat, epithelial-like cells, whereas the structure of the choroidal tumor does not present any such appearance. The highly vascular connective-tissue network is filled with round cells, and the areas of cholesterin deposit is merely a sac-like compartment within the tumor mass,

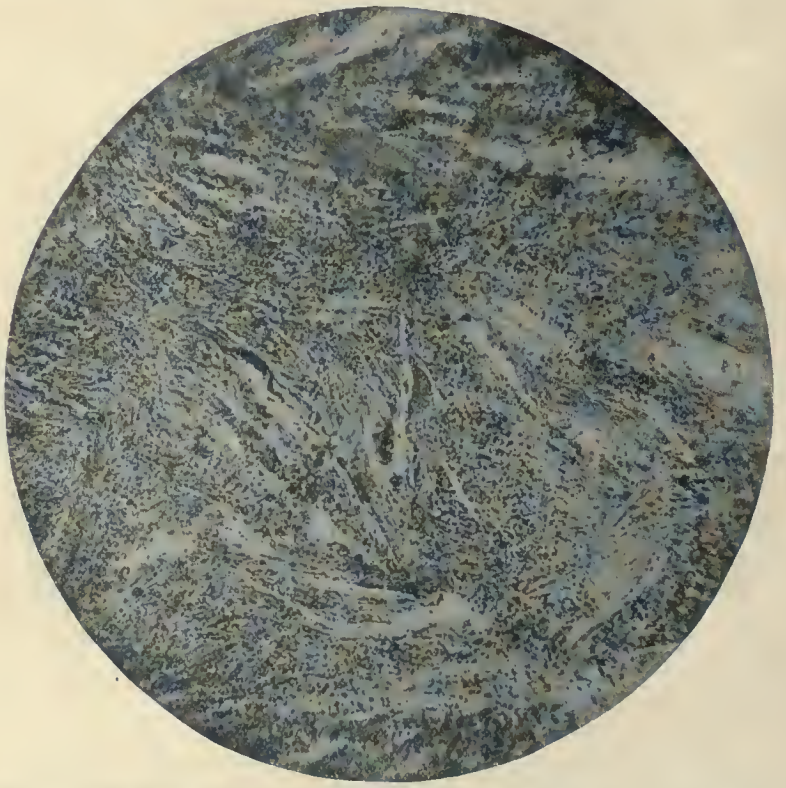


FIG. 2.—Central area of tumor mass, showing the arrangement of the crystalline areas and round-cell infiltration. Under a low power. (Leitz ob. 3, oc. 4.)

covered by connective tissue. Between the cholesterin crystals round cells of irregular nuclei, probably leukocytic in origin, are arranged in rows, giving the appearance of an endothelioma type of tumor.

The origin of this tumor mass is very obscure. It has been found in horses dying of glanders, and one explanation given is

that of an infection of the ventricles and choroid by the organism causing this disease. But why a suppurative process within the ventricles should be so localized, without evidence of infection elsewhere in the brain, is not very clear. Proliferative changes in the connective tissue of the choroid is not at all infrequent in other infections. It is seen in its most intense form in forage poisoning in cattle. To a less intense degree it is frequently met with in tuberculosis in the lower animals and the human. It was present in the choroid plexus of a patient who died from acute internal hydrocephalus. That an irritating substance in the ventricular fluid, such as is present in forage poisoning, or a bacillary infection not going on to suppuration, but producing a non-purulent inflammatory process, is a more likely explanation of the condition than a single infection such as glanders. The deposition of cholesterin is undoubtedly a secondary process, and may correspond in the lower animal type to the calcified concentric bodies so frequently met with in the choroid plexus of the human being. A careful study of the choroid plexus some years ago, in an attempt to get some explanation for meningitis serosa in the human being, led me to the conclusion that little was to be gained from the literature or autopsy findings in the choroid plexus of man. In the lower animals a much wider field is presented in the study of the physiology and pathology of this part of the brain which may have some bearing on the obscure conditions met with in clinical medicine.

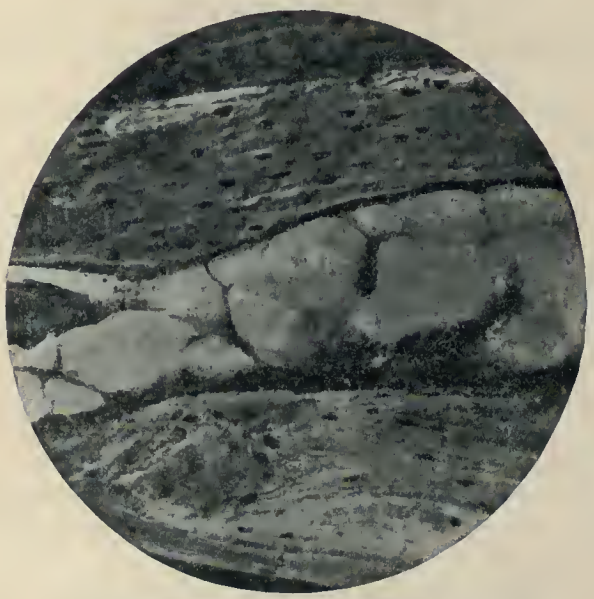
THE FORMATION OF BONE TISSUE WITHIN THE BRAIN SUBSTANCE. A CONTRIBUTION TO THE INCLUSION THEORY OF TUMOR FORMATION.

By D. J. McCarthy, M.D.,
Associate in the William Pepper Clinical Laboratory.

(From the William Pepper Clinical Laboratory, Phoebe A. Hearst Foundation.)

The presence of true osseous tissue with all the histological structure of bone within the brain is of such rarity as to justify placing the following case on record: In April, 1900, a series of experiments was begun to determine the results in the lower animals of constant cortical irritation. Small pieces of serrated copper wire were sterilized and inserted beneath the dura of growing cats. In one of these kittens, a month old, the wire penetrated the brain substance near the superior longitudinal fissure and about a centimetre behind the motor area. The animal died during the very hot spell of August, 1900, after repeated convulsions. After the brain had been hardened in formalin a section was made through the brain transversely at the point where the wire had penetrated. The knife came in contact with a hard cartilaginous-like mass, the size of a small bean. This mass seemed at first to be encapsulated, but upon closer examination small portions of it were found in the tissue of the apparent capsule infiltrating the surrounding brain tissue. This tumor formation had the appearance and consistence of cartilage, but upon microscopic examination no trace of cartilage or cartilage cell could be found. The tumor tissue and the surrounding brain area, including the track of the wire puncture, were embedded in celloidin and sectioned. Sections of 25μ were cut without decal-

cification and stained by hæmalum and eosin. There was no gritting on section or other evidence of calcification of the tissue. This is of considerable importance, because the absence of any extensive calcification points to the recent formation of the neoplastic tissue; the deposition of lime salts in diseased brain tissue, when conditions are favorable, frequently takes place, and the microscopic examination of the sections reveals here a beginning calcification in the peripheral areas of the growth. An examination of the finer structure of the tumor reveals a fully



Section from bone mass within the brain substance.

formed bone matrix, a well-developed Haversian system, and a very rich vascular supply. The blood channels are formed in sinuses in the tumor mass, with walls composed of the tumor structure, and in which a distinct cell layer cannot be made out. In one of the larger of these blood channels a distinct angiomatous cell network is distinctly seen. Around the periphery of the tumor mass there is a very dense staining of the tissue, such as is seen in calcified areas stained with hæmalum. Sections of the supposed capsule reveal some thickening of the glia and

spindle-shaped areas of calcification penetrating the normal areas of brain substance. These spindles did not have the bone structure of the larger mass. In the dorsal portion of the capsule considerable free blood and blood pigment and an infiltration of small mononuclear cells was found. From this point to the surface of the brain the puncture wound could be easily traced by the capillary hemorrhages, round-cell infiltration, and rarefaction of surrounding brain tissue. The pia on the free brain substance was thickened, and contained numerous accumulations of small round cells.

There is little if any doubt as to the recent formation of this growth. The absence of calcification in the central areas of the tumor, the beginning calcification in the peripheral areas, the very vascular nature of the growth, the hemorrhages and round-cell infiltration, all favor such an assumption. The histological nature of the growth, and its direct relation to the copper wire in the brain substance over a long period of time, would lead us to the conclusion, although we cannot be absolutely positive on this point, that the presence of the wire was in direct causal relation to the presence of the tumor mass. If this be true, and there is very little doubt in my own mind that it is, how are we to explain the bone formation? Either a small portion of the dura or the periosteum or, possibly, some grains of bone from the needle opening were carried down into the cerebral tissues with the wire, and, as these tissues so early in life are very vascular and active in their growth, they continued to carry out their primary function of bone formation. This process was favored by the free hemorrhage into the tissue following the puncture, and the resulting clot formed a nidus about which the bone grew. The skull wall of the kitten is of the thickness of paper; this was merely punctured with a needle and the fine wire then inserted. As there was no displacement of the bone and the tumor was $\frac{1}{2} \times \frac{3}{4}$ c.m. and of irregular spherical shape, there is no question of mere transposition of bone from the skull.

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UREMIC HEMIPLEGIA, WITH CHANGES IN THE NERVE CELLS OF THE BRAIN AND CORD, AND RECENT PRIMARY DEGENERATION OF ONE CENTRAL MOTOR TRACT.[1]

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of Philadelphia,

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Some of the effects of the disorder known as uremia upon the nervous system have been well recognized in recent years, although it is not so long ago that this was denied. Of the different manifestations of this disease none have been of more interest or have excited more study than the hemiplegia produced by the uremic condition. In spite of the large number of cases with necropsy, and of experiments upon lower animals, the cause of this disease still remains in doubt.

The usual findings at necropsy have been more or less edema of the brain substance and its membranes, and at times dilatation of the ventricles. A number of cases have been reported, however, where no edema was found. (Level, Chauffard and Lancereaux.) The edema may be symmetrical, it may be localized to the side of the brain opposite the hemiplegia (Pätsch, Charpentier), or it may be on the same side as the hemiplegia (Charpentier). A case was reported by Mann where in a right hemiplegia preceded by Jacksonian convulsions, the left ventricle was distended to about three times the size of the right ventricle.

It is hard to explain why a bilateral edema should produce a unilateral paralysis, or why the edema should produce paralysis at all. In the great number of cases of uremia which come to autopsy, in which there are no nervous symptoms, edema of the brain or membranes is a common finding.

The well known experiments of Raymond may perhaps throw some light upon the physiology of this condition. The left superior cervical ganglion was removed from a rabbit and

[1]From the Philadelphia General Hospital. From the William Pepper Laboratory of Clinical Medicine, Phœbe A. Hearst Foundation.

Read before the Philadelphia Pathological Society, Dec. 17, 1904.

several days later the vessels at the hilum of the kidney were ligated, producing an artificial uremia. Convulsions occurred and were limited to the right side of the body. When the right ganglion was removed and the vessels tied, the convulsions were limited to the left side; or, the uremic disturbances showed themselves on the side governed by the cerebral hemisphere, the vessels of which had been paralyzed by the removal of the ganglion. At the necropsy, however, there was found a diffuse bilateral edema.

As a result of more recent research the theory that edema is the primary cause of uremic hemiplegia has been abandoned, and it is believed that definite organic changes in the central nervous system are the causes of this condition. Such changes, however, have not been heretofore described.

The cellular changes in the central nervous system in experimental uremia of dogs, have been studied by Acquisto and Pusateri. In the anterior horn cells of the spinal cord these investigators found loss of peripheral chromatic bodies, while the perinuclear bodies had undergone granular disintegration. In the cerebral cortex different stages of chromatolysis were noted. In some cells the peripheral chromatic bodies and the dendritic processes were normal, while in the perinuclear zones there was advanced chromatolysis. Other cells were homogeneous, and their nuclei dark and indistinct.

Sacerdotti and Ottolenghi also examined the central nervous system in dogs dying four to seven days after ligature of both ureters. By Golgi's method they demonstrated varicose atrophy of the dendrites, while the axis cylinder processes remained normal. The lesions were most marked in the cerebral cortex, where all the cells were affected, but were also abundant in the pes hippocampus. Nissl's stain failed to show the chromatolytic changes in the cortical cells described by Acquisto and Pusateri.

Donetti examined by Golgi's and Nissl's method the central nervous system of rabbits dying from uremia after bilateral nephrectomy. By Golgi's method he found varicose atrophy of dendrites with other less definite changes in the cortical and cerebellar cells. By Nissl's method there were no distinct alterations in the cortical cells. In the medulla and

the cord the nuclei of the large cells were very often eccentric, the chromatic substance was reduced in amount, the bodies were finely fragmented, and many cells contained vacuoles. He does not believe that these lesions are characteristic of uremia.

Gabbi, as a result of bilateral tying of the ureters, found in the cerebral cortex of guinea pigs and rabbits, in most of the cells a perinuclear chromatolytic process with a homogeneous condition of the nucleus. In the medulla there were examples of peripheral chromatolysis. With Golgi's method varicose atrophy of the nerve cells was found. Some of the cells in the anterior horns were deformed.

Ewing studied microscopically the nerve cells of the brain and cord of six cases of uremia. In none of his cases were there any accompanying paralysis of the upper and lower limbs of either side, except in one case where one arm was paralyzed. He came to the following conclusions: "Uremia as it occurs in the human subject is associated with rather marked changes in the chromatic substance of the nerve cells, but these changes are very irregular in character and distribution. As a rule the spinal cells are but little changed in uncomplicated cases. The lesions are most marked in the medullary nuclei, especially in the nuclei of the tenth nerve and above, as well as in the deeper cells throughout the medulla. Here nearly every variety of chromatolysis may be observed, excepting very advanced or complete bleaching of the cells, which is rare.

"The cortical cells are usually better preserved than might be expected from the very marked cerebral symptoms of fatal and prolonged uremia. In the case dying with severe convulsions the cortical as well as the medullary lesions were most marked.

"The condition of Purkinje's cells was very uniform in the cases examined, the chromatic bodies of these cells being very irregular in size and shape, and considerably deficient in number.

"The effects of the pial edema could not be distinctly traced in the cortical cells.

"No distinct or uniform nuclear changes were detected in these cases, although the nuclei were often abnormal in appearance. The achromatic substance of the cortical archyo-

chromes frequently appeared greenish and opaque, suggesting an early stage of pigment degeneration.

"The most advanced cellular alteration of the series were seen in the nuc. X and deeper cells (nuc ambiguus), in the case in which severe dyspnea had been the chief complaint for five days before death.

"In general, it seems reasonable to conclude that the lesions of the nerve cells in uremia are largely referable to local influences and partly also to general toxemia. Among such local influences may be suggested, (1) altered condition in the peripheral fibers of the cells; (2) local circulatory disturbances; (3) overaction of particular groups of nerve cells; (4) and possibly also the effects of pyrexia.

"Finally, in the above cases, there was a fair parallelism between the grade of cellular change and the general severity of the symptoms."

So far as I know there are no cases of uremic hemiplegia with changes in the nerve cells and in the central motor system on record. The first case I have to report is as follows:

L. W., seventy-one years old, washerwoman, was admitted to the Philadelphia Hospital, June 6, 1903, service of Dr. C. S. Potts, from the outwards. The patient had complained of weakness for some time, and suddenly lost power of her left side. No history of her previous condition could be obtained. The following notes were made by Dr. Potts, to whom I am also greatly indebted for the post-mortem material.

"Patient is dull mentally, but can understand and does answer questions intelligently. The mouth is drawn toward the right side. She can close both eyes equally well, but there is a weakness of the occipito-frontalis and corrugator supercillii muscles on the left side. The left arm and leg are completely paralyzed. Sensation is not altered. The biceps and triceps jerks are present and equal on both sides. The knee-jerks are prompt and equal on either side. The Achilles jerks are present. No ankle clonus on either side. Both plantar reflexes are active, more so on the left side, where the great toe is slightly extended. The pupils are equal, and react sluggishly to light. There is no conjugate deviation of the eyes, and no difficulty in swallowing."

The patient gradually grew weaker and died fourteen days

after the onset of the paralysis. The temperature varied between 97° and 98° F. during her illness. The urine examination was undoubtedly made, but the record has been unfortunately lost from the history sheet.

The necropsy was performed by Dr. C. H. Bunting, who made the following notes regarding the patient's kidneys: "The kidneys are small, the capsule is thickened, leaving a granular, roughened surface when stripped. On section, the cortex is narrow, the striæ irregular and the glomeruli are injected and prominent."

The pathological diagnosis was:

Arteriosclerosis, chronic diffuse nephritis, cardiac hypertrophy and dilatation, chronic interstitial pleuritis and enterocolitis.

There was no note made of edema of the membranes of the brain or cord. The ventricles were opened and the specimens put into Orth's fluid. Horizontal sections made show no gross lesions, and a careful examination showed no small lacunæ, nor areas of softening as described by Marie.

Microscopically the changes in the nerve cells as stained by the thionin stain are as follows:

Lumbar region.—The cells here are similar to those in the cervical region. The cells of the column of Clarke are much degenerated. The chromophilic elements in many of the cells have entirely disappeared, and are replaced by a mass of fine granular yellow pigment filling up the whole cell body. In most of the cells the nuclei are at the periphery.

Cervical region.—The cells of the anterior horns are intensely pigmented, which is not remarkable considering the age of the person, which was seventy-one years. Some of the cells are probably atrophied, the nuclei are not displaced and the alteration in the cells is slight.

Paracentral lobule.—The Betz cells of the left paracentral lobule are intensely pigmented. In some of the cells the pigment fills the whole cell body, and in these cells the nucleus cannot be observed. The Betz cells of the right paracentral lobule are similar to those in the left paracentral lobule, but the alteration is more intense than in the left. In some cells chromatolysis and peripheral displacement of the nucleus without an excessive amount of pigment, are found.

Cerebellum.—Many of the cells of Purkinje are swollen, and in some the nucleus is eccentric and the chromophilic elements are more or less broken up. Pigmentation of these cells is not pronounced.

Medulla.—The cells of the nucleus ambiguus of each side are in fair condition, however here and there a much altered

cell is found. In these cells the nucleus is displaced to the periphery and the chromophilic elements are disintegrated. Nerve cells from the frontal, temporal and occipital regions do not show any distinct pathological changes.

The Weigert hematoxylin and acid fuchsine stains show no changes in the spinal cord.

In the lumber region degeneration as shown by the Marchi method is present in the left crossed pyramidal tract. It is slight, but unmistakable. In the cervical region the degeneration in the crossed pyramidal tract of the left side is greater than that in the lumbar region. It is moderate in degree, and is such as would be found in a primary degeneration of short duration. It is, however, unmistakable and is confined to the left crossed pyramidal tract. There is much less intense degeneration in the right direct pyramidal tract.

In the right pyramid there is still degeneration by the Marchi method, but it is much less intense than in the left crossed pyramidal tract in the cervical region. Degeneration by the Marchi method is still shown in the middle portion of the foot of the right cerebral peduncle. It is much less intense than in the left crossed pyramidal tract of the cervical region.

In the right internal capsule by the Marchi method a number of degenerated fibers can be seen, but these are so few in number that it is impossible to state definitely that there is degeneration of the motor fibers.

The Betz cells of the paracentral lobule show no change by the Marchi method.

Case II. W. E., seventy-seven years old, was admitted to the Philadelphia Hospital August 31, 1903, service of Dr. Wm. G. Spiller. The notes made by Dr. Spiller on the same day are as follows: "The patient is completely unconscious. The left palpebral fissure is larger than the right. The left pupil is larger than the right. The lower distribution of the left seventh nerve is paralyzed. The man makes no effort to draw up either side of the mouth when he is stuck with a pin. The left upper limb is completely paralyzed and is spastic at the elbow. The biceps, triceps and wrist reflexes are exaggerated on both sides. Both lower limbs are somewhat spastic. The left lower limb is almost completely paralyzed. When stuck with a pin he moves the left toes slightly. Both patellar jerks are present, but diminished. The right upper and lower limbs are moved voluntarily, and also when he is stuck with a pin."

The patient's temperature on admission was 101.4° F., but was normal when he died four days after the onset of his paralysis. Here also the urine examination report was lost.

The necropsy was performed by Dr. John Funk, who made

the following notes: "The kidneys are small and show fetal lobulation. The capsule strips with difficulty, revealing a granular area. The cortex is narrow, and is diffused into the medullary portion, which is inconspicuous. The pyramids are visible only here and there. The pelvis contains considerable fat." The other pathological diagnoses were: Fibroid myocarditis, chronic endarteritis and atheroma of the vessels at the base of the brain.

Here also there was no note made of the edema of the cerebral or spinal membranes. Horizontal sections of the brain show no gross lesions.

There is no degeneration of either crossed pyramidal tract by the Weigert hematoxylin, acid fuchsine or Marchi methods.

The nerve cells of the anterior horns of the lumbar region are about normal and not nearly so much pigmented as one might expect in a person so old as seventy-seven years. Chromatolysis is seen in some of these cells, but is not intense.

The nerve cells of the anterior horns of the cervical region are much like those in the lumbar region, except that they are more pigmented.

Many of the Betz cells of the left paracentral lobule are nearly normal, but some are in a state of chromatolysis.

The changes in the cells of the Purkinje are slight. Some of the nuclei are displaced and there is a slight chromatolysis.

The cells of the nucleus ambiguus are in a very good condition, many of them are deeply pigmented and here and there some cells are much altered.

We have here, therefore, two cases of hemiplegia of uremic origin where macroscopically no gross lesion was found. In the first case the paralysis lasted 14 days before death, while in the second case the man lived only 4 days after the onset of the hemiplegia. The changes in the nerve cells as shown in the Betz cells of the paracentral lobule in the first case, while intense on both sides, were distinctly more so on the side opposite the paralysis. The alterations in these cells were not uniform, except that an intense yellow pigmentation was present in nearly all the nerve cells. The cells of the anterior horns of the spinal cord were not much altered, but here too the yellow pigment was abundant.

The degeneration of the motor fibers as shown by the Marchi method was traced from the lumbar region of the spinal cord to the internal capsule.

The degeneration, while not intense, was unmistakable, and was of such a character as would be expected in a primary degeneration of recent origin, in this case fourteen days. It was most marked in the crossed pyramidal tract of the cervical region, and became less intense in the medulla, and cerebral peduncle, and in the internal capsule it was hard to find traces of it.

The degeneration was essentially a primary degeneration, i.e., not due to any destruction of the fibers in a limited part of their course, and was in association with the changes in the nerve cells in the motor cortex. That the degeneration was found only in the motor fibers of one side, is explained by the more intense changes in the cortical cells belonging to these fibers, and it is a fair presumption that had the uremic poison or poisons had time to act further, there would have been also a primary degeneration of the motor fibers of the opposite side.

I hardly expected to find recent degeneration by the Marchi method in the second case, for here the hemiplegia was only of four days' duration. Changes were found, however, in the nerve cells of the cortex, cerebellum, medulla and the anterior horns of the spinal cord, but these were not as intense as in the cells of the corresponding regions of the first case.

It is hard to explain why the alterations in the nerve cells were more intense on one side of the cortex, except by the theory of *locus minoris resistantiæ*, which is hardly an adequate explanation.

As a result of the study of these cases we must come to the conclusion that a toxic process like uremia may produce definite changes in the nerve cells of the brain and spinal cord, and that these changes may be more marked in the motor cells of the cortex, and in association with these alterations in the nerve cells of the motor cortex we may have a primary degeneration of the motor fibers, provided the duration of the hemiplegia is long enough.

The effects of other toxic processes upon the central nervous system have been carefully studied, and changes in the nerve cells of the brain and cord have been repeatedly ob-

served. These alterations, however, have not been uniform or characteristic, and it may be that the findings in the first case may have an important bearing on the future study of these conditions.

I am indebted to Dr. Charles S. Potts for the material and notes of the first case, and to Dr. Wm. G. Spiller for the material of the second case, and for his assistance.

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CONJUNCTIVITIS NODOSA, WITH HISTOLOGICAL EXAMINATION.

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AND

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As is well known, the first case of ophthalmia nodosa, a name suggested by Saemisch, was described by Pagenstecher[1] in 1883 before the Heidelberg Ophthalmological Society. Since this time numerous cases have been reported, in many of which positive proof has been given that the condition was caused by irritation of the hairs of certain species of caterpillar, which had found lodgement in the conjunctiva, cornea, or iris. We are particularly indebted for studies of this subject to Baas, Wagenmann, Hillemanns, Krüger, Hanke, Lawford, Stargardt, and others, and a complete analysis of the literature of this subject in condensed manner will be found in the works of Ginsberg,[2] Greeff,[3] and J. Herbert Parsons.[4] It does not seem, therefore, necessary to do more than mention these authors, in whose writings full bibliography will be found. In our own country we have not noted the reports of many examples of this affection, although George

[1] Klin. Monatsbl. f. Augenheilk., 1883, xxi.
[2] Grundriss der pathologischen Histologie des Auges, Berlin, 1903, p. 68.
[3] Pathologische Anatomie des Auges, p. 70.
[4] The Pathology of the Eye, Vol. I., Part I., London, 1904, p. 84.

Knapp[1] has described three cases, and Colburn one case. Our own case is as follows :

Theresa C., a negro girl aged fifteen years, an inmate of the Asylum for Colored Orphans, in Philadelphia, came to the hospital of the University of Pennsylvania on July 20, 1903, for relief from an inflammatory condition of the left eye.

History. The patient stated that while playing in the yard attached to the asylum a few days prior to her entrance into the hospital her eye became inflamed, owing, as she expressed it, to "something getting into the eye." At that time she gave no intimation of what that something might have been. The girl was a well-formed negress, healthy in all respects, and having no ordinary intimations of general disease.

Examination. Vision of O.D. 6/9, the ocular structures normal, and the depreciation in vision due to slight refractive error. Vision of O.S. 6/12; the conjunctiva of the lids, especially in the lower retrotarsal fold, was slightly congested and velvety in appearance. There was marked pericorneal injection downward and inward, and an area of patchy congestion with faint nodes at the lower and inner portion of the bulbar conjunctiva. The case books do not record any more accurate description than the one that we have given at this time, and the eye was treated with the usual antiseptic lotions, the patient reporting with a good deal of irregularity during the next six weeks, and apparently without benefit from whatever treatment was applied. The case was then referred to Dr. de Schweinitz for more particular examination, and the following conditions were evident: The cornea and iris were unaffected and the deeper media clear. Downward and inward on the bulbar conjunctiva were a number of flattened, grayish-yellow nodules, between which was a marked congestion of the conjunctival and episcleral vessels. Twenty-seven nodules could be differentiated, those directly in the centre of the collection being somewhat confluent and assuming a crescentic and circular appearance. The whole condition strongly suggested tubercle of the conjunc-

[1] American Journal of Ophthalmology, 1897, vol. xix. p 247.

tiva, and, indeed, this was the tentative diagnosis at the time, as there was not then the least suspicion of the true nature of the case.

The patient was admitted to the wards of the hospital on September 20, 1903, chloroformed, and the greater portion of the nodules excised, those failing to come away with the strip of conjunctiva thus removed being touched with the actual cautery. The surface was dusted with iodoform, the eye bandaged, and the patient treated as after an ordinary operation. The healing was kind and the patient was dismissed in a few days with a good deal of congestion remaining, but no distinct nodules. She came somewhat irregularly to the dispensary, and then disappeared. We have ascertained that subsequently she went to another hospital, where the nature of the case was not suspected, and where, with some local treatment, which included the usual antiseptic lotions and dilatation of the punctum, the remaining congestion disappeared.

Microscopic Examination. A portion of the strip of conjunctiva was introduced into the anterior chamber of a rabbit's eye through a corneal incision. The remainder was placed in formalin and embedded in paraffin. The wound in the rabbit's eye healed promptly, and the eye showed very little reaction. The bit of tissue lay on the iris below, and was slowly absorbing, when the rabbit unfortunately developed a purulent infection of the air passages, three weeks afterward, which commenced in the nose and produced a purulent pleuritis and pericarditis, to which the animal succumbed within two days. The infection proved to be due to the bacillus pyocyaneus and was, of course, accidental, and not connected with the inoculation of the eye. The eyeball was removed, fixed in formalin, and embedded in celloidin. Sections passing through the tissue introduced into the anterior chamber show that this has been partially included in the iris tissue, and is reduced to a condensed mass of connective tissue. The eye itself shows very little reaction. The iris contains a moderate round-cell infiltration, but there is no sign of miliary nodules, so that the tubercular character of the tissue may be excluded.

The sections of the original strip of conjunctiva reveal the presence of numerous nodules beneath its surface. The conjunctival epithelium is very greatly thickened and contains leukocytes. Beneath the epithelium the tissue is composed of coarse bundles of connective tissue, which contain a great many round cells and numerous distended bloodvessels. The nodules measure about 0.25 mm. in cross diameter and from 0.4 to 0.6 mm. in their long diameter. The outer portion of each is composed of a layer of spindle cells and round cells arranged concentrically, outside of which the tissue is condensed into a capsule. The interior consists of epithelioid cells, between which there is considerable intercellular substance. Each nodule contains a number of giant cells, the nuclei of which are irregularly distributed through the body of the cell instead of being marginal. Directly in the centre of a certain number of the nodules is the section of a hair. When this is evident in longitudinal position, as may be seen in the accompanying drawing, or in the microscopic sections, it consists of a long cylinder with moderately refracting walls, and in the centre contains a somewhat brownish-yellow, broken material. Irregular cross-hatching of flat sections is visible. In one section at least, what at first appears to be a notching of the edge, is really a slight, spike-like prolongation into the surrounding tissue, and represents, we think, the remnant of the long spines which form so conspicuous a component of caterpillar hairs. Each hair is surrounded by a mantle of small round cells. No micro-organisms could be discovered, and the nodes must therefore be regarded as typical foreign-body tubercles, produced by the presence in the tissue of the fine hairs. The histological appearances which we have described closely correspond to those already recorded by Wagenmann, Krüger, Hanke, and others, although we have not noted anywhere in the drawings which accompany the papers of these authors so typical an example of the hair shaft as we here picture, nor have we seen anywhere described an appearance which suggests at least the remnant of the spines on caterpillar hairs.

If we come to consider the previously reported cases of this affection, the records of which may be found in the literature, to

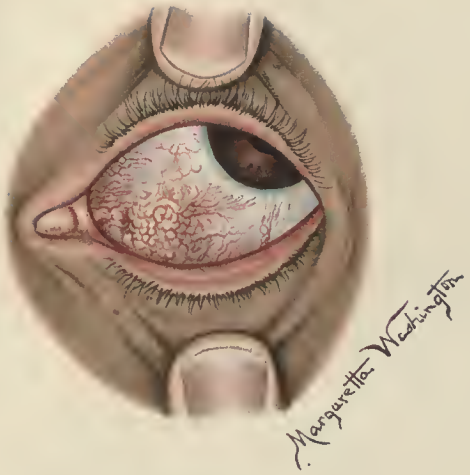

FIG. 1.—CONJUNCTIVITIS NODOSA.

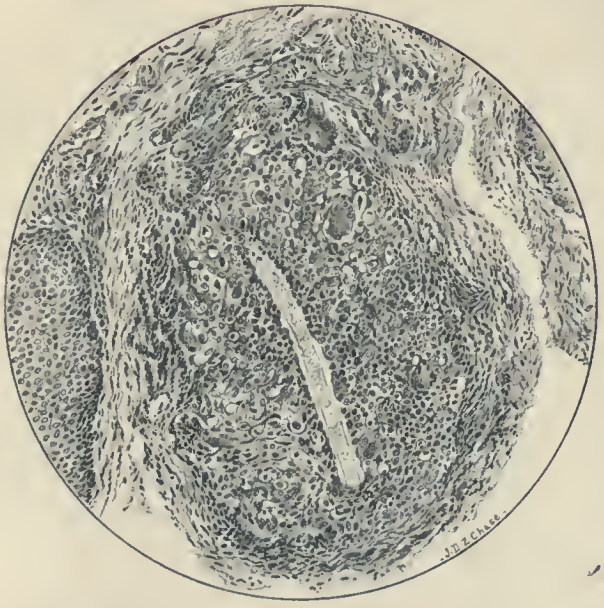

FIG. 2.—MICROSCOPIC APPEARANCE OF SECTION OF A CONJUNCTIVAL NODULE. IN ITS CENTER IS A CATERPILLAR HAIR, SURROUNDED BY ROUND CELLS AND GIANT CELLS; EXTERNALLY, SPINDLE CELLS AND CAPSULE.

which we have already made reference, and particularly in Mr. Parsons' admirable *résumé* of the whole subject, we find that ophthalmia nodosa, or, as Wagenmann prefers to call it, pseudotuberculosis of the conjunctiva, has been caused by the irritation of certain species of caterpillar, particularly Lasiocampa or Bombyx (*B. rubi, B. pini.*), Liparis (*L. monacha, L. dispar.*), etc.; other species—*e. g.*, *Cnethocampa* (*C. processionœ*)—also cause conjunctival irritation, but it rarely becomes so severe as with the other species, nor are the deeper parts of the eye (iris, etc.) affected (Baas, Wagenmann). Particularly interesting studies of the caterpillar species concerned in this affection have been made by Mr. Lawford, with the aid of Lord Walsingham. The affection has been seen as early as the month of June, but more commonly appears in August, September, and October, when caterpillars are more common and are at the period of their greatest activity. Our case began in July. As is well known, the nodules in this disease may be present in the conjunctiva, episclera, and even in the iris, but most often are found in the bulbar conjunctiva in the position in which they are shown in the accompanying water-color by Miss Washington. In general terms they resemble very much real tubercle of the conjunctiva, not only on external examination, but in minute microscopic investigation. The hairs when embedded in the conjunctiva are surrounded by round-celled infiltration, which is a conspicuous element in our sections. Frequently numerous giant cells and lymphocytic infiltration are present, and the giant cells are of the foreign-body variety. Spindle cells, which we also have described, have been noted in a number of instances, and sometimes a fibrous capsule seems to be present, as, for example, in one of Krüger's sections, as it may also be seen in those which we have prepared.

There is much difference of opinion as to whether the irritation is mechanical, or whether it is due to some constituent of the hairs. Stargardt thinks that the first irritation is mechanical, but that this is followed by a chemical irritation to which the pseudotuberculosis formation is due. As is well known, formic acid is present to a considerable extent in the hairs of caterpillars. The hairs, encouraged by frequent rubbing of the lids, can

travel, base forward, very deep, but probably owing to the presence of the spines, which come off from the hair shafts at acute angles, are prevented from making a return journey. They may penetrate the cornea, enter the iris, and there form the nodules which have been described. It is probable that they may even reach the choroid, if we may trust a case reported by Reis. Bacterial infection seems absent. Micro-organisms have not been found, either in our own or in other cases in which search was made for them. Experiments on animals by Krüger and others have not led to definite results, and implantation of the excised tissue in the anterior chamber of a rabbit has not led to the development of similar nodules, as is evident from our own experiments. Greeff maintains that according to his researches the caterpillar hairs do not produce this condition by virtue of a mechanical irritation, but by reason of the presence of a toxic substance, and further declares that if the hairs are dried and then introduced into the tissues the nodules do not develop. Parsons believes, however, that the innocuousness of dried hairs requires confirmation.

A somewhat similar disease clinically resembling trachoma has been described by Markus[1] as the result of the implantation of plant hairs, and it is possible that some of the reported cases of ophthalmia nodosa may have been due to this type of irritation, and not to caterpillar hairs.

Referring again to our own case, when the diagnosis by virtue of the microscopic examination became evident, the interesting problem presented itself, whether we could prove or not what species of caterpillar had produced this conjunctivitis. The diagnosis was not made until long after the caterpillar season, and therefore a search in this respect had to be postponed until a suitable time. Therefore, last summer one of us (Dr. de Schweinitz) went to the yard in which the children of the Colored Orphanage are accustomed to play, and made a search for the caterpillars then present. The date of this visit was July 5th. The following interesting facts were developed: Children are

[1] Zeitschr. f. Augenheilk., 1899, ii. p. 34.

much accustomed to playing with caterpillars, and are in the habit, as one of the children stated, "of scaring the young ones by throwing caterpillars at them." The caterpillar which is most used in this playful proceeding we found, or rather the children found it for us, and is here exhibited. It is the *Spilosoma virginica*, or the yellow, woolly bear caterpillar. Three other varieties are common at this season in the region named: the *Orgya leucostigma*—that is, the tussock moth larva—and the *Empretia stimulæ*, or the saddleback caterpillar of common parlance. One last variety, which the children of the home call the doctor caterpillar, we could not find, and therefore cannot give its true name. In determining these varieties of caterpillars we are indebted to Dr. Henry Skinner, the distinguished editor of the *Entomological News*, and a member of the Academy of Natural Sciences of Philadelphia. He has examined the sections and believes there is no doubt that the hairs are caterpillar hairs, but said that no one could positively determine from what species they came with no more to guide him in his investigations than the hairs which are here embedded in the tissues. He suggested that as the saddleback caterpillar is notoriously irritating and produces even on the skin a stinging sensation followed by large welts, this might be the caterpillar that had produced the mischief. We do not think so, however, because the children are well acquainted with this caterpillar, and call it the nettle caterpillar, know that it stings, and never touch it. The *Orgya leucostigma*, or tussock moth larva, belongs to the group of the Bombyces of the family Liparidæ, and, as we have seen from the European investigations, the Liparians may cause conjunctival irritation, but they apparently do not produce the severe types of ophthalmia nodosa, certainly not those in which the iris is involved, and probably not such as we have described. Now the yellow, woolly bear caterpillar, or the *Spilosoma virginica*, belongs to a family of the Bombyces called the Arctiidæ, derived from a Greek word meaning bear, so given on account of the thick hairs which cover the body. This caterpillar, which the children call the pussy, is used in their sports, and they constantly throw it at one another. We could not positively prove

that the child who had the conjunctivitis had been struck with this caterpillar, although this was the opinion of the children who knew about her ocular afflictions.

While this case does no more than record another example of this interesting affection, it is, so far as we know, the first American instance of the disease in which, in all probability, the species of caterpillar concerned has been identified. Doubtless, however, the hairs of any caterpillar of the various species named could produce an analogous, if not exactly identical, disease. It is further interesting because the implantation of the tissue into the anterior chamber of the rabbit was negative in its results.

Finally, we should call attention to an observation of Markus, namely, that there is only one certain criterion upon which a differential diagnosis between a nodular conjunctivitis caused by caterpillar hairs and by plant hairs can be made. According to him, longitudinal and cross-sections of plant hairs show strong polarization, which is not the case with the caterpillar hairs. We have submitted our sections to the professor of physics in the University of Pennsylvania, who has examined them in this respect, and reports the entire absence of any signs of polarization. How valuable this test may be when applied to hairs embedded in tissue we are unprepared to say. We have, however, we think, definitely shown that the case reported should be properly classified as a conjunctivitis nodosa due to the introduction of caterpillar hairs, in all probability the hairs of the *Spilosoma virginica,* into the conjunctiva of this patient.

Extracted from the American Journal of the Medical Sciences, January, 1905.

HISTOLOGICAL EXAMINATION OF THE EYES IN A CASE OF AMAUROTIC FAMILY IDIOCY.[1]

By Edward A. Shumway, M.D.,

AND

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OF PHILADELPHIA.

(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

The eyes upon which we desire to report are from a patient presented by Dr. James H. McKee before the Philadelphia Pediatric Society in June, 1903, the history of which is given in full by Dr. McKee in a preceding article, in the same number of this Journal. The ophthalmoscopic appearances, seen first in March, 1903, were typical of the disease, and are well illustrated by Dr. Buchanan's sketches. Directly in the macular region of each eye there was a horizontally oval, white area, in the centre of which was a sharply defined cherry-red spot. The white area measured about two disks' diameter across, and faded off gradually into the surrounding retina. The fine retinal vessels were not veiled, and ran uninterruptedly across it. The optic nerves were in a condition of white atrophy, the arteries being especially reduced in calibre. Later examinations made by Dr. Buchanan showed a gradual reduction in the size of the white spot, which took the shape of a vertical instead of a horizontal oval, and became grayish in color, while the red spot assumed a brown hue. The lesion did not disappear entirely.

The child died of pneumonia at St. Christopher's Hospital, February 23, 1904, at the age of twenty-nine and one-half months. Permission to perform an autopsy was difficult to obtain, because of religious beliefs, and after eight hours 10 per cent. formalin was injected into each eye, to prevent, if possible, post-mortem changes.

[1] Read before the Section on Ophthalmology of the College of Physicians of Philadelphia, April 19, 1904.

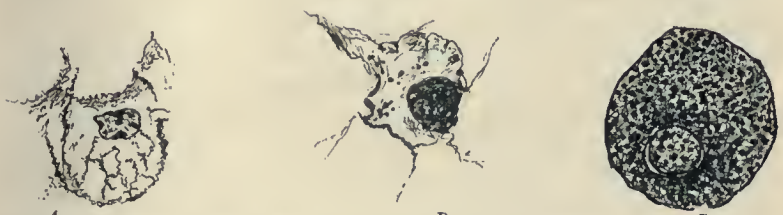
The autopsy was finally made nineteen hours after death. The eyeballs were removed entire; one was placed in 10 per cent. formalin and the other in Müller's fluid. The one placed in formalin was removed after twenty-four hours and hardened in ascending strengths of alcohol until 75 per cent. was reached. It was then divided in a horizontal plane, the section passing through the macular region, in which the discolored area was still visible macroscopically. Portions of the retina in this region were cut out and embedded in paraffin, so that study could be made of the ganglion cells. The other half was embedded in celloidin, and serial sections were cut and stained with hæmatoxylin-eosin, by the Van Gieson method, and with thionin. The eye placed in Müller's fluid, together with the optic chiasm, remained in this solution, with several changes into fresh fluid, for four weeks, and was subsequently hardened in alcohol, bisected, and embedded in celloidin for study of the changes in the optic nerve by the Weigert method.

The sections cut in paraffin pass directly through the macula and fovea centralis. They were stained with a 2 per cent. solution of thionin, for ten minutes, washed in water, differentiated in absolute alcohol, and mounted in xylol balsam. Microscopic examination shows the following conditions: Post-mortem changes are inconspicuous, and no œdema of the retina can be found. The ganglion cells, however, are in an advanced stage of degeneration. Many of them have disappeared completely, so that in the macula, where the cells are ordinarily present in rows of from three to six or even more, only a single, interrupted row can be seen. The cell bodies are so lacking in chromophilic elements, that they can be detected only in the very deeply stained, and slightly differentiated sections. Then the distorted nucleus is seen to be surrounded by a network which represents the framework of the cells. The cell outlines are irregular, in many cases rounded, and without any dendritic process. The Nissl bodies have disappeared entirely. Compared with the cells in the normal retina of a child they are swollen. In many cases the cell body has disappeared, leaving the nucleus alone. Sections of the Müller solution eye, stained by the Weigert method show the swollen cell bodies better, and reveal the presence of closely packed granules in the cell, which stain dark brown. Sketches made by Dr. Buchanan (Fig. 1) illustrate these changes very distinctly.

The retina, as a whole, is thinner than normal, and the thinning seems to be at the expense of each of the layers. The nerve fibre layer is narrower, the ganglion cells are reduced in number, as has been described, and those of the inner and outer nuclear layer,

representing respectively the bipolar ganglion cells, and the nuclei of the visual cells, are also fewer than in the normal eye. Many

FIG. 1.

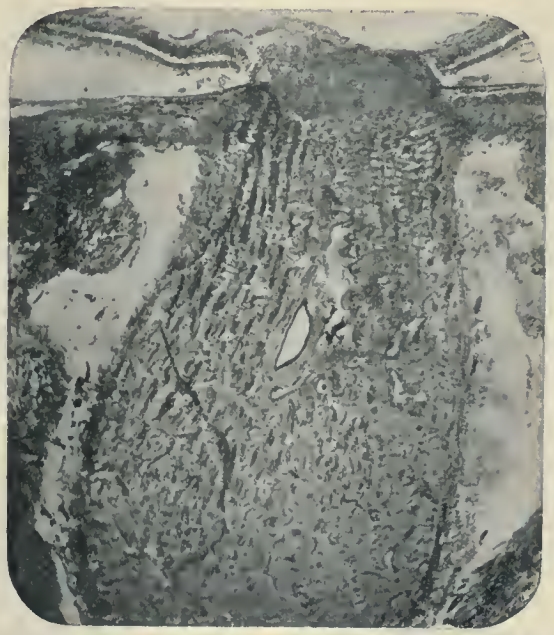


A *B* *C*

Degenerated ganglion cells: *A* and *B*, stained with thionin; *C*, stained with Weigert stain.

of the former are irregular in outline, and show nuclear degeneration. The inner segments of the rods and cones are preserved,

FIG. 2.



Photomicrograph of the optic nerve at its entrance to the eyeball, showing entire atrophy of fibres on the nasal side, with some normal fibres on the temporal side. Weigert stain.

but the outer segments are degenerated. This degeneration is possibly in part due to post-mortem changes, but not entirely so,

as the sections show penetration of this layer, here and there by clumps of the characteristic pigment granules from the retinal pigment layer. In the formalin eye, the retina has remained in place throughout, and the sections of the part removed for paraffin embedding show that the choroid is included with the retina, although the retina is ordinarily much more easily removed from the choroid than is the choroid from the sclera. In the macular region, the retina, in the celloidin sections, measures 132μ, while in similar sections from a normal child's eye, hardened and embedded in the same way, it measures 247μ. The retina is therefore reduced almost one-half in thickness, and the adhesion of the retina and choroid, with the pigmentation of the outer layer, show that a decided atrophy, with adhesion between the retina and choroid must have been present during life. The sections of the optic nerve, stained by the Weigert method reveal an entire absence of normal fibres in its temporal half, and a great reduction in those on the nasal side; this part of the nerve, however, shows many normal fibres, as the photo-micrograph (Fig. 2) by Mr. Walmsley at the Pepper Laboratory demonstrates. Sections of the chiasm and optic tract show complete atrophy of all the nerve fibres.

In the 11 cases in which the anatomical examination has been made, the conditions present in the eyes have been recorded in only 5. The first 2 were Kingdon's cases, in which the eyes were examined by Treacher Collins,[1] [2] who found œdema of the retina, especially located in the outer molecular layer, and atrophy of the optic nerves. At the time of these examinations, however, very little attention was paid to the study of the ganglion cells, and nothing is said specifically about their condition. Moreover, in both cases, the eyes were fixed in Müller's solution, so that the retinas were detached from the choroid and exhibited folds in the macular region. Müller's solution was shown to be a poor fixing solution for the retina by Schultze.[3] The membrane is inevitably detached, and its elements are distorted by the pulling of the shrinking vitreous humor. Very deceptive pictures of œdema are produced in this way, as is shown in a striking manner by comparison of the eyes in our case. In the formalin eye the retina is in place, and in the celloidin sections, measures 132μ in thickness at the macula; in the Müller solution eye the retina is completely detached, there is decided spacing out of the layers, and it measures 336μ, or nearly three times that of the retina in the fellow eye. On the other hand, formalin does not disguise an existing œdema, as examination of sections of eyes with detachment of the retina or high-grade optic neuritis will prove. We believe, therefore, that

the findings of Collins were due in part to the fixing solution used, and to the deceptive appearances caused by the folds in the macular region.

In the third case (Peterson's) examined by Ward A. Holden,[4] the autopsy was not made until forty hours after death, so that the results were unsatisfactory, owing to the advanced post-mortem changes.

The fourth case (Hirsch's) was also examined by Holden.[5] He reported enlargement of the ganglion cells, which had become globular and had lost their chromophilic elements. The cells stained by the Weigert method showed coarse, black granules. The cell membrane and the cytoreticulum could be made out under a $\frac{1}{18}$ immersion, but no Nissl granules were present, and the cell body had the appearance of having had its liquid contents withdrawn, leaving the naked cell framework.

Finally Mohr's[6] case, published in 1899, in which the eye was fixed in Flemming's chromic-osmic acid solution. Mohr reported œdema of the outer molecular layer, especially of the so-called Henle fibre layer, which makes up the outer portion of this layer, in the region of the yellow spot, a degeneration of the outer segments of the rods and cones, and the formation of a granular substance between the external limiting membrane and the choroid, which measured 380μ in thickness, although the retina itself in this region measured but 70μ. The thickness of the Henle layer was 350μ against 170μ normally found in the adult retina. These conditions Mohr ascribes to œdema, probably caused by angioneurotic disturbances, the result of pathological alterations in the cervical cord. Such a marked thickening of this region, however, if present during life, would be surely evident ophthalmoscopically, and as Higier[7] observes, if œdema were caused by such alterations in the cervical cord, we would see the same fundus changes in other forms of organic disease such as syringomyelia, amyotrophic lateral selerosis, cervical spondylitis, etc. Mohr's findings suggest very strongly that the retina was cut obliquely in this situation, and that the marked thickening was due to this fact. He makes no mention of the condition of the ganglion cells, although Holden's results were known to him, as they are mentioned in the summary.

Our examination, therefore, confirms Holden's view that the essential changes in the eyes are degeneration of the ganglion cells of the retina, and of the nerve fibres of the optic nerves and tracts, which are genetically a portion of the central nervous system. The process is in a more advanced stage, but this is what we should expect, as the child lived about eight months longer than did

Hirsch's patient, while the disease was first noted at about the ninth or tenth month in each. It seems more reasonable to explain the white area in the fundus as the result of the swollen and degenerated ganglion cells, which are present in much greater numbers in the macular region than elsewhere, than to conceive it as due to œdema of the tissue. As Falkenheim[8] says, two facts speak against the assumption of an œdema: in the first place the unchanging appearance of the lesion for months, and the absence of any veiling of the finer vessels in the area. Nor would this theory be incompatible with the gradual reduction in size of the area, which was noted in our case by Dr. Buchanan, as the disappearance of the ganglion cells by degeneration would make the spot less conspicuous. What the condition is which causes this intense and widespread degeneration of the nerve cells and fibres, is as yet undetermined. Sachs[9] was at first of the opinion that it was due to an arrest of development, but he has altered his views, and now believes,[10] with other investigators that the condition is a true degenerative one, and that it occurs so early in life because of an imperfect development of the nervous system. In other words, he accepts Gowers' term of "abiotrophy" or essential failure of vitality, and thinks that this is present as an inherited condition in these unfortunate cases. This seems to be the best explanation offered, at present, to account for the facts. Why certain children of a family are affected while others remain healthy, and why the children of Jewish parentage are especially liable to the disease, are questions which still remain to be settled.

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Extracted from The American Journal of the Medical Sciences, July, 1904.

PRIMARY TUBERCULOSIS OF THE BREAST.*

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(From the William Pepper Laboratory of Clinical Medicine, Phœbe A. Hearst Foundation.)

When the function of the breast is taken into account, one would expect mammary tuberculosis to be as frequent as genital tuberculosis. This is certainly not true. Among 300 gynecological cases Stratz[11] found 22 per cent. of tuberculosis; Martin had 10 in 287 cases, and Whitridge Williams reported that 8 per cent. of inflammatory adnexal disease was due to the tubercle bacillus.

Mammary tuberculosis is more rare. Bartsch[9] in 1901 could find but 65 undisputed cases in the literature. Probably 30 of these were primary. The primary form of genital tuberculosis has been open to doubt. Such pathologists as Klebs, Scanzoni,[11] Bollinger, von Recklinghausen, Schmorl, Ribbert, Aschoff and Albrecht[12] deny its existence in the adult. It is as difficult to prove the actual primarity of tuberculosis of the breast as it is of the genital organs. This does not apply to cases of direct inoculation, for well-attested instances of the latter are on record. Thus, Pluyette[1] reports primary tuberculosis of the breast in a girl aged twenty-three years, who was infected through a slight abrasion of the nipple, and Spinelli[13] speaks of a woman who developed the disease after intercourse with a male who suffered from tuberculosis of the testicle.

Whenever the infection is conveyed by means of the circulatory systems the question always arises whether, if autopsy were possible, the primary focus of the disease would not be found in the visceral organs more often affected by tuberculosis. Without an autopsy, therefore, a diagnosis of primary tuberculosis is not scientifically justified.

Primary genital tuberculosis does occur, however, and Veit,[22] after scrutinizing all of the available cases, accepts 15, 10 of the tubes and 5 of the uterus, as actual primary forms.

There are no cases of primary tuberculosis of the breast on record in which the diagnosis was made after autopsy. But as the primary form occurs in the genitalia, it is reasonable to suppose that it may develop in the breast. It is certain that tubercle bacilli may produce characteristic lesions remote from their point of ingress without affecting the parts through which they pass. Dobroklonski,[18] work-

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ing under Cornil, and Ravenel[18] have produced experimentally primary tuberculosis of the lungs through the alimentary tract without any lesion of the tract itself. Attention has recently been directed to the tonsils as frequent portals of entry for the tubercle bacillus. That tubercle bacilli may be present in the tonsil without producing any anatomical alteration is evident from the work of Friedmann.[18]

Goodale and Hendelsohn[14] have observed that the tonsils possess marked absorptive powers. The crypts of the tonsils represent afferent lymph vessels, and carmine granules placed on the tonsils are rapidly absorbed and pass thence through the interfollicular tissue to the efferent lymphatics. As these facts might explain the occurrence of primary tuberculosis anywhere in the economy, we may accept, for clinical purposes at least, those cases of tuberculosis of the breast as primary in which there is no evidence of tuberculosis elsewhere, even after the most careful physical examination.

The importance of primary tuberculosis of the breast lies in the possibility of its transmission from the mother to the nursing child.

While it would be quite unusual, at least in the better classes, for a woman with any disease of the breast to suckle her infant, yet Coles[7] saw, in the out-patient department of the Philadelphia Polyclinic, two women with tuberculous breasts nursing tuberculous infants, and Davis[7] believes that he has made the same observation at the General Hospital in Vienna.

So far as I know there is but one case in which tuberculous infection of the child has been traced to its mother's milk. This case, reported by Roger and Garnier,[10] may be briefly summarized as follows:

A pregnant woman came under observation on February 16th, suffering with pharyngeal tuberculosis. On March 7th she gave birth to a child that weighed 2685 grams. The infant was nursed until March 12th, when, on account of the progressing illness of the mother, it was weaned. On March 24th the woman died, and at the autopsy tuberculosis of the lungs and other viscera was noted. The child gradually failed and died on April 25th from tuberculosis of the mesenteric glands, spleen, and kidneys. Two guinea-pigs were inoculated with the milk of the mother on March 11th. Both of these pigs died, one with tuberculosis, the other with fibrous peritonitis and enlarged lymph glands; no tubercle bacilli nor actual tubercles were found in the second case, but the lesions were evidently due to the tubercle bacillus.

While such an observation is exceptional in woman, it has been frequently made in the cow. Pearson[17] quotes many instances of infection arising directly from the milk of tuberculous cattle. Ernst found tubercle bacilli in the milk of 33 per cent. of cows in which a complete post-mortem showed that while the animals were widely tuberculous the udder was free; and Hirschberger, by the experimental inoculation of milk, produced tuberculosis in 55 per cent.

of cases from tuberculous cows whose udders showed no sign of disease.

We may therefore believe that the milk of a tuberculous woman is always dangerous for the child, and that, although rare, tuberculosis of the breast may occur in a primary form and be unsuspected, and that the possibility of this condition ought always to be borne in mind during the period of lactation. If the breast is itself the seat of tuberculosis its milk must be highly infectious, for in the analogous affection of the cow the milk almost invariably contains tubercle bacilli.

There is some difficulty in reaching a satisfactory estimate of the frequency of primary tuberculosis of the breast. Freiburg[6] mentions 50 cases, Scudder[8] 80, Carrel 120. Bartsch[9] has thrown out of consideration all those in which a positive diagnosis was not made. Thus in all of his cases, either there was the histological picture of tuberculosis or the bacilli were found or inoculation experiments were positive. There were but 65 such cases, and this is the number Bartsch includes in his series. So much for the existence of a tuberculous lesion.

When we attempt to separate the primary from the secondary forms there is difficulty also in determining which are primary. While it is unscientific to diagnose primary tuberculosis of any part without an autopsy, we may safely consider a given lesion primary if there is no evidence of tubercuIosis elsewhere. If in a given case symptoms exist which may be attributed to tuberculosis in another part, then the disease of the breast cannot be regarded as primary, although the breast may have been its primary seat. This is the opinion of Piskacek,[16] and with it there are no grounds for disagreement.

Tuberculosis of the breast as a secondary lesion has no especial significance, whereas the fact that the mammary gland alone may be affected by the tubercle bacillus is of practical importance. It is well recognized, of course, that in the later stages other organs may be involved.

Reviewing Bartsch's series, in 35 there seems to have been tuberculosis elsewhere. All cases designated as being of a scrofulous habit and those in which there was coincident but less-marked tuberculous infection have been excluded. I have also excluded those cases where the affection was first noted in the axilla. Many of the tabulated cases are incompletely reported and details for determining the actual primarity of the case are scanty. At any rate, Bartsch has no more than 30 primary cases, and 2 of these are in the male. To these I have been able to add 12; some of the latter were not included by Bartsch in his list because suitable literature was not available. The impression one has in going over the reports of tuberculosis of the breast is that its primary form is extremely rare. Bull[21] in 1894 had had 185 amputations of the breast; all of these

were submitted to histological examination, and in but one instance was tuberculosis found, and that was primary. Since that time Bull has not observed another case, although he has no record of the number of his breast amputations.

If we analyze the entire number of accepted cases in the female we find that of 40 patients, the entire number—

28 were married	70	per cent.
19 had borne children	47.5	"
12 were single	30	"
12 had hereditary taint	30	"
6 had history of trauma	15	"
8 suffered from mastitis during lactation	20	"
2 were directly inoculated	5	"

The youngest patient was sixteen, the oldest was fifty-nine years. From these figures it is difficult to draw many conclusions in regard to the predisposing causes of mammary tuberculosis. While most of the cases were found in married women, the age at which the disease occurs would explain this fact, because most women between the ages of twenty and forty are married. No case up to this time has been observed in the female before the age of puberty, although Demme reports a case in a male child four days old, due to direct inoculation. There seems to be no direct connection between lactation and the disease; but 47.5 per cent. of the women had borne children. Trauma has played an inconsiderable part. Perhaps the relative infrequency of mammary compared to genital tuberculosis is to be explained upon other grounds. Hegar, Martin, and Amann[11] have dwelt upon gonorrhœa as a predisposing factor in genital tuberculosis. Eisendrath[19] has recently made the same observation and believes that the gonococcus often prepares the soil for a later invasion of the tubercle bacillus. He quotes Casper,[20] who found 33 per cent. of 35 cases of tuberculous vesiculitis to have been preceded by gonorrhœa. Casper believes that an attack of gonorrhœa, especially in those predisposed to tuberculosis, acts like a trauma in aiding its development. It is similar to an injury in syphilis which is able to produce the manifestation of the disease at the injured spot.

Pathological Anatomy. Tuberculosis of the breast occurs in either a (1) confluent or a (2) disseminated form.

The confluent form may be an instance of (*a*) mixed infection or of the (*b*) true tuberculous abscess.

The confluent abscess in the presence of mixed infection is the usual variety. It may involve the entire breast; it breaks down, forming fistulæ, and in the later stages produces retraction of the nipple. There are the usual signs of inflammatory processes in this region; the axillary glands may be secondarily involved.

An abscess purely the result of the tubercle bacillus, the so-called "cold abscess," is quite rare. It forms an elastic fluctuating tumor,

mostly well circumscribed and sharply bordered. It is but seldom surrounded by infiltration; the skin remains unbroken and there are no fistulæ. The axillary glands are not involved.

In the disseminated form there are small nodes of the tuberculous disease scattered throughout the breast. There is not much general enlargement of the gland; the skin remains unaltered; the disease is slow in course, years passing, perhaps, without cognizance of the patient. This form is so rare that it is denied by some authors.

Diagnosis. Many tumors of the breast and the inflammatory affections have to be distinguished from tuberculosis. The differential points here would be like those of tuberculosis in other parts and need not be repeated. In suspected cases the mammary secretion should be stained for tubercle bacilli, as was successfully done by Bevan,[7] or animal inoculation should be made. From simple pyogenic mastitis tuberculosis may be, as a rule, distinguished by its more chronic course. Carcinoma usually occurs later in life and is accompanied by retraction of the nipple. This does not often result in tuberculosis except after the formation of sinuses.

Prognosis. As in genital tuberculosis, the disease in itself is favorable. The result depends upon the existence of visceral complications. Bartsch's data relative to the results of treatment in his series is too meagre to draw conclusions. In my own series of 12 cases, 2 were not heard from after operation; 4 are reported cured within a year; 1 died at the end of three years, and in 1 the after-condition of the patient is not noted. The duration of cure in the remaining cases is put down at 8, 4, 3, and 2 years.

Treatment. Although simple evacuation and curettage or extirpation of the diseased nodules alone has sufficed in some cases, the gravity of the disease usually demands amputation of the breast and the removal of enlarged axillary glands.

The details of the case I have added to those found in the literature are as follows:

History. Woman, aged fifty-nine years, the mother of three children; there is no tubercular history; there is no clue whatever to the probable source of infection. Husband and children are all living and well. Parents died of old age. Patient married at the age of twenty-eight; menopause at forty-eight; last child when forty-two years of age. She always used both breasts during lactation and never had pain in them. Never had any pulmonary disease nor any illness that might be construed as being tuberculous in nature. Three years before coming under observation a nodule appeared in the right breast; it increased slowly in size and caused retraction of the nipple. There was no ulceration. Pain occurred in the right arm.

Treatment. The breast was amputated by Dr. J. G. Clark, who saw the woman in consultation with Dr. James Tyson. I wish to thank these gentlemen for the privilege of reporting the case.

Pathological Report, Path. No. 607.

Macroscopic Description. The specimen consists of an amputated breast including a portion of the pectoral muscle, together with axillary fat and lymph glands. The skin surface is intact; the nipple is considerably retracted, and at this area and to the right of it there is an irregular nodule about the size of a walnut. The mass is not well circumscribed, but fuses with the surrounding tissue. Upon section the breast appears atrophic. Beneath the nipple and continuous with it there is an irregular mass made up of fibrous tissue. Here and there are dark spots which appear to be areas of necrosis. The entire glandular portion of the breast is represented by this nodule. Its fibres are continuous with the trabeculæ of the fatty tissue which makes up the bulk of the specimen.

Histological Description. The surface epithelium and that of the ducts appear normal. The glandular elements are quite atrophic and there is a relative increase of connective tissue. The lymph spaces throughout the specimen are crowded with small cells having round nuclei which occupy most of the cell body. Such collections are directly continuous with areas comprising giant cells surrounded by epithelioid cells and the small round ones above mentioned. The nuclei of the giant cells are at the periphery, and the picture is typical of tuberculosis. A few sections were stained for tubercle bacilli, but none were found. It is unfortunate that no animal inoculations were made, but as the case was clinically one of carcinoma the specimens had been hardened in formalin before the value of such proof was apparent.

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Reported by	Age and social state.	Hereditary history.	Previous disease.	No. of labors.	Last labor.	Lactation.	Breast affected.	Original seat of disease.	Trauma.	Treatment.	Duration of cure.	Remarks.	Axillary glands involved.	Upon what diagnosis is based.
Pluyette,	23 years; single.	.....	.....	.....	.....	.....	.....	Breast.	.....	.....	.....	Direct inoculation.	.....	Bacilli were found in the nipple.
Salomoni,	21 years; single.	.....	Nodule in breast 2 years.	.....	.....	.....	Right.	Breast.	.....	Amputation of breast.	2 yrs.	.....	Yes.	Bacilli.
Salomoni,	23 years; married.	.....	.....	.....	.....	.....	Left.	Breast.	.....	Amputation of breast.	4 yrs.	.....	Yes.	Bacilli.
Warthin,	40 years; married.	.....	.....	5	11 mos. before.	Breast pained while nursing 3d child, 2 yrs. before last.	Right.	Breast.	.....	Excision of nodes.	1 yr.?	.....	.....	Bacilli; histological examination
Warthin,	39 years; single.	Yes.	Blow on breast 5 yrs. bef're	.....	.....	.....	.....	Breast.	Yes.	Amputation of breast.	Not heard from.	.....	Yes.	Histological examination.
Davis,	17 years; married.	.....	.....	.....	Pregnant 7½ mos	.....	Right.	Breast.	.....	Amputation of breast.	1 yr	Allowed to go to term; baby died in 6 mos. of marasmus.	.....	Bacilli.
Davis,	25 years; single.	.....	.....	.....	.....	.....	Left.	Breast.	.....	Amputation of breast.	8 yrs.	.....	.....	Histological examination.
Powers,	40 years; married.	Yes.	Pain in rt. breast ten years before at 2d child.	6	.....	Never nursed with right breast after second child.	Right.	Breast.	.....	Excision of nodules.	3 yrs.	.....	.....	Histological examination.
Powers,	26 years; married.	.....	.....	1	2½ yrs. before.	Had not used left breast for nursing; no reason given.	Left.	Breast.	.....	Amputation of breast.	3 yrs.	Patient subsequently died of phthisis.	Yes.	Histological examination.
Ely,	35 years; married.	.....	.....	.....	.....	.....	.....	Breast.	.....	Amputation of breast.	Not given.	Direct inoculation.	.....	Histological examination and animal inoculation.
Schifone,	32 years; single.	.....	.....	.....	.....	.....	Right.	Breast.	.....	Amputation of breast.	Not given.	.....	.....	Histological examination and animal inoculation.
Anspach,	59 years; married.	.....	.....	3	17 years before.	.....	Right.	Breast.	.....	Amputation of breast.	1 yr.	.....	.....	Histological examination.

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THE NATURE OF PARATYPHOID FEVER AND ITS CLOSELY ALLIED INFECTIONS.[1]

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It shall be the object of this paper to trace the relations of, and classify in order, typhoid fever, paratyphoid fever, paracolon infection, and meat poisoning by reference to the literature, to which is added some work of the writer, the full details of which will be published in a later paper.

The aberrations of typhoid fever have been long recognized, and an early concrete example of the appreciation of this is offered by the study of Eberth who describes the epidemic at Kloten in which there were 600 cases, the general clinical picture of which corresponded as much to the usual typhoid as to meat poisoning; the origin was undoubtedly the distribution of the meat of a sick calf. There were roseola and enlarged spleen, but it was unlike the fever in its short incubation, mild course, and low mortality (under 1 per cent.). Eberth made an autopsy on each of the two fatal cases and found in the gut and mesenteric glands changes which corresponded to a true typhoid. In reviewing this epidemic he considers the following questions open: Was the Kloten epidemic the usual abdominal typhus? Was it an abortive type or an infectious process probably related? Is there only one true typhoid fever, or is the so-called typhoid fever met with in several forms?

The reasonable doubt of the identity of these atypical

[1] Read before the Philadelphia Pathological Society, March 9, 1905

cases has become a fact, proven by the same criteria as true typhoid fever, the etiological factor differing from the bacillus of Eberth and Gaffky about as the symptoms approach or disagree with that disease—*i. e.*, the closer the symptoms of the attack the more alike are the biological characters of the organisms apt to be.

The first account of paratyphoid dates at 1896, when Achard and Bensaude isolated from the urine of one case, and pus of an abscess at the sternoclavicular articulation of another, organisms which were practically identical. These cases were clinically typhoid fever with striking symptoms, but sufficiently typical to justify the diagnosis until the micro-organisms were found.

The patients' blood reacted in dilutions of 1:1000; no tests were made with bacillus typhosus with the patients' blood, but antisera of animals immunized against the isolated organisms had no effect upon it, while they agglutinated the corresponding organisms highly, justifying to the reporters the assumption that they were the responsible factors. Again in Paris, Widal, 1897, found a para organism (para is used for all the intermediates of the typhocolon group, pathogenic for man, when a specific type is not needed or given, for the sake of simplicity) in an abscess in a phthisical patient, and considered it the cause of the pus and the slight constitutional symptoms accompanying it.

Gwyn, 1898, and Schottmüller, 1900–01, contributed reports of 7 typhoidal cases from whose blood they obtained paratyphoid organisms. The specificity of their cases was shown by serum reactions, while the bacillus typhosus was not affected by the sera.

Cushing reports finding a bacillus which he calls bacillus "O" in an osteomyelitis of a rib during what was clinically a typhoid relapse. This was also shown to be the causative bacterium by serum tests. In the 5 cases of Kurth, 1901, only 2 gave results to bacteriological search, but the reporter diagnoses the remaining ones by serum tests. The advisability of this will be questioned later.

The reported cases now are approaching a hundred, the diagnosis of some being complete, while that of others is questionable. They were in part sporadic, in part small epidemics, so that a general picture may be drawn to compare with typhoid fever.

Clinical Consideration. No effort is made to describe a new disease on clinical evidence alone, but the variations of this clinical picture can be made comparable to the relation of their causative factors, the paratyphoid bacillus with its subdivisions "A" and "B," and some differences, not absolute or well defined, but reasonably clear, may be said to be presented by the literature at present in each of these types.

The clinical picture of a single case of paratyphoid fever offers nothing to serve as a diagnostic criterion, but many cases collectively may show considerable deviation from the classical picture of abdominal typhoid. The most suggestive fact is the absence of the serum reaction with the bacillus typhosus.

According to the statistics of the Johns Hopkins Hospital 2 per cent. of all cases of typhoid fever present a negative Widal, but only 0.4 per cent. of proven cases give no reaction with the bacillus typhosus.

Here is a discrepancy that may be explained by the inclusions of paratyphoid fever cases in the first figure.

The mortality to date is about 6 per cent., but this will depend upon our opinion of the completeness of data used in making the diagnoses.

The incubation is placed as the same as typhoid fever by Hunermann, who studied the epidemic at Saarbrueken. The stage of invasion is quoted by authors varying from three to eight days, and consists of headache, malaise, sometimes epistaxis, weakness and depression occasionally quite marked. Schottmüller and others especially mention congestion of the conjunctivæ and upper air passages.

A few times mention is made of swellings of the cervical lymph glands and twice of the inguinal. Herpes has been

noted and in Longcope's fatal case were present on lips and nose. Neither diarrhœa nor constipation seem to show any supremacy in percentage; they are sometimes accompanied by severe pain in the abdomen.

The onset of the fever is very frequently rapid, and I find three references to an initial chill (A and B, no type) (W and Sc., type A) (Sch. 6). In the majority of cases, however, it is the usual step-like advance to the height. After attaining its height the temperature *may* assume the continued type for a few days, but this period is rarely long and is succeeded by marked remissions that do not ascend and descend near the same time of day as in the case with typhoid fever. This may end in an irregular lysis or a crisis with the symptoms usually accompanying such a temperature fall. The duration of the fever is quoted by Clemens as varying from ten to twenty-two days, but by averaging the days mentioned on thirty-one temperature charts the writer obtained an average of 23.3 days.

Brill, 1898, reported 17 cases of continued fever ten to twelve days resembling typhoid fever, but without the Widal reaction. If these be added it will reduce the duration considerably. While this may have been paratyphoid fever it does not seem proper to admit them because they were not proven so to be. Brill's cases showed no premonitory symptoms; a great depression and marked remissions in temperature after a rapid rise over four days.

Roseola are to be found in 80 per cent. of the cases and may be single or in clusters on the abdomen, hands, face, and, according to Brill's cases, very frequently quite marked on the back. According to Hunermann's observations in the epidemic before mentioned, they appear quite regularly about the twenty-first day after the infection. The spots are clear and frequently dark red. Among other skin eruptions are mentioned scarlatinoid, dark macular spots, and petechiæ differing clearly from roseola.

The tongue and pulse are the same in character as seen in typhoid fever, including dicrotism of the latter.

Bronchitis is mentioned in 25 per cent., and more serious pneumonic processes do not seem to be uncommon.

Epistaxis is mentioned in 5 cases, in 1 of which it occurred twice during the invasion period.

Of intestinal symptoms we may find noted all that are present in typhoid fever; vomiting is found occasionally, and in 1 case it was especially obstinate.

Diarrhœa is found at one or another time of the course in 60 per cent., and Brion gives a percentage of 18 for the presence of pea-soup stools. Some cases have during their course both diarrhœa and constipation. At least no material difference can be made out concerning the bowel movements of these disease forms. Pain in the upper part of the abdomen is occasionally mentioned. In some cases of this form of typhoid intestinal symptoms are entirely lacking.

The spleen is enlarged and usually palpable in two-thirds of the cases; only three times is mention made of its normal size.

Intestinal hemorrhage is encountered nine times, or 10 per cent.; this percentage is made on the whole number of cases regardless of certainty of diagnosis, and when this is taken into consideration with the pathological anatomy it will be difficult to explain. So, too, the pathology will suggest a reason why perforation is not yet mentioned—*i. e.*, the few intestinal lesions noted are quite superficial. The urine is usually febrile, containing albumin, sometimes casts, very many times bacilli, and the diazo reaction may be obtained in about a third of the cases. Four times is mentioned indican in excess and once peptone. Brill's cases gave no indican, acetone, or diacetic acid reaction.

Any degree of mental disturbance from depression to the typhoid state may be present. I do not find any reference to the symptoms of spinal irritation called meningismus.

The leukocyte count, according to Gütig, establishes an analogous picture to typhoid fever, especially with the neutrophiles. There is leukopenia, followed, in the de-

cline, by lymphocytosis (54 per cent.), and a relatively large number of eosinophiles (10 per cent.).

Relapses are mentioned in about the same percentage as typhoid fever, and may follow the initial attack or occur sometime later. They bear the same relation to the main attack as is the case in typhoid fever, while in 1 case (A) two relapses are reported, the second being complicated by a phlebitis in the left thigh.

The limits of the disease, including the relapse, is placed by Johnston at twelve to eighty-four days, but he says "with the exception of the mild cases and in Gwyn's case, the duration of the fever is little indicative of the severity of the attack." The age of the patients varies between seven months and sixty years, the greater majority being between twenty and thirty years. Men are more frequently affected than women, three to one. The largest number of cases have occurred from July to November.

This short account of the clinical course of this type of disease suffices as example of its similarity to enteric fever, but some examples as aberrations are necessary.

The cases of Gwyn and Longcope (fatal) probably best illustrate the similarity to classical and severe typhoid fever, to which they coincided in everything but a serum reaction. In these the bacteriological findings in the blood were the proof of their nature. In contradistinction to these the case of Libman is the most striking. This case assumed the picture of an acute cholecystitis which began suddenly with nausea, vomiting, prostration, followed by distention of the abdomen and pain in the epigastrium and right hypochondrium; last to appear, jaundice. From the gall-bladder by aspiration, and at operation, and the blood, Libman was able to cultivate paratyphoid organisms. The operation revealed a perihepatitis and cholecystitis with an enlarged Riedel lobe.

The objection is raised to the admittance of this case to the class of paratyphoids, that at a limited autopsy fairly typical healed typhoid ulcers were seen, together with some

other evidences of typhoid infection, and that the patient's serum reacted in higher dilutions to bacillus typhosus than to the isolated organisms. Nevertheless it can at least be considered here as secondary infection of paratyphoid organisms, since they were undoubtedly the cause of the general septicæmia seen at autopsy. This is the view of the author and is to be emphasized later in contrast to paratyphoid fever.

A quite similar case is one reported by J. H. Pratt, of Boston. This patient had typhoid fever four years before and for two years previous to the present illness complained of pain in the right hypochondrium. At an operation for gall-stones the stones showed on culture the bacilli paratyphoid (type "B").

A case reported by G. B. Smith and Walker ("A") shows very clearly how this infection may assume a profound toxæmia. The stage of invasion required seven days; the fastigium presented a continued fever of forty-eight days' duration, followed by a slight return of fever and a distinct relapse three weeks after the main attack. During the forty-eight days of the main attack chills appeared eighteen times; two chills accompanied the slight rise of temperature after the main attack; the relapse was a mild picture of the first, and was accompanied by two chills. The chills were followed by various degrees of sweating. Bacillus paratyphosus ("A") was isolated from the blood. The fever ended very rapidly, twenty-six hours.

Another of Smith's cases was a simple continued fever with two hemorrhages, one amounting to three pints of bright blood and some clots, but no roseola or enlarged spleen (Type "A") was found.

Another of Pratt's cases was a suppurative orchitis (Type "B") and reminds one of the suppurative process mentioned by earlier authors. Allaria in reporting 2 cases in children at two and seven years, lays special stress on a crisis at the thirty-second day in the younger.

Complications. The organisms isolated from the foregoing referred to or described cases have been divided biologically into two groups, but let it be emphasized that

it is not necessary to consider these two very widely different organisms. As they vary or resemble the two ends of the typhocolon group, they have been called paratyphoid and paracolon. For the sake of simplicity now let us call all intermediary members of the colon group that are pathogenic for man, paratyphoids. In the laboratory the nomenclature "A" and "B" paratyphoid is given.

The number of cases in which Type "B" has been found outnumbers the cases of Type "A" infection about five to one, according to Pratt. Since his report no material change has taken place in the ratio.

Four "A" cases can be added to 12 described by Pratt; among the 16 hemorrhage occurred four times, or twenty-five per cent.

We find mention of 1 case each showing as complications thrombosis of the femoral vein, cystitis, bronchitis, and bronchopneumonia (Cushing's osteomyelitis).

Consideration of the complications of Type "B" cases will show a large percentage, especially of the serous membranes (veins, pleura, gall-bladder, peritoneum), which were present in 25 per cent; this figure also represents the proportion of cases showing some involvement of the respiratory tract. Intestinal hemorrhage was present in 5 of 69 cases, 7.2 per cent. of "B" infection. There is mention of 1 case each of embolic softening of the brain, gallstones, nephritis, acute suppurative orchitis, decubitus, furunculosis, and osteomyelitis. Whether the paucity of cases of Type "A" infection is the reason for this low percentage of complications remains for future reports to show. At least one fact is indisputable, that intestinal hemorrhage is more frequent in Type "A" infection. It must be remembered that some cases were afebrile.

The duration of the Type "A" cases is 29.9 days from an average of 13, while that of Type "B" cases is 20.7 days from 16.

Bacteriology. Having recited the clinical phases in a general way it is meet that we should critically examine the

etiology of this condition which has been proven biologically different from true typhoid fever. A strict classification of the colon group that is without objections has not been published for many reasons which are not in the province of this paper, but it suffices to say that there are very many different groups within this series, and while the members of these groups are not identical, they agree sufficiently to be classed together. The classical paper of Durham and the description of six strains of paratyphoid organisms obtained by Schottmüller approach the classification of these intermediates from the cultural standpoint, while Buxton combines clinical and bacteriological characters in his orders. The study of this latter supplies a very good working basis since it broaches the subject in this way, thereby serving us as a good introduction to the colon group. This author studied twenty-five cultures of many members of this series, including B. coli communis, B. typhosus (4), B. enteritidis, B. typhi murium, B. cholera suis, B. dysenteriæ (4), B. Hatton (Durham), two of Schottmüller's strains (different types), strains isolated by Gwyn, Cushing, Strong, Johnston (3), Libman, Hewlett, Kurth, and himself. He suggests the following classification for all members of the intermediary groups (except B. dysenteriæ) between the B. coli communis and B. typhosus: 1. Paracolons causing no typhoidal symptoms in man, composed of many different members, but culturally alike. 2. Paratyphoids causing typhoidal symptoms in man, and subdivided into (A) those cultures distinctly unlike the paracolons; (B) those culturally resembling paracolons, but a distinct species. The work of Cushing, Johnston, Schottmüller, Brion, and Kayser in their end results have established nearly identical pictures of the biological reactions of these paratyphoids, and the few individual differences displayed by some of their cultures, and strains described by other authors in their notes of sporadic cases, do not sufficiently disagree to be mentioned. It should be emphasized that these cultures do exhibit individualisms like different strains of any other

type. This is notoriously true of the colon bacillus and their allies. The overlapping of biological characteristics is so common as to be misleading at times, and some hope is laid in special serum reactions for the separation of those closely allied. Another point which should be mentioned in the etiological and clinical aspects of these intermediates are the meat-poisoning symptoms caused by some of them, and one group is called the meat poisoners. The paratyphoid "B" are very near biologically to this group, and further on analogies will be made to symptoms and pathology found in cases caused by them. In a personal communication from Dr. Buxton he says: "Between the paratyphoids 'B' and paracolons no sufficiently clear cultural difference can be observed, and I doubt if it is desirable to attempt to classify the paratyphoids 'B' and separate them from the paracolons." In Buxton's grouping the paracolons, group I., consist of B. enteritidis (Gärtner), B. Hatton (Durham), B. cholera suis, B. typhi murium, and one strain isolated by Johnston. The "A" paratyphoids include strains isolated by Gwyn, Cushing, Schottmüller ("A"), Johnston (2), Hewlett, and himself. Among the paratyphoids "B" he places organisms obtained in the cases of Schottmüller ("B"), Kurth, Libman, and possibly Strong, but this last will be found to give some points which seem to exclude it.

For reasons stated above the paracolons and paratyphoids "B" are described together.

Group I. and II. B. They are of typhocolon morphology, usually more actively motile by reasons of flagella peripherally arranged in about the same number as B. typhosus, but by some authors mentioned as longer. Schottmüller describes his members of this class upon gelatin tubes and plates as more luxuriant than B. typhosus and colon, and, after a few days, of porcelain whiteness. He also noted the absence of radial striations seen upon plate colonies of B. typhosus and B. coli communis. Upon Piorkowski's urine gelatin the colonies are round or oval, sometimes

yellow, but lacking the long colorless sprouts extending from the oval colonies of B. typhosus on this medium. Upon agar these strains are more luxuriant than the ends of this series. Upon bouillon they produce marked cloudiness. Potato, by Durham and Buxton, receives little respect in separation of these groups, probably because of its varying reaction. However, if there be any characteristic growth of this class, it is in producing a visible brown-tinted covering. After an initial acidity in litmus milk, appearing over twenty-four hours, members of this group gradually dissolve the casein by production of alkali (average 0.5 per cent.), this alkalinization being permanent, with complete opalescence of the medium in about twenty days. Schottmüller strains gave terminal alkalinity of 1.4 per cent. to 2.8 per cent. Litmus whey will agree with this in behavior to this group. This group will ferment glucose, mannite, fructose, and galactose, but not lactose or saccharose. One per cent. solutions of glucose in sugar-free bouillon and peptone solution are completely fermented in two days, and in yeast broth fermentation ends after twenty-four hours. Neutral red agar is fermented and changed to yellow in twenty-four hours (never over forty-eight hours), which color is permanent.

The other group, A. paratyphoids, resembles those just described in morphology, motility, and in producing a more luxuriant growth in general than B. typhosus. On gelatin it is also without radial furrows and of porcelain whiteness. Upon urine gelatin it appears in very pale round or oval colonies with even margins. Bouillon is moderately clouded (Schottmüller). Potato growth is moist and scarcely visible. Milk is rendered a permanent acid, averaging about 2.2 per cent. at the end of three weeks. Cushing's bacillus is slightly aberrant from this type in the medium. After its initial acidity it returns to a slight alkalinity, 0.3 per cent., and this reaction renders the medium opalescent. One per cent. solution of glucose in sugar-free bouillon require three days

for full fermentation, and this process goes on for three days in yeast broth. The other sugars, except as before lactose and saccharose, are fermented. The amount of gas, however, is greater in the paracolons and it requires longer for the subdivision I. to complete fermentation. Neutral red agar is not changed to yellow until forty-eight hours, some of the group losing all the red color, while others retain a little at the surface or at the bottom; this yellow remains for a few days, but at the average of ten days the medium regains its original color. Dr. Buxton in the above-named communication says that a return of color may sometimes be noted among the paracolons, but that it is not complete.

Because of the reaction in milk being supposedly due to some changes in the sugars contained normally (glucose galactose) the previous implantation of B. typhosus to break up this sugar (without gas) renders much clearer the changes produced by these two groups. There is never any coagulation of milk. Under ordinary conditions no indol is produced, but in a peptone solution I find three notes of indol in slight amount with the paracolons and paratyphoids "B."

Very few references are made to the pathogenicity of these organisms, but those mentioned concern the cases when Type "B" was isolated. The organisms isolated by Pratt and Libman when injected into guinea-pigs gave rise to areas of suppuration at the site of inoculation, and post-mortem universal congestion; in one pig a few hemorrhages; and with Libman's organism seropurulent peritonitis resulted in animals injected. Kurth's organisms ("B") produced septicæmia in mice and guinea-pigs. I find no detailed references of value with injections of Type "A," and while these cases may be too few, yet they are supported by clinical facts. The symptoms of septicæmia in Libman's case (cholecystitis, etc.), the suppurative orchitis reported in one and saphenous phlebitis in another of Pratt's cases, and the pictures of septicæmia of Allen's cases are all examples of Type "B" infection. Type "A" can pro-

duce pus as shown by Cushing's growth from an osteomyelitis. But the point is made that from the standpoint of pathogenicity, as well as in biological relations, Type "B" stands near the group of meat poisoners. The picture of septicæmia and toxæmia in meat poisoning is well known both in man and in experimental animals; the latter taking the infection by mouth as well as by injection with the same results. Pus at the site of injection is common. The complications of meat poisoning are the same as those detailed for Type "B," but of greater severity.

These organisms have been obtained, some at post-mortem, but most of them during life, in the blood, urine, feces, rose spots, spleen, by puncture, vagina, and pus of abscesses. They appear in some cases to be in large numbers, for Gwyn, Brion, and Kayser, instead of using large quantities of bouillon requisite for the isolation of the B. typhosus, simply spread a few cubic centimetres of blood over solidified agar.

Serum Tests. For the purpose of separating this paratyphoid fever and allied infections from typhoid fever, many serum reactions were undertaken, as was to be expected, coming, as these new descriptions did, so soon after the introduction of serum diagnosis in disease. The first results seem to be more conclusive than the later ones, and it is questionable whether the refinements will assist much, since the first few observations proved fairly conclusively that here we have to deal with an infectious disease close to typhoid, especially in etiological consideration, and therefore probably subject to the same disseminating factors.

As was first thought, the high percentage of clinical typhoids with negative serum agglutinations was probably due to the inclusions of some para infections. When the first results were obtained it was thought that the agglutination of paratyphoid organisms with a patient's serum that showed no such reaction with the bacillus of Eberth was a nearly or quite pathognomonic point for the existence of para fever. This was used as a substantial support to the acceptance by Schottmüller, and those following him,

of the specificity of their isolated germs. Later some interaction of members of the intermediary groups with B. typhosus led several investigators to work out these relations.

To return to some of the old work for a moment, we find the Achard and Bensaude's organisms were clumped by the patients' serum and slightly by antityphoid serum, while the patients' serum reacted with three strains of B. psittacosis (Nocard), giving rise to the suspicion in the observers' minds that they were dealing with an organism like this last.

Widal's patients' serum agglutinated the isolated organism, but did not affect other members of the colon group. Schottmüller's experiments showed that his Type "A" (two strains) were not clumped or only slightly affected by the serum of Type "B," while this group were well clumped by their own patients' sera, and besides this interagglutinated. However, the serum of one of the patients belonging to each group agglutinated all organisms; Type "A" serum acting in the same dilution for all, while Type "B" serum was more potent for Type "B" strains.

Cushing obtained a highly potent antiserum for his strain (1:8000) which had no effect on Gwyn's strain, B. typhosus or colon bacilli. This antiserum did interagglutinate with B. cholera suis, and an antiserum of this latter germ reacted with Cushing's organism, but with no other member of the series.

Durham demonstrated this absence of interaction of Gwyn and Cushing in a manner reversing that mentioned above, but says he can hardly distinguish these two organisms culturally.

Other observers, Kurth ("B"), de Feyfer, and Kayser ("A"), Wells and Scott ("A"), and others mention that no considerable agglutination took place with their antipara sera and the bacillus of Eberth, while they reacted in high dilutions with their own and analogous strains. Here also the extensive work of Buxton comes into consideration. He immunized animals against all the strains mentioned

before in this paper and tried each of these antisera with every organism. Unfortunately the anti-Gwyn rabbits died before its serum was tried with all the strains. The trials made, however, are sufficient to be accepted when taken into account with others of this group.

His dilutions and time limits were 1:400 and four hours respectively. In so far as the members of his paratyphoid "A" group are concerned, they mutually interacted completely, but not with any other of the colon series, and he considers these results ample proof that these strains are a true species and not merely a group. He found, contrary to the results of Cushing and Durham, that strains "Gwyn" and "Cushing's 'O'" did interact, and is at a loss to explain the failure of these observers. Let it be remembered here that B. "O." varies a little from Type "A," of which Gwyn is a good representative.

Type "B" was not uniform in its reactions, but he makes plain that those organisms which do not cause typhoidal symptoms in man and the typhoid bacillus do not inter-agglutinate with these "A" and "B" paratyphoids.

With regard to this last statement much further discussion will be necessary, for it has not been found absolutely true. Buxton immunized an animal against both types and found that the serum may have a clumping effect on both types without losing its effects on the one first used for injections. Still the foregoing facts will not answer the questions which arise to our minds: Will the serum of a true typhoid fever patient agglutinate the paratyphoid organism? And will, on the other hand, the serum of a paratyphoid fever patient clump the B. typhosus?

With reference to the first, the writer offers the results of the experiments mentioned before at the University Hospital, where the serum of all cases coming for Widal examinations are routinely tried with "A" paratyphoid organisms. With the exception of 12 cases among 94 the results were negative, 4 of which were proven to be true typhoid by blood culture. In 3 were the dilution limits

for "A" paratyphoid the same as for B. typhosus, 1:500; in 2 were they 1:250 and exceeded by the limits for B. typhosus. Two cases giving reactions with "A" paratyphoids in dilution 1:500 and 1:250 were proven typhoid fever, the remaining 2 only reacting in 1:50. The agglutination curve for the highest reactions is given here (Chart I.) outlined for B. typhosus, paratyphoid "A" and "B," and bacillus of

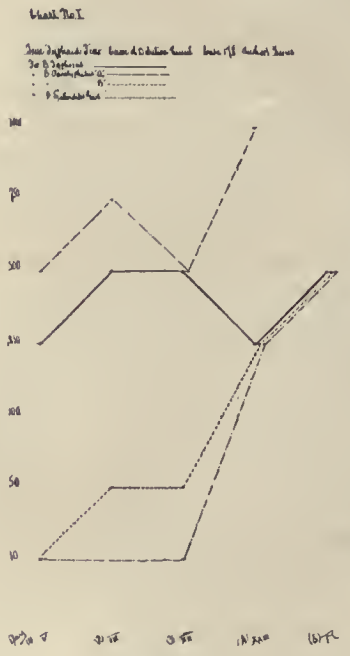

Chart I.

Gärtner. It will be noticed that the curve of the "A" paratyphoids throughout the attack, and even more so in the relapse, exceeded that of the typhoid bacillus. This would seem to indicate that the blood culture missed the "A" paratyphoid. This question came up during the illness. but as the patient was a private one in the hospital, a further study was not permitted. The result of the blood culture was considered final, but if we assume that the isolated bac-

terium was the only cause of the attack an explanation of these curves is not easy. Some light on a possible explanation will be given later.

This contributes to work by Jürgens, von Drigalski, and Conradi who worked with Type "B" and found that unlike the foregoing the reaction of the twenty-two patients in a typhoid epidemic at Trier, with one exception, reacted quite strongly with this "B" type. They found that this reaction usually appeared about the same time as the antityphoid, but sometimes it was several days later, once eighteen days later. However, five times the reaction to the paratyphoid appeared earlier than that to the typhoid bacillus. Their first case died when the reaction to the former was higher than that to the latter, yet at autopsy there were found only the bacillus of Eberth. Usually this organism was agglutinated in higher dilutions than the other, but in four cases was the reaction appreciably higher at one time or another; especially was this the case at the beginning and end of the attack. The agglutination dilution curves did not coincide exactly throughout, but in general rise and fall they followed the same course (Chart II.). In those cases where the absolute limit of the dilution was considerably above the B. typhosus, for the paratyphosus "B," nothing but the first mentioned was found on bacteriological search.

With this evidence may be coupled the studies of Bruns and Kayser, who carried out a large series of experiments with various colon group antisera.

When using a very highly potent antityphoid serum (1:50,000) they were able to obtain with Schottmüller's two types strains of Kayser ("A") and Kurth ("B") positive reactions in dilutions of 1:500, the same dilution giving similar results with some of the meat poisoners—*i. e.*, corresponding to Buxton's paracolons, and with the strains Gaustad and Friedebergensis particularly the dilution limits reached 1:1000.

When they used sera of potencies 1:5000 and 1:1000 respectively the difference is striking, for with no organisms

but B. Friedebergensis, which reacted feebly at 1:100 with the more potent serum, did they obtain a positive diagnostic reaction. On the other hand, the use of a Type "A" antiserum showed clearly the relationships in all dilutions between organisms decided culturally to belong to this species. Two Type "B" antisera (Schottmüller "B," 2500 potency; Kurth "B," 2500 potency) clearly outlined their

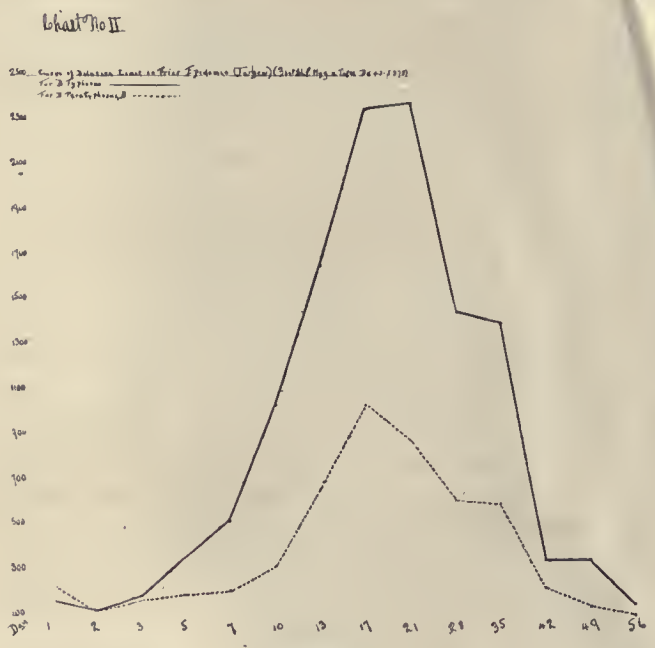

CHART II.

effects to their own group, but at the same time agglutinating one meat poisoner, which is closely related biologically, and certainly affected several strains of B. typhosus in dilution of 1:100. A B. coli antiserum agglutinated some of the paracolons indistinctly and gave a questionable reaction with one typhoid strain and one paratyphoid "B."

Rolly tested the serum of 40 true typhoids with types "A" and "B," B. enteritidis (Gärtner), and the B. typhosus.

Seventy per cent. of these sera clumped the paratyphoid bacilli regardless of type, and half that number gave reactions in higher dilutions than the B. typhosus did. Only 16 of these 40 cases were examined between the first and fourth week, the remainder being tried during the convalescence; 19 reacted to the Type "A," of which 5 sera gave no reaction to Type "B." Nine of this 19 reacted to Type "A" in higher dilutions than they did to the B. typhosus. To Type "B" the typhoid serum reacted twenty-two times, and 8 of this number did not clump Type "A." Seven of this 22 gave higher limits for Type "B" than for the typhoid bacillus. A noticeable point that the author does not mention is that of the 16 cases examined during the fastigium only 3 gave a more positive reaction to paratyphoids than to typhoid bacillus. Notwithstanding these results, which are contrary to those just described, the work of Rolly concerns too few cases at unfavorable times and only one test in each case, thereby giving no basis for causes or conclusions. He obtained positive agglutinations of Type "A" in 48 per cent. of his typhoids, while the writer observed this in only 12 per cent.. One of Rolly's results is worth mention, and that is in these sera the B. enteritidis (Gärtner) and Type "B" were not clumped at or near the same dilutions.

Having proven fairly conclusively that typhoid serum may react to the B. paratyphosus, let us consider the second question—*i. e.*, whether the reverse is true. If we look over the literature of cases we find that some were absolutely negative to B. typhosus, while others reacted in low dilutions; and the lowest limits and for a positive Widal, so far reported, have been in cases of Type "A" infection. In examining the Saarbrücken epidemic, which was of the "B" type, marked agglutination of B. typhosus will be found. Thirty of the 38 cases showed a positive "B" paratyphosus reaction in dilution of 1:100 or higher, while of this number 26 gave an agglutination of the Eberth bacillus at the same time. The 4 in which the reaction was absent were

examined early in the disease in 2 and quite late in the others, so that the reaction to the B. typhosus may not have appeared or had already disappeared. In nearly all of these cases were the paratyphoid bacilli proven in the stools.

Upon consideration of the foregoing conflicting evidence the following questions naturally present themselves for decision:

1. What relation does a negative Widal bear to the existence of paratyphoid fever?

2. What is the relation of Types "A" and "B" of paratyphoid bacillus to the B. typhosus and members of the intermediary groups?

3. How shall we decide upon the existence of a mixed infection when a double agglutination occurs?

4. What shall be our diagnostic criteria and what shall be our dilution limits when there is coincident agglutination of two or more organisms?

In reference to the first question, may it be called to mind that an absence of a Widal reaction is not a sure proof that the patient is not inhabited by the typhoid bacillus. A positive reaction may be wanting in cases which are clinically and indubitably typhoid and also where B. typhosus has been found in the stools without subjective signs of an attack. Given a negative result in two hours after combination of a patient's serum with two or more strains of B. typhosus in 1:100, when the case closely resembles enteric, one would be inclined to search for a positive para-reaction, but we must not forget to take into consideration the days of disease. Early in the disease, for example, probably the entire first week, may no positive Widal be obtained. Again, after the disappearance of the fever the same result is sometimes seen. The curve, which is made by the limit of agglutination, is by no means regular.

The relation of Types "A" and "B" paratyphoids to B. typhosus seems to differ when considered from biological and serum agglutinative standpoints. If one review the cultural characters of the former group it will be found

quite near to the B. typhosus, and, as mentioned several times, Type "B" approaches the meat poisoners of the B. enteritidis type. According to Schottmüller Type "A" resembles organisms of the type paracolon of Buxton—*i. e.*, B. Breslaviensis and B. Friedebergensis, which are meat poisoners, the former being classified by Van Ermengen as quite near to B. Hatton (Durham). Schottmüller found no organism reported which he considered identical with Type "B."

Notwithstanding Schottmüller's dictum, antisera of Type "A," according to the extensive work of Bruns and Kayser, had no agglutinative effect upon B. Morseiliensis, B. Friedebergensis, B. morbificans bovis, or B. Breslaviensis. The last named, however, was given a place near Type "B" because it reacted with antisera of this type nearly as strongly as the homologous bacillus. Antisera of high potency produced by injections of B. typhosus, as before detailed, clumped both "A" and "B" types to the same limits, while those of lower potencies had no effect upon these groups. The antisera of Types "A" and "B" had no effect upon the heterologous strains and were clearly special for their own groups. The B. typhosus was clumped by antibacillus "B" sera up to 1:100, which would seem to indicate a close relationship between these two organisms.

The results of these experiments agree in part with Buxton's work, except that he found no interaction between Type "B," B. typhosus organisms, and sera.

All these facts remind one of Durham's statement that organisms culturally near one another may show no tendency to interagglutinate, while types easily differentiable biologically may show this mutual interaction. By this is explained the failure of the writer to obtain reactions with Type "A" with the typhoid patients at the University Hospital, and raises the question why the twelve exceptions occurred. Durham's dictum also is admissible in connection with Jürgen's work with paratyphoids "B" in the Trier epidemic.

The presence of the bacillus of Eberth in some healthy intestinal tracts is not doubted; therefore, may it not be accompanied by some closely related organism? Conradi was able to isolate B. of Eberth and a paratyphoid from a true typhoid stool and a normal one. They were of the "A" type. This is the first question which presents itself, especially when we consider the coincident clumping of this organism and another. This possibility is not doubted, and that they might both gain entrance to the blood stream is not questioned. It has been suggested that they produce some common agglutinating body and thereby a twofold reaction occurs. It has been shown with regard to the microorganisms in question that it is not necessary that two types of germs be present; that one may produce an agglutinating body to which the other is susceptible. It would be supposed, because of bacteriological similarity of the Type "A" paratyphoids and the B. typhosus, that they would give rise to some such mutually reactive product. Schottmüller is the only observer to note the interagglutination of these two types, while experiments on immunized animals do not establish it. The explanation of these curious phenomena *may* be found in Durham's hypothesis. He supposes an agglutinin to be a complex body, while the bacillary components capable of giving rise to this agglutinin are equally complex. The agglutinin he represents with capitals, and the bacillary components with the corresponding small letters. Since B. typhosus and B. enteritidis (Gärtner) are known to interagglutinate, and B. Hatton will not react with either, he takes them for examples. He supposes B. typhosus to be composed of a+b+c+d+e and its corresponding agglutinin to be A+B+C+D+E. B. enteritidis agglutinins he represents as C+D+E+F+G+H, B. Hatton as E+F+G+H+J+K, with the small letters like the capitals representing their bacillary components.

When homologous bacilli and clumping body are added together in like amount the maximum results are obtained. But suppose the B. enteritidis be added to B. typhosus anti-

serum (e+f+g+h+c+d)+(A+B+C+D+E) the reaction will be in proportion as the common elements C, D, and E can combine. If to the bacillary components of B. Hatton are added the agglutinating bodies of B. typhosus the strength of the latter will have to be relatively stronger to obtain an appreciable reaction because they contain only the common element *e*. Durham further supposes that these various constituents are not present in the same amounts in any two cultures or any two members of a species, but considers that they may be multiplied by various factors. Now, if the common constituents of two organisms which are tried together were only in low proportion, so much the greater would have to be the amount of the serum in order to affect their common members among the bacillary components of the other organism.

This may be accepted as partially explaining these crossed reactions. The real question of positive establishment of a mixed infection can only be reached by proving a double bactericidal property of the serum in question and whether this later may or may not be saturated by one or the other organism. These are called Pfeiffer's and Castellani's tests, respectively.

Of course a double bacterological result to cultures from blood or other site is positive if there be at the same time a double reaction to the organisms isolated or to members of their type. A body cannot be said to be infected with an organism unless it has reacted to the same, which reaction may be demonstrated by subjective symptoms or objective phenomena—*i. e.*, agglutination or bactericidal influence. If we obtain from a typhoid case a repeatedly positive agglutination of Type "A" paratyphoid and no reaction at all to B. typhosus we may consider it a Type "A" infection, but this may not be taken unquestioned with Type "B." Even if Type "A" give a positive result and B. typhosus a negative one, still will the bactericidal influence of the serum render all questions answered.

With Type "B," however, the positive character of the

infection must be determined by an unquestionable agglutination of this type throughout the attack with no result when B. typhosus is used, if we desire to absolutely justify its etiology. But this cannot be done, since Type "B" infection will clump B. typhosus; so that we must take refuge in isolation of the causative bacillus from the blood, feces, or other means. If this gives a Type "B" culture and one still raises the question of mixed infection, certain graded dilutions of the patient's blood, to which is added established amounts of Type "B" culture in the first experiments and B. typhosus in a second set, may be injected into guinea-pigs' peritoneal cavities. The organisms rendered harmless by the least amount of serum may be considered as the type of germ giving rise to the attack in question. Should these results be conflicting as to leave doubt, the test of Castellani is left to us. This depends upon the fact that the agglutinating property or body of a serum may be exhausted for the both organisms giving the positive results, when it is saturated with the etiological bacterium, while saturation by the co-agglutinated organism will not decrease the limit of agglutination for the causative factor.

Bruns and Kayser say that a quick diagnostic test may be made by 1:75 dilution using a twelve-hour bouillon culture of the organism, "but it is desirable to obtain the limit of dilution possible to give a reaction." Be it emphasized again, it depends upon the organism used and that the reaction must be repeatedly positive in higher dilutions than that obtained by any other organism, to which should be added, if possible, the proof of bacteriological culture, saturation, or bactericidal phenomena. According to many observers, agglutination in disease is only an elevated value of the normal agglutinating bodies of the blood, and if a sufficient study of low dilutions were made on all bacterial diseases it would probably show an agglutination on higher dilutions for all organisms, pathogenic for man, than is present normally.

If this enhanced value of the normal agglutinin in dis-

ease is accepted as explaining all co-agglutinations, why then should not so closely related an organism to the B. typhosus as the Type "A" be affected by true antityphoid sera? Apparently we must search further for an explanation, and the suggestion of Meltzer, Durham, and others, that some constituent of a specific agglutinin is also produced by another organism, gains in weight.

With reference to the relation of this paratyphoid fever in man to meat poisoning in man, the work of Bruns and Kayser before mentioned shows an agglutination of the causative bacteria of these diseases about the same as is the case with typhoid bacillus. Especially are the meat poisoners B. Gaustad and B. Breslaviensis related to the Type "B" paratyphoids, if we were to accept serum reaction as proof. Probably the same criteria suggested for the diagnosis of typhoid-like cases in man may serve as means for differential diagnosis, should there be any question of the relations of acute septicæmic symptoms to this "B." type or its closely related forms.

Pathology. The point the writer wishes to make with reference to this subject, coupled with the clinical phases of the reported cases, is that differences can be noted in Types "A" and "B" infections, even though the lines may be ill-defined.

After reviewing the known pathology of this condition, Kieth comes to the conclusion that for the present this form of disease must be considered as a general acute infectious process for which a certain determined local lesion does not exist.

According to observers of autopsies on para infections no close similarity exists in the pathological picture to that of typhoid. So rises the question whether some cases that have been classed as typhoid without intestinal lesions have not been of this type. This question may, I think, be answerable in the affirmative if one refers to those cases of paratyphoid "B" where a positive agglutination of the B. typhosus was observed. But of the pathology of those instances

where there was more than a suspicion of the existence of a para infection, we have only a few cases. Wells and Scott have collected four autopsies of such cases and add one of their own. Of these cases four were of the "B" type, one of "A" type. I can do no better than quote verbatim the summary of their investigations: "There is little characterizing this type of infection or differentiating it from other septicæmias anatomically however much it may differ clinically. The most constant change is the enlargement of the spleen, which was present in all five cases. In most respects this enlargement seems to be the same as that of typhoid or ordinary septicæmia, and in our case the microscopic findings are similar. The loading of the splenic endothelial cells with pigment and erythrocytes is evidently the results of the hæmolysis of the disease. The intestinal lesions are, however, quite variable. Because of the occasional occurrence of intestinal hemorrhage it had at first been thought that intestinal ulcerations probably were present, although the first cases autopsied, those of Strong and Longcope, showed the intestines to be quite unaffected. In the last cases, however, there have been numerous ulcers, although entirely different from those of typhoid. In our case, in which the hemorrhages were a prominent feature of the attack, the largest amount of ulceration of any of the five was found. The reporters of the cases in which the ulcerations were described, agreed in likening them to those of dysentery rather than to those of typhoid. In all cases there was also a practical absence of any alteration of Peyer's patches or of the solitary follicles. Likewise the mesenteric glands were almost unaltered. Strong alone reports swelling of the glands, which were not microscopically examined. Lutksch found one enlarged gland with endothelial proliferation. In the other three there were no gross changes in them and in none does there seem to have been any generalized glandular hyperplasia. In Longcope's case and in ours (Wells and Scott) there were typical focal necroses in the liver differing from those

in typhoid fever in not containing endothelial cells. Beyond these changes there seem to be none of significance."

If to this is added a description of the ulcers found by Wells and Scott the difference to those of typhoid is not difficult to see. Those described by these observers were seated in the lower ileum, quite superficially, rarely going through the muscular wall, indeed many having the submucosa as a base. They were sharply outlined, frequently coalescing and lacking any reactive inflammatory process in their margins or beyond them. They were, however, slightly undermined. There was *no* congestion of the intestinal wall in this case. This is the representative case of Type "A" infection.

Type "B" pathology may be represented by Longcope's case, which was a typical clinical case of typhoid fever, yet upon autopsy there were found only enlarged solitary follicles, soft spleen with a few hemorrhages, and cloudy swelling of the liver. There were ascaris lumbricoides in the intestine and the mesenteric glands were free from lesions. From various organs the same bacillus was isolated as was obtained from the blood ante-mortem.

Besides this case may be taken the one reported by Strong. From the spleen of a typhoidal case this observer cultured a bacillus conforming to Buxton's "B" type, which was pathogenic for mice. The mesenteric lymphatics were swollen, and some along the small intestine were hemorrhagic. The only pathological offerings of the intestinal tract was a catarrh and a few hemorrhges. The lymphatic apparatus of the bowel was not affected.

Sion and Negel's case may be mentioned in which, besides an embolic softening of the brain, bronchitis, and pneumonia, there was a dysenteric inflammation of the lower ileum; no ulceration, but a swollen, injected intestinal wall covered by necrotic detritus, while the lymphatic structures were not affected.

Libman's fatal case was not accepted by Wells and Scott for the reason already stated—*i. e.*, a positive Widal, thereby

sharing the reporter's opinion that it was a mixed infection. Also at autopsy typical healed typhoid ulcers were found, which strengthened this opinion. Nevertheless, the B. paratyphosus, Type "B," was isolated; and because it serves to represent a case of Type "B" infection and because by styling this case a mixed infection the author must have accredited to the isolated germ some etiological significance, it is included here. It is the opinion of the writer that this organism was the cause of the attack, because the Widal was positive after several negative results had been obtained while the organisms were clumped, which were obtained shortly after their isolation and before the appearance of the Widal, even if only in a low dilution. The correctness of this opinion cannot positively be asserted. This attack was quite acute and assumed the picture of an acute cholecystitis with symptoms of septicæmia. An autopsy, which was limited by the patient's family, showed the typhoid scars as mentioned above, together with evidences of congestion of all the organs, especially the liver and spleen. It appears here that the attack and pathological results were more like a septicæmia than a true typhoid fever. The existence of the healed ulcers of typhoid fever (limited autopsy) cannot be satisfactorily explained.

Perhaps the one case of Type "A" autopsy is not enough upon which to base arguments; still some deductions may seem justifiable when this case is taken into consideration clinically.

As noted above, the greatest amount of ulceration of any autopsy was found in this case of Wells and Scott, which gave a clinical course of typhoid fever including intestinal hemorrhages. In these two respects do they agree. The duration of Type "A" infections from an average of 13 cases is 25.9 days; while the duration of proven Type "B" cases from an average of 16 is 20.7 days. The former figures are surely nearer the average length of typhoid fever than the latter. The Type "B" epidemic at Saarbrücken would rather tend to shorten this time. On the other hand, Type "B" infec-

tions give more strikingly the picture of a septicæmia, and in these the part taken by the intestine is usually a general catarrhal or hemorrhagic enteritidis without so great tendency to localize itself into ulceration. The case of Longcope may be cited as one clinically approaching the "A" variety, but cases of meat poisoning have repeatedly given a clinical picture very like this case. Most of the attacks produced by the meat poisoners are of short duration, but this is by no means absolute. Sometimes, indeed, the convalescence is slow in appearing and very tardy in disappearing. The pathological anatomy of meat poisoning may vary from a slight catarrh to a virulent hemorrhagic inflammation of the entire gastrointestinal tract. In our Type "A" case, as in typhoid, the changes in the mucous membrane of the gut were limited to the region of the ileum, while in the other cases they were not determined in location. Lutksch noted changes in the stomach and colon, Longcope in the colon, Sion and Negel in the ileum, while Strong's notes seem to indicate that the lesions were scattered.

Objection may be made to this likening these "B" cases to meat poisoning, because in some autopsies on the latter Peyer's patches have been swollen. In answer to this it may be said that those cases of meat poisoning which came to autopsy early enough to have these agminated glands enlarged, show also lymphatics involved having no connection with the intestinal tract, while I find no references to peculiar ulceration of Peyer's glands. Vomiting, which is common in meat poisoning, is noted in some "B" cases, but none of the "A" type.

To these arguments for the more septicæmic nature of Type "B" than may be ascribed to Type "A," let us examine the complications of the former. The pyogenic properties have been well demonstrated and metastatic processes noted. The involvement of the endothelial membranes has been mentioned. All of these results may occur in meat poisoning more frequently than typhoid fever. The greater number of complications in this type speaks for a more acute

septicæmic process. The percentage of hemorrhages per rectum is greater in Type "A," as would be expected, if the opinion that this form is nearer to enteric fever than the other is considered admissible. Hemorrhages, for reasons cited in the pathological details, may *also* be expected in the "B" types.

A case may be quoted in objection to these views. It is Smith's prolonged case, in which there were so many chills and clinical evidence of toxæmia, while Type "A" organisms were isolated. Some cases of typhoid fever may evidence toxæmic symptoms, and while such a course as described by Smith is uncommon in true typhoid, could there not have been a mixed infection with some of the kind of bacterium? Even if this contingency is not allowed—and we admit that clinically this oversteps the line of distinction defended here—it does not materially alter the general classification. I wish to impress upon my readers that I make no sharp distinction between typhoid fever, paratyphoid fever ("A" and "B") infections, but have attempted to point out that the relationships existing between the clinical symptoms and pathological pictures are very similar to the positions in which we place the etiological factor—*i. e.*, the organisms. If we begin at the end of the colon series where the bacillus of Eberth and Gaffky is placed and proceed toward the colon type, we meet in order the Type "A" first, the Type "B" next, which is closely followed by the meat-poisoning groups, and such may be described the order of the clinicopathological demonstrations of these bacteria. This accords with Trautman's views that clinically we may consider the meat-poisoning symptoms in general as hyperacute, para cases on the whole as acute, and those of true typhoidal nature as more subacute.

A point which must receive some consideration is the favorable prognosis given by some authors, notably Schottmüller and Kurth. The cases reported by these two observers probably were true para infections, but when we consider some of the cases, especially of the "B" type, that were

diagnosed by serum tests which are notably liable to error, we must have care as to our mortality percentage. Of the "A" type there is surely one autopsy of 16 cases here referred to, while of the *diagnosed* "B" infections 5 deaths occurred. The latter are so much the more numerous, and at the same time rather untrustworthy, that the actual mortality is difficult to obtain. In the Saarbrücken epidemic no fatalities happened among 38 cases ("B" type), which would speak for a favorable prognosis. At any rate, the only thing that seems justifiable to say is that the statistics obtained do not differ greatly from those of typhoid fever. Certainly 90-odd cases of this may be picked indiscriminately from the same various places in which para cases have been reported and not show more than 6 deaths. Of *proven* paratyphoid infections the mortality is *about* 10 per cent. Until we have more positive diagnoses we can lay no stress upon a more favorable prognosis.

As is the case when any differentiation in form of a general idea of a disease is presented, so is there a discussion regarding the name of this new variation of the typhoid etiology. The name of this presentation is best described by the introductory remarks, and justifiably may be considered as a type of typhoid fever varying in different ways from its classical picture and sufficiently in etiology to deserve special description. But all the cases to which have been given this name are not of the enteric form, to wit: Libman's cholecystitis, Pratt's gallstone case and suppurative orchitis case, Smith's prolonged toxæmic case, Widal's case of an abscess in a phthisical patient with slight constitutional symptoms, while the pictures of Allen's cases vary less from typhoid than the foregoing. There are others where noticeable differences were mentioned and the majority in percentage are of Type "B" infection, so that we may say "paratyphoid" is with greater propriety applied to Type "A". To object to this may be cited the very typhoid-like case of Longcope. In answer may be said that acute tuberculosis assumes this form, while malaria has been

known to be confused. Then again we are not drawing any sharp lines and speaking more in generalisms. Meltzer defends the name paratyphoid for the whole class, because it suggests the clinical phase of the attack and the organisms are nearer the B. typhosus than the B. coli. "Bacillus paracolon" and "paracolon" fever he thinks are not sufficiently specific. Libman objects to "paracolon" because it relates the attack and the bacterium too closely to the B. coli communis, while "paratyphoid," according to his opinion, should be used for organisms identical to the bacillus of Eberth, but not interagglutinative with it. He concludes the choice lies between these two until we have differentiated the micro-organisms more clearly.

If it be necessary to name these forms some reference will have to be made to the etiology and pathology mentioned in part of the foregoing remarks. So far as attempting to entirely destroy the present conception of typhoid fever and its various abortive or atypical forms, no good can be hoped for unless at some early time we find specific therapy. If it be considered advisable to apply names to the cases which display all of the characters of the infection and the etiology detailed to the extent of our present knowledge obtained from the literature of cases and of experiments, the following nomenclature is offered for discussion.

Let us consider the true typhoid fever, no matter what its manifestations, but in which the etiological role of the B. typhosus is undoubted, as typhoid or enteric fever or typhus abdominalis. Its next relation whose etiology is the "A" type let us call the paratyphus infectiosa and the organism B. paratyphosus infectiosa or B. paratyphosus "A." Because of the greater septicæmic character of the "B" cases, the name of paracolon septicæmia is suggested, and an analogous name for the bacillus. The cases partaking of both characters are thereby considered as transitional types varying in like manner as do the various members of the groups.

A consideration of all the facts in this general review of the position of paratyphoid fever seems to offer the following conclusions:

1. Paratyphoid fever differs from typhoid fever in (*a*) a shorter invasion stage and rise of temperature; (*b*) shorter or absent period of continued fever; and (*c*) marked diurnal remissions of temperature, much deeper than enteric and without periodicity. An absence of the Widal is suggestive, if it persist in reasonably high dilutions.

2. The duration is on the whole shorter than typhoid, and the cases where Type "B" was adjudged the etiological role this fact is more striking than in the Type "A" cases.

3. The general findings of the Type "A" cases are nearer to typhoid than Type "B," the latter presenting a picture more like septicæmia.

4. The complications of Type "B" infections are more numerous, more purulent, and the course is more fulminating in these cases.

5. The causal germs belong to the intermediates of the typhocolon series, the Type "A" being nearer to the bacillus of Eberth and Gaffky, while Type "B" approaches the meat-poisoning group.

6. The clinical evidences of the respective organisms just named agree with their general properties and relations to infections in this order, ranging from the subacute typhoid to the hyperacute meat poisoning.

7. Antityphoid serum will clump the paratyphoid "B" at the same time as the B. typhosus, sometimes even in higher dilutions; so that a positive reaction of a patient's serum to both B. typhosus and paratyphosus "B," even if the latter be in higher dilutions, will not permit a diagnosis. On the other hand, only twelve times in 94 cases of typhoid fever did the serum react with the Type "A" paratyphoid; so that a positive reaction with Type "A" and not with the bacillus of Eberth may be taken as nearly a proof of the existence of an "A" paratyphoid infection.

8. That there must be some other factor responsible for

eoagglutinations than an increased value of the agglutinins normally present in the blood seems probable.

9. That the best proof of the existence of a para infection is the isolation of the bacterium, the saturation test, and, last, the bactericidal action.

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A COMPARISON OF THE AGGLUTINATING PROPERTIES OF THE SERUM OF TYPHOID FEVER PATIENTS ON THE B. TYPHOSUS, B. ENTERITIDIS (GAERTNER), AND B. PARATYPHOSUS (A.), AND THE RELATION OF THEIR INDIVIDUAL ANTISERA.

By Herbert Fox, M.D.

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Phoebe A. Hearst Foundation.)

During the year 1904 the sera that were sent to the Pepper Laboratory from the University Hospital for Widal tests were tried with the three organisms mentioned in the title of this contribution. In all there were 148 cases, of which 94 were true typhoid fever. The dilution used for diagnostic purposes was 1:50, but for scientific examination 1:500 was employed. The cultures (twenty-four hours in peptone broth) were always filtered through a close paper in order to obtain a small number of micro-organisms and establish a control that was without clumps or in which spontaneous segregation could be observed.

The spontaneous clumping of these germs deserves some mention. The organisms arranged themselves perpendicularly or parallel when such uninfluenced action occurred in controls of B. enteritidis. These clumps varied in size as spontaneous clumps of any other bacterium, but the rectangular arrangement seems peculiarly single and is not difficult to recognize. The voluntary segregations of the B.

typhosus and B. paratyphosus did not display this regular distribution and resemble the active ones.

Also in the active or forced clumping of these bacteria the Gaertner bacillus stands alone. The clumps of this organism are compact and quite rarely contain moving elements. The other two species give rise to clumps which are loosely interwoven at many angles and may contain one or more moving individuals. Large clumps of the B. typhosus and paratyphosus appear wavy and streaked, while corresponding masses of the meat poisoner are finely grained. This last observation may be explained on the ground that the flagella are probably fewer and shorter on this meat-poisoning bacillus, thereby allowing closer approximation of the single cells. This is, however, by no means always true of these species.

These differences are not marked enough to be diagnostic, and are only noticeable when several comparative tests are made.

The Action of Typhoid Serum with B. typhosus and B. paratyphosus. Only 12 of the 94 sera of the clinical enteric fever cases showed any agglutination of the paratyphoid organism. Four of these 12 cases were proven to be true typhoids by blood culture, the entire 12 cases giving diagnostic reactions with the B. typhosus.

Cases No. 56 (typhosus 250, paratyphosus 50), No. 59 (typhosus 250, paratyphosus 50), No. 66 (typhosus 50, paratyphosus 50), No. 86 (typhosus 250, paratyphosus 50), No. 111 (typhosus 50, paratyphosus 50), and No. 117 (typhosus 500, paratyphosus 50), it will be seen, reacted only as high as 1:50, while cases No. 33 (typhosus 250, paratyphosus 250) and No. 169 (typhosus 250, paratyphosus 250) reacted at a dilution of 1:250. The serum potency reached 1:500 in cases No. 78 (typhosus 500, paratyphosus 500), No. 123 (typhosus 500, paratyphosus 500), and No. 137 (typhosus 500, paratyphosus 500). In only 1 case (from which the typhoid bacillus was obtained in the blood) was the dilution for the paratyphoid higher than for the typhoid bacillus. Chart I. gives the

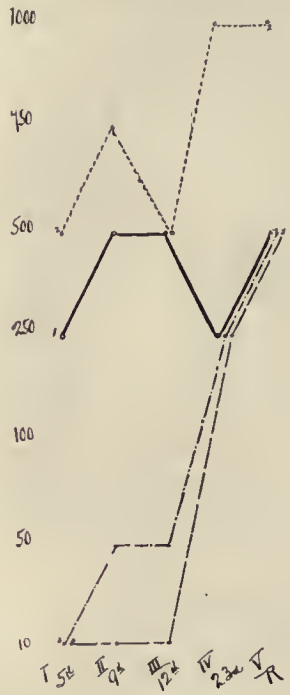
dilution limits for these 12 cases, and case No. 179 will show the exception. Chart II. gives the curve for this case. This was a prolonged typical attack of enteric fever, and a blood culture was taken because of the marked paratyphoid reaction. As stated above, only the B. typhosus in pure culture was found. The patient was a private one and, the results being considered final, no further study was allowed. That this was a mixed infection may be surmised, especially when we take into consideration the low percentage of paratyphoid reactions in true typhoid fever, but such an opinion may not be made positively. The cases in this series which were proven typhoids are No. 78 (typhosus 500, paratyphosus 500), No. 86 (typhosus 250, paratyphosus 50), No. 117 (typhosus 500, paratyphosus 50), and No. 179 (typhosus 500, paratyphosus 1000). It will be seen that in 6 cases these two organisms were clumped to the same limit, while in 5 the typhoid bacillus was affected in higher dilutions, and in only 1 case was the reverse true.

CHART I.—POSITIVE PARATYPHOID REACTIONS.

		Typhoid Bacillus.							Paratyphoid "A."						
No.	Day.	10	50	100	250	500	750	1000	10	50	100	250	500	750	1000
33	?	+	+	+	+	+			+	+	+	+			
56	4	+	+	+	+				+	+					
59	12	+	+	+	+				+	+					
66	6	+	+						+	+					
T. F., 78	9	+	+	+	+	+			+	+	+	+	+		
T. F., 86	?	+	+	+	+				+	+					
111	8	+	+						+	+					
T. F., 117	12	+	+	+	+	+			+	+					
123	8	+	+	+	+	+			+	+	+	+	+		
137	?	−							+	+					
		+	+	+	+	+			+	+	+	+	+		
		+	+	+	+				+	+					
169	11	+	+	+	+				+	+	+	+			
T. F., 179	5	+	+	+	+				+	+	+	+	+		
(Vide Chart No. 2)	9	+	+	+	+	+			+	+	+	+	+	+	
	12	+	+	+	+	+			+	+	+	+	+		
	23	+	+	+	+				+	+	+	+	+	+	+
	R.	+	+	+	+	+			+	+	+	+	+	+	+

R. indicates relapse.

CHART II.—CASE 179. TRUE TYPHOID FEVER



Curve for B. paratyphosus "A" - - - - - (2)
Curve for B. typhosus ——————— (1)
Curve for B. enteritidis —— —— ——
Curve for B. paracolon or paratyphoid "B" —— . —— . ——.

THE ACTION OF SERA OF ANIMALS IMMUNIZED AGAINST B. TYPHOSUS AND B. PARATYPHOSUS. The animals were inoculated in the usual manner, injections being made every eight days and bleedings done two days after the second, fourth, and seventh injections. This time of bleeding was adopted to obtain the agglutinating body produced by the first, third, and sixth injections respectively, because at that time, ten days after the injection, it has about reached its climax, and passed the temporary diminution following the immediately preceding injection, and probably called into greater activity by this immediately previous inoculation.

The serum of the rabbits immunized against B. typhosus had no effect upon B. paratyphosus except in one rabbit; when the serum had a homologous potency of 1:10,000 a reaction of 1:10 was observed. The serum of the animal inoculated with B. paratyphosus clumped the typhoid bacillus, in dilution of 1:10, throughout the process of immunization—that is, at all three bleedings. The limit for the latter remained the same whether the potency for the former was 1:10 or 1:5000, as was the case at the last bleeding.

Furthermore, the writer has had for over a year four samples of Parke, Davis & Co.'s antityphoid serum; this clumped the B. typhosus to very high limits, but had no effect whatever on the B. paratyphosus.

The Action of Typhoid Serum with B. typhosus and B. enteritidis. Of the 94 cases of clinical enteric fever, 82 (87 per cent.) gave a positive reaction with the B. enteritidis (Gaertner) at some time or other during their course. This fact has been known for a long time, but the precedence of the reaction was the point for solution. Nineteen of these 82 cases were tested more than once, and 14 of these 19 gave a reaction to the Gaertner bacillus which appeared before the reaction to the B. typhosus, or was obtainable in higher dilutions. (Chart III.)

CHART III.—CASES WITH HIGH VALUE FOR BACILLUS ENTERITIDIS.

Case No.	Occasion and day of disease.	B. typhosus.				B. enteritidis.			
		1:10	1:50	1:250	1:500	1:10	1:50	1:250	1:500
21	1st–8th	+	—			+	+	+	+
	3d–25th	+	+	+	+	+	+	+	—
50	1st (?)	—				+	+	+	+
	2d (?)	+	+	—		+	+	+	—
83	1st (?)	+	—			+	+	—	
	2d (?)	+	+	+	+	+	+	+	+
58	1st, 2d	+	+	+	—	+	+	—	
	2d–9th	+	+	+	+	+	+	—	
89	1st–4th	+	—		+	+	+	+	+
	2d–11th	+	+	—		+	+		
91	1st–9th	—				+	+	+	+
	2d–15th	+	+	+	—	+	+	—	
116	1st–8th	—				+	+	+	—
	2d–14th	+	+	+	+	+	+	—	
124	1st–7th	—				+	+	—	
	2d–10th	+	+	+	+	+	+	+	+
126	1st–8th	+	—			+	+	+	—
	2d–11th	+	+	+	—	+	+	—	
137	1st (?)	—				+	+	+	+
	2d (?)	+	+	+	+	+	+	—	
	3d (?)	+	+	+	—	+	+	—	
198	1st–9th	—				+	+	+	+
	2d–20th	+	+	+	+	+	+	—	
127	1st–6th	—				+	+	+	+
	2d–13th	+	+	—		+	+	—	
199	1st–8th	—				+	+	+	+
	2d–15th	+	+	+	+	+	+	+	+
200	1st–13th	—				+	+	+	+
	2d–20th	+	+	—		+	+	—	

Especially is this marked in cases Nos. 21, 50, 89, 91, 116, 127, 137, 198, 199, and 200. De Nobele noted in animal experiments that the typhosus agglutinins disappeared more slowly after an infection than did the enteritidis agglutinins. If we examine the limits of dilution in 70 cases of typhoid fever, for these two organisms according to first, second, and third week of this disease, we will find an analogous curve. The remaining 12 cases are so indefinite in their history as to nullify attempts to date them, even approximately: 24 cases first week, limit for B. typhosus 222, B. Gaertner, 325; 43 cases second week, limit for B. typhosus 275, B. Gaertner 260; 3 cases third week, limit for B. typhosus 500, B. Gaertner 175.

Among those 14 cases examined more than once, 9 (64 per cent.) exhibited a superior potency for the meat poisoner

at the first examination, followed by a decline of this value and a corresponding rise in the limit of dilution for the B. typhosus. In the five exceptions to this the limits at the first and subsequent examinations were practically the same. This seems to indicate that agglutination of the enteritidis appears early and disappears likewise early, while the special clumping body of the B. typhosus appears somewhat later and persists for a longer time than the substance which affects the coagglutinated bacterium.

Additional proof of this is given by a study of sera of animals immunized against these bacilli. The antityphoid serum at the first examination—*i. e.*, after the second inoculation—clumped the B. enteritidis much more highly than the homologous species, but at the second test the dilution limits were the same for both. At the third trial the limit for the meat poisoner had remained as before, while that for the typhoid bacillus had forged ahead, in one rabbit fivefold, in another tenfold.

The previously mentioned therapeutic serum agglutinated the B. enteritidis to about a half the limit of the typhoid organism. In the microscopic preparations of the lower dilutions of these tests, small swellings and depressions of their envelopes could be discerned in single cells of both species. These grew, upon standing, into clear spaces within the capsules, which, on examination with the oil immersion, appeared finely granular. This was probably a lysogenic process. This distortion and vacuolization was not observed in the tests with the B. paratyphosus and this serum, nor during the experimental immunization by the writer.

The serum of the anti-Gaertner rabbit possessed the same value at first for the B. enteritidis and typhosus. At the second bleeding the homologous bacillus was agglutinated twice as highly as the coagglutinated species, while at the third test this serum contained ten times the amount of agglutinin for the organism used for injection.

In the 12 cases that showed an agglutination of the B.

paratyphosus there was also clumping of the meat poisoner, and since these cases gave a coincident reaction to the B. typhosus, no deductions can be drawn. There was no relationship existing between the relative values of the 12 sera with regard to these species. The antisera of these two organisms showed no mutual interaction above the dilution of 1:10.

As control experiments, 6 samples of normal blood, 8 samples of blood of cases with fermentative diarrhœas of childhood, 4 cases of bloody diarrhœa in adults (in which the dysentery group was supposedly the cause), 3 cases of chronic constipation, 2 cases of gastroenteritis, were tried with all these species. In no one was there a reaction above 1:10.

These studies seem to justify the following conclusions:

1. That only a small proportion (12.5 per cent.) of typhoid-fever sera show an agglutinative effect upon the B. paratyphosus (A.).

2. That a great majority of typhoid fever sera give a concomitant reaction with the B. typhosus and B. enteritidis.

3. That early in the attack the reaction to the meat-poisoning bacillus is greater than to the B. typhosus, and the limit for the former declines as the special reaction to the latter rises during the advancing infection.

4. That the behavior of the agglutinins in typhoid fever blood to all the organisms investigated is essentially the same as in the blood of immunized animals.

5. That the experiments show a close relationship of the agglutinating bodies of the B. typhosus and B. enteritidis, or a similarity in their binding power to certain products of body cells that form these agglutinins.

6. That there is no similarity or relationship in the agglutinins or binding powers of the B. typhosus and paratyphosus (A.), and that the coagglutination of these species may be accounted for by group agglutinins or by previous infection. The possibility of a mixed infection is not entirely nullified.

It has lately been declared by Parke and Collins, who worked on the Shiga group and its serum relations, that the species used for immunization is agglutinated in higher dilutions throughout than a coagglutinated organism is. In these experiments the antityphoid sera clumped the B. enteritidis more strongly at the first test than the homologous organism, while the antienteritidis sera gave as high (or higher) values for the organisms injected as for the B. typhosus. The strains used were all good agglutinators and possessed excellent agglutinogenic power; they were not affected by the rabbit's blood at 1:10 before injections were begun. To explain these results, we may hope for assistance in the mechanism of the production of agglutinins.

The body cells which produce agglutinins, or any other antibodies, cannot be supposed to react immediately to all kinds of chemical matter with which they come into contact, and must therefore be considered as possessing receptors of simple nature. The simple receptors become specialized after having been once attacked by a certain influence, and we can safely assume that thereafter they would only react to the same stimulus or one akin to it. The general receptors that have not become specialized, but which have increased their activity because of the distraction of specialized receptors, might therefore have a greater influence than normally upon these kindred but not identical stimuli.

To apply this to the foregoing experiments we may consider antityphoid sera as reacting to the B. typhosus because the stimulus is homologous, and as reacting to B. of Gaertner because the stimulus of this species is similar; therefore, it may be said that an agglutinating serum contains a special agglutinin to the injected organism, and an indefinite amount of normal agglutinin. The special agglutinin is composed of some elements which are truly specific, and other elements which find a mutual activity with a heterologous bacterium. Now, assuming that the non-specific elements act upon their mutual elements in the heterologous bacterium, aided by the probably increased activity of the

normal agglutinins, the result would probably be greater with this bacterium than with the homologous species early in the infection. Before the bonds of union between the individual components of the specific and shared portions in the special serum had become firm, the binding power of the shared or common elements might be greater for the heterologous bacterium. Later, however, the bonds of union of the integral parts of the special serum may have become so firm that the weaker binding power of the coagglutinating bacterial elements cannot attract any combination with their mutual relations in the shared portion of this special serum; therefore, it may be that the high dilutions that clumped the B. Gaertner at the first bleeding of the antityphoid rabbit resulted from a strong avidity of the mutual elements of the antityphoid serum and the meat-poisoning bacillus, aided by activity on the part of the non-specialized normal agglutinin. (Indeed, in three controls from cases in which none of these organisms could have been active, a 1:10 reaction with the B. Gaertner was noted.) Later, however, the value of the serum for the meat poisoner did not increase, because the constituents of the special antityphoid serum were firmly combined and reacted more strongly to the homologous elements of their bacteria.

On the other hand, to explain why the anti-Gaertner serum clumped itself as high or higher than the B. typhosus, we must assume that the binding power of the common elements in this special serum and in the typhoid bacteria was less than the strength of the bonds of union between all the elements of the special serum.

Antityphoid serum will behave with the B. coli communis as it has in these experiments with the B. enteritidis, and the anticolon serum resembles the anti-Gaertner when tried with the B. typhosus.

The effect of the antityphoid serum on the paratyphoid organism may be limited to the ability of the abnormally active, non-specialized receptors to affect it, while the special

receptors find no mutual activity present. Group agglutinations are, therefore, due to kindred combining powers of agglutinin on the one hand and agglutinable body (or agglutinogen) on the other, the difference in dilution necessary for reaction being proportionate to the quantities of their relatively mutual constituents.

The following, for instance, is Durham's hypothesis. He represents, for example, the B. typhosus agglutinin as A+B+C+D+E, and its agglutinogen (agglutinable substance) as a+b+c+d+e. B. of Gaertner agglutinin he indicates as C+D+E+F+G+H, while the bacillary agglutinable body is correspondingly c+d+e+f+g+h. Now, when homologous agglutinin is added to the components of the bacillary agglutinogen, the maximum result occurs. But if the agglutinin and agglutinogen (B. typhosus, A+B+C+D+E)+(B. Gaertner, c+d+e+f+g+h) be not homologous, a partial combination of the elements (c, d, and e) takes place and the limit of the reaction would depend upon the relative amount (in factors?) of those mutual constituents, and their avidity for one another. Possibly the other elements, not susceptible to the employed agglutinin, may be affected by the highly active, non-specialized receptors of the agglutinating serum.

Now, suppose the agglutinogen of another organism be made of e+f+g+h+j+k and its agglutinin be E+F+G+H+J+K (Durham's article, B. of Hatton, and, to modify Durham's argument to apply to these experiments, let us suppose that this formula represents the B. paratyphosus [A.]). The agglutinin of the typhoid bacillus and the agglutinogen of B. paratyphosus (A.), therefore, have only one common element, E.; so that were they combined the strength and concentration of the serum used would have to be so much greater to obtain a result. Furthermore, Durham supposes that any constituent, either of an agglutinin or agglutinable body, is not necessarily in the same quantity as the other constituents, or the same as that particular element would be in another serum or culture. If its amount might vary,

so might its chemical combining powers, and the reaction described between heterologous agglutinin and agglutinogen might not occur at all.

The exceptions (twelve) noted in the experiment with typhoid sera and paratyphoid organisms may be explained on the basis that the particular strains of organisms, which were the etiological moment in these twelve cases, gave rise to an agglutinin which contained elements mutual to the strains of paratyphoid organisms used, or that the binding powers of these individual constituents may have been very active.

Another possible explanation of these exceptions is a previous infection (typhocolon, since we are considering them) of the intestines, gall-bladder, or other location, which produced and left in the blood traces of an agglutinin which had individual elements that found a mutual activity in the elements of the bacillary composition of the paratyphoid strains used for the agglutination tests.

It appears to the writer that the last explanation offers a suggestive solution to those cases giving a high clumping value with a coagglutinated organism.

The theory of partial similarity of two agglutinins or agglutinogens seems to present a more satisfactory explanation for the lower dilution limits of coagglutination.

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DIAGNOSIS BY MEANS OF THE FORMED ELEMENTS OF THE BLOOD.[1]

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The title of my paper (which was suggested by the Business Committee) suggests for discussion the four following subjects:

1. The absolute diagnosis of disease by means of the formed elements of the blood.

2. The analysis of the blood as a part of a thorough examination of a patient.

3. The thoroughness of the blood examination. It should not be simply the estimation of the hæmoglobin and the enumeration of the corpuscles, but it should also include a thorough morphological study, and, where indications are present, a complete chemical and bacteriological analysis.

4. The consideration of such a thorough examination, in connection with the complete history of the case, with the duration of the disease, with the results of other clinical methods, and with possible complications.

1. I know of no disease that can be diagnosed absolutely by means of the formed elements of the blood. Even in malaria the diagnosis depends upon the finding of the parasite which infects the erythrocyte. Likewise, to be included in this statement, are the extra corpuscular parasites found in relapsing fever and in filariasis. An apparent exception to this statement is presented by leukæmia. The blood picture in a typical case of splenomyelogenous leukæmia, with a high corpuscular (leucocytic) count, a high percentage of myelocytes, and a marked degeneration of the erythrocytes is scarcely to be mistaken for any other disease. In lymphatic leukæmia, however, one is not as sure of the diagnosis as one is in the mixed (splenomyelogenous) form of the disease, when a high count of the leucocytes is present, as other conditions may show similar blood changes. Cases of sarcoma have presented blood pictures identical with those of lymphatic leukæmia, and the lymphocytosis found in pertussis (Frölich and Meunier) and in pneumonia of children (Cabot) is at times difficult to distinguish from this form of leukæmia with low leucocytic counts. Furthermore, in both forms of leukæmia—splenomyelogenous or lymphatic—an intercurrent disease may so alter the blood picture, by changing the type of the leucocytosis, by causing the number of leucocytes to be reduced within normal numbers, or by changing the blood so that it suggests a simple secondary anæmia, that the usual pictures in these diseases are entirely lost.

The intercurrent diseases reported as producing this change are: typhoid fever (Eisenlohr), miliary tuberculosis (Quincke), chronic tuberculosis (Stintzing), icterus (Mosler), erysipelas (Freudenstein), purulent pleuritis (a later complication of articular rheumatism gave no change, Heuck), sepsis (Frölich, Müller, Fränkel, Cabot), influenza (Kovacs), pneumonia (Thorsch), "tubercular infection" (Zappert, Lichtheim). Here may also be included the effects of drugs upon the blood findings in a number of typical cases of leukæmia. Taylor, and McCrea report cases—the former three and the latter one—in which the therapeutic action of arsenic, even after relapses, brought the blood back to nearly a normal condition. The splenic tumor in these cases did not disappear as the blood picture returned to normal. Osler, Stengel, and Rensselaer report similar cases.

Strattmann and Huesner each report a case of leukæmia in which the abdomen was opened, the blood picture afterward returning to normal. In the latter's case a relapse is recorded. Further, the picture of leukæmia has changed in the ante-mortem stages of the disease, the change here being probably due to terminal infections or to circulatory disturbances.

[1] Read before the Pathological Society of Philadelphia, February 27, 1902, Symposium on Blood.

2. That the examination of the blood is an essential and valuable part of a thorough examination of a patient needs no comment. Careful and thorough clinicians, medical men or surgeons, have long since learned the importance of blood examinations. Such general expressions about the blood as "of scientific but often of no practical value, and may misguide the surgeon," only show that the authors of such statements have a very, very limited knowledge of the subject upon which they attempt to write, or that they seek one sign alone upon which to make their diagnosis, and failing, as they have undoubtedly failed, they now condemn entirely the value of blood examinations. On the other hand, the man who makes all his diagnoses from the cover-glass preparation—from scarlet fever to obscure sarcomata and distinguishing bacteria—will inevitably make as many mistakes as his colleagues who do not know the value of that which they condemn.

3. The blood analysis should be a thorough one. This is a rule which is, unfortunately, too often overlooked. Attracted by the apparently simple technique of blood examinations, many have sought this field with the idea that corpuscular counts and estimation of the hæmoglobin would make a diagnosis easy and rapid. The numerous tables of corpuscular counts, which have been compiled to convince the profession that in certain diseased conditions the corpuscles should be found in definite numbers per cubic millimetre, have surely failed their purpose. Thus it will be seen from Cabot's tabulated counts of seventy-two cases of appendicitis, that Case I. showed 52,000, and Case LVII. 9000 leucocytes per cubic millimetre; both cases showed pus at the time of the operation. In the purulent cases reported by Da Costa one showed a leucocytosis above 50,000 cells per cubic millimetre, while in seven other purulent cases the leucocytic count varied between 5000 and 10,000 per cubic millimetre. These counts represented practically the same pathological condition at the time of the operation—appendicitis, with abscess formation—and yet the leucocytic counts varied between very wide margins.

That the formed elements of the blood should be studied from their morphological stand-point, as well as from the number of corpuscles per cubic millimetre, is well attested by comparing those diseases which, from a clinical stand-point, are at times difficult to separate. Time will not allow a complete analysis or comparison of all these diseases; therefore only the most important will here be considered.

The so-called Essential Progressive Pernicious Anæmia *versus* Carcinoma. From the clinical stand-point these conditions may not be distinguished by the physical signs and the symptoms they present, nor can they be distinguished in some cases after the usual blood examination of corpuscular counts and hæmoglobin value. Yet, as a rule, cases of progressive pernicious anæmia have a very low erythrocytic count when they first come under observation. This count is usually in the neighborhood of 2,000,000 cells per cubic millimetre. The leucocytes per cubic millimetre are normal or their number is slightly below the normal figures. The total amount of the hæmoglobin of the blood is reduced, often to a very marked degree. However, this reduction in the coloring matter is rarely as great as it is in other conditions with equal corpuscular counts. On the other hand, in the majority of cases of this disease an increased richness of hæmoglobin per cell is to be found; this increase may reach to twice as much per cell as is found under normal conditions. In 183 cases collected from various authors of this disease 72 per cent. showed an increased corpuscular richness in hæmoglobin. The color index in these cases averaged 1.19.

In carcinoma, as a rule, the erythrocytic count is rarely low when the case is first observed, and even in advanced cases with severe cachexia the counts seldom fall below 1,000,000 cells per cubic millimetre. The leucocytes may vary in number per cubic millimetre, according to the size, location, and the rapidity of the growth. When the erythrocytic count is very low the leucocytic count almost invariably shows an increase (Cabot). However, cases of carcinoma may show, as stated above, the same results in the estimations of corpuscular counts and hæmoglobin as cases of progressive pernicious anæmia. When the counts and the hæmoglobin value are not suggestive of either disease the study of the morphological changes in the cover-glass preparation may add very much to distinguish the two diseases.

Progressive Pernicious Anæmia. Marked erythrocytic degeneration is an early and constant finding in cases of progressive pernicious anæmia. Poikilocytosis—an irregularity in the shape of the cell—is a degeneration which is seen early in the disease, and very soon becomes marked in the progress of the case. Aniscytosis—an irregularity in the size of the cell—is noted early, the macrocytes or the larger cells, as a rule, predominate. Polychromátophilia—a condition where the ery-

throcytes stain homogeneously with a combination of several stains—is invariably to be found, and it usually accompanies the enlargement of the cell. Basic granulation, or granular degeneration of the erythrocyte, is almost always found. These degenerated cells may be very numerous; in some severe cases the number may be equal to the excessive numbers found in chronic lead poisoning. The smaller cells—the microcytes—may show an unusual depth of staining power with the acid stain. Nucleated erythrocytes—erythroblasts—are always present in the peripheral circulation; often they are very numerous, and all types are to be seen—normoblasts, macroblasts, microblasts. Macroblasts almost invariably predominate; these cells are rarely to be seen predominating in conditions simulating this disease, except in bothriocephalus anæmia. Karyokinesis is rarely seen in these larger cells; if found with the above blood picture it forms almost a pathognomonic finding of progressive pernicious anæmia.

The corpuscular richness in hæmoglobin, as stated above, is, in the majority of cases, increased; this is seen histologically by the deeper staining of the cells than is normal. Many of the cells are larger and flatter, and therefore contain more coloring matter. The flatness is due to the fact that the bi-concavity is lessened or entirely absent in many of the cells.

The leucocytes may be present in normal numbers, or as usually the case, a leucopænia—a decreased number of leucocytes per cubic millimeter is found. The reduction in the number of leucocytes is usually due to a decrease in the polymorphonuclear leucocytes; consequently, a relative lymphocytosis is the rule. Schrieber has noted an increased number in the divisions of the nucleus of the polymorphonuclear cells which, he suggests, is characteristic of the disease. This can scarcely be accepted, as other conditions—sepsis, so-called splenic anæmia, and carcinoma—may show the same condition of the nucleus.

Carcinoma. In this disease rarely are the degenerative changes in the erythrocytes, as above noted, in such evidence. Poikilocytosis is only moderate even in the severe cases, and rarely does it become marked. Aniscytosis is moderate in degree; the microcytes usually outnumber the macrocytes. Granular degeneration and polychromatophilia are to be seen in moderate degrees in the severer cases. Nucleated erythrocytes are almost always present in advanced cases. Normoblasts and macroblasts are found; the latter are, however, infrequent; rarely indeed, if ever, is the larger cell to be found in excess of the normoblasts. Deficiency in hæmoglobin is the rule; histologically, this is noted by deficiency in stain and an enlargement in the normally pale central area of the cell.

In this disease a leucocytosis is usually present; however, tumors of slow growth, localized or away from vital parts, may not produce an increase in the leucocytes. In cases where these cells are not increased in numbers the predominance of the polymorphonuclear leucocytes is the rule.

Another instance in which this same difficulty arises is that of chlorosis *versus* secondary anæmias. The distinction between chlorosis, on the one hand, and the numerous conditions which come under the class of secondary anæmias, on the other, is frequently very difficult, if the findings of the blood alone are considered. Especially is this true if one is dealing with a slight grade of anæmia. In both conditions the corpuscular counts may be the same, and the hæmoglobin slightly or only moderately reduced.

Chlorosis. In chlorosis the deficiency in the coloring matter and an undersized condition of the erythrocytes are the characteristic changes, and in moderately severe cases these may be the only abnormal changes in the blood. Usually, when there is a great decrease in hæmoglobin the erythrocytic count generally falls; rarely, however, below 3,000,000 cells per cubic millimetre. The other degenerative changes in the erythrocyte are not marked. In the severer cases a slight poikilocytosis, and a few granular degenerated cells may be found. Nucleated erythrocytes may at times be seen; these are of the normoblastic type. The number of leucocytes per cubic millimetre is generally within normal boundaries. A relative increase in the lymphocytes is usually to be found.

Secondary Anæmia. In secondary anæmias, which may be produced from various causes, the blood may show a more or less similar picture to chlorosis. The erythrocytes are reduced in numbers, and the degenerations in these cells may be only very slight, or marked, according to severity and to the nature of the cause. The hæmoglobin is usually reduced slightly more than the reduction of the erythrocytes. The leucocytes are generally increased in number; this, however, depends upon the cause. A normal number of leucocytes, or a normal number with an increase of the polymorphonuclear leucocytes, or a leucopænia, may be found. The difficulty in diagnosis arises only in the moderately severe cases, and then the blood picture of a moderately severe case of chlorosis may

be seen in cases of secondary anæmia from almost any cause.

Toxic Substances. These substances are mentioned here simply because they produce changes which are similar to the changes found in the blood of the primary or secondary anæmias mentioned above. The action of toxic substances or of drugs in toxic doses upon the blood has lately received considerable attention. These substances produce a pronounced change in the erythrocytic count and marked degenerative changes in these cells. The action upon the leucocytes—*i. e.*, the production of a leucocytosis or of a leucopænia varies according to the substance or to the class of substances encountered. From the view of hæmatology, these toxic substances should receive more careful study both from a clinical as well as from an experimental stand-point, as they will undoubtedly throw some light upon the etiology of some of the obscure anæmias.

Some of these substances which have been partially studied are: snake poisons, poisoning from toadstools, nitrites, guaiacol, nitrobenzol, potassium chlorate, antifebrine, antipyrine, pyrogallol, pyrogallic acid, pyrodine, corrosive sublimate, aniline. All of these have a direct action upon the erythrocytes, causing a marked reduction in their numbers within a very short time after toxic quantities have been ingested. Ehrlich and Lindenthal, in one case of poisoning from nitrobenzol, were able to make a complete study of the blood from a few hours after the drug produced the first symptoms of its toxic action to death. The erythrocytic count fell rapidly to 900,000 cells per cubic millimetre before death on the nineteenth day. All forms of erythrocytic degeneration were noted and became marked early in the course of the case. Nucleated erythrocytes were seen early, and were present in great numbers; all types were seen. The leucocytes varied in numbers; at first there was no increase; later, after the ninth day, a mixed leucocytosis was present, and this was so marked at times that the blood picture was not unlike leukæmia.

The effects of lead salts, either as a drug or in lead workers, have received careful study of late, from the fact that this metal brings out an almost characteristic change—in granular degeneration of the erythrocyte. The usual blood findings in cases of saturnism are a mild chlorotic anæmia, with or without a mild leucocytosis. The constant and almost characteristic finding in these cases is the presence of the granular degeneration in the erythrocytes. This peculiar degeneration is seen very early, even before subjective symptoms are noted. (Experimentally within twenty-four hours, after 7.5 grs. were taken.) The number of degenerated cells increases with the severity of the intoxication and they disappear with the elimination of the metal from the system. This form of degeneration also appears in progressive pernicious anæmia, leukæmia, and slightly in some other common conditions. However, these conditions rarely present symptoms which might be mistaken for cases of saturnism.

4. Having a complete analysis of the blood, this complete analysis should be considered *only* with the results of the complete clinical findings, the history of the case, the duration of the malady, and the presence of possible complications.

The differential diagnosis between chlorosis and secondary anæmia cannot be made absolutely—and it can be suspected only in a very small percentage of cases—from the blood examination alone. But when the blood examination is coupled with the results of other examinations, the history of the case, and the presence or absence of sufficient cause to produce a secondary anæmia, the diagnosis becomes comparatively easy. In other words, the diagnosis here must be made by exclusion.

The differential diagnosis between progressive pernicious anæmia and carcinoma, especially carcinoma of the stomach, may be approached only from the blood in some cases. And here a *complete* analysis of the blood must be made before the consideration of the blood can be of any value. Cases are observed, however, where a differential diagnosis between these two diseases cannot be made from the blood nor from the blood and clinical findings, nor by any other methods known in medicine today. Fortunately, these cases are rare.

That the results of a complete analysis of the blood should be considered *only* in connection with other complete clinical data applies with no less importance to the class of cases which might be included within the broadest meaning of the term septic infection. The rule in this class of cases is a leucocytosis if the patient is reacting. In slight infections or in severe infections (when the patient is overwhelmed with the products of septic infection and not reacting) no leucocytosis is observed.

Certain well-known facts should be observed in studying the blood in cases of septic infections before the results of a complete blood examination can be of any possible value.

A. That in the earliest stages of an inflammation, when simple engorgement of the vessels and begin-

ning exudation alone are present, as well as in the later stages when pus is found, a leucocytosis is the rule. Exceptions to this rule are infections from typhoid, influenza, tuberculosis, etc. Hence slight catarrhal inflammations, as well as phlegmonous conditions, may be accompanied by an increase in the number of leucocytes.

B. The degree of the leucocytosis may go hand-in-hand with the severity of the inflammatory process; and this may perhaps be considered a general rule. A much better rule in regard to the degree of leucocytosis is: Every patient is a law unto himself. For example, a small stitch abscess produced 20,000 leucocytes per cubic millimetre in one patient; while in another a general peritonitis from a ruptured tubal abscess, with "quarts of pus," produced 19,000 leucocytes per cubic millimetre. Two cases subjected to the same operation—*i. e.*, ventral suspension and curettement—had practically the same number of leucocytes before operation—*i. e.*, 9760 and 9440 cells per cubic millimetre; each reacted to the operation (post-operative leucocytosis), the first increased to 17,000 and the second to 24,520 leucocytes per cubic millimetre.

C. After the acute or infiltrating stages of the inflammation have subsided the leucocytic count decreases. This is true, whether the exudate is absorbed or walled in—localized. Considering this known fact, the common expression, "I found ounces of pus, and without any indication of it in the blood," scarcely seems warranted.

D. Cases of low leucocytic counts (normal for these patients), counts of 4000 to 5000 cells per cubic millimetre, may show a marked leucocytic reaction to irritations—as an operation—without the increased number of cells exceeding the boundaries of the normal leucocytic count. An increase of over 75 per cent. in the leucocytic count has been observed in this class of cases, the count still coming within normal or practically normal limits. The leucocytic count, or the blood analysis, if considered simply as an estimate of the number of cells per cubic millimetre, is, of course, misleading in this class of cases. If, however, a differential count of the leucocytes were made in such cases, and from it the absolute count of the polymorphonuclear cells determined, an increase of these cells above their normal numbers per cubic millimetre would be of almost as much value as an actual increase in the total number of leucocytes.

Case XXIII. ("Observations of Blood Changes following Cœliotomies," *University Medical Magazine*, June, 1900) showed before the operation, which was for a ventral suspension of the uterus: leucocytes, 4885 per cubic millimetre, and 71.5 per cent. of polymorphonuclear leucocytes, which equalled an absolute count of these cells of 3493 per cubic millimetre. Within five hours after the operation the leucocytic count numbered 8680 cells per cubic millimetre, the polymorphonuclear leucocytes had increased to 81.4 per cent., which equalled an absolute count of these cells of 7066 per cubic millimetre. The reaction in this case of a primary low leucocytic count to the operation was an increase of 3795 cells per cubic millimetre in the total leucocytic count, or a 77.6 per cent. increase in the leucocytes. The polymorphonuclear leucocytes showed a relative increase of 9.9 per cent., or an actual increase of 102.3 per cent., which equalled an increase of these cells to 3573 cells per cubic millimetre as the result of the operation. This case shows the value of a complete analysis of the blood, and at the same time the value of considering the case from the point of view of the surgical intervention in its relation to a leucocytosis. Had a count of this case been made after the operation, and the blood not further studied, it might have been thought that it was an exception to the general rule of a post-operative leucocytosis, *i. e.*, that it had not reacted to a cause that usually produces a leucocytosis.

The polymorphonuclear leucocytes alone may show a relative or an absolute increase, or both, in their number, during the course of a disease or during the convalescence of a patient from a surgical operation, which increase is indicative of alterations in the condition of the patient.

Case XXIV. (Same series as above.) Operation, ventral suspension of the uterus. The third day after the operation the leucocytic count numbered 12,000 cells per cubic millimetre, polymorphonuclear leucocytes 67.7 per cent., which equalled an absolute count of these cells of 8530 per cubic millimetre. During the night of the third day, after the above count had been taken, the patient developed a slight catarrhal pharyngitis which caused pain on swallowing. The leucocytic count on the next day showed 9000 cells per cubic millimetre; polymorphonuclear leucocytes 73.4 per cent., which equalled an absolute count of 6606 cells per cubic millimetre. In this case the throat condition, which was very slight indeed, caused a relative increase in the polymorphonuclear cells of only 5.7 per cent., while the total number of the leucocytes and the absolute number of the polymorphonuclear cells decreased.

Case I. (Of the same series.) *Exploratory Cœliotomy.* A large tubal abscess was found, but not opened. Before operation the leucocytic count was 12,640 cells per cubic millimetre; polymorphonuclear leucocytes 78.6 per cent., which equalled 9935 cells per cubic millimetre. Within five hours after the operation the leucocytic count was 17,720 cells per cubic millimetre; polymorphonuclear leucocytes were 86.6 per cent., which equalled 15,346 of these cells per cubic millimetre. This count fell gradually for three days to 14,840 leucocytes per cubic millimetre; polymorphonuclear leucocytes 70.0 per cent., which equalled 10,388 of these cells per cubic millimetre. On the fourth day after the primary operation the abscess was aspirated per vagina. In the blood count the reaction to this simple operation was marked; leucocytes, 10,680 per cubic millimetre; polymorphonuclear leucocytes, 83.1 per cent., which equalled 8875 of these cells per cubic millimetre. Here an acutal decrease in the total count of the leucocytes and the polymorphonuclear cells per cubic millimetre, with a relative increase of the latter cells of 13.1 per cent., marked the aspiration of the abscess.

Case VII. (of the same series) shows, in the daily leucocytic count, the result of the removal of a drain to be a decrease of 320 cells per cubic millimetre, a relative increase in the polymorphonuclear leucocytes of 3.3 per cent., and an actual increase of 124 of these cells per cubic millimetre. This case shows practically a stationary condition in the daily count of the leucocytes. The same condition was noted in other cases whenever a drain was removed. Several cases in the series above referred to showed a slight increase in the total number of leucocytes or in the polymorphonuclear leucocytes, during the course of convalescence, which could not be assigned to definite causes. These cases were few, and might have been caused by trivial changes in the patient's condition which were not noted or recognized.[1]

Case II. showed a relative increase in the polymorphonuclear leucocytes in the daily leucocytic count, which increase preceded all other signs or symptoms of a beginning suppuration of the abdominal wound. Frazier and Holloway report a similar finding in their cases.

One blood analysis in a given case may give data of the utmost value, or it may be of very little or of no importance in the case; if, however, two analyses are made within several hours, information may be gained which may precede all other signs or symptoms in the case. This is true in the class of cases referred to above—operative cases, and is, therefore, of great value to the surgeon.

The Duration of the Illness. Acute diseases with high fever do not produce marked changes in the erythrocytes; a slight increase from concentration of the blood may be found, which is very soon lost after the temperature returns to normal or when the fever becomes chronic in its course. The leucocytes in acute infections vary in number and in proportions, according to the nature and the severity of the infection and the resisting powers of the patient. In chronic infections the drain on the blood, as on other tissues of the organism, is more or less marked, depending in each case on the nature of that infection. The duration of the illness is of eminent importance and always to be considered in the class of cases which are infected by the usual pus-producing organisms. The acute stages of inflammation from the action of pus-producing organisms almost invariably show a leucocytosis. When the acute stages have passed, and the process becomes limited or localized; when pus is present and it becomes limited or walled-in (an abscess cannot be said to be walled-in until it has ceased to increase in size)—the leucocytic count may remain stationary; it usually decreases. The decrease in the count is generally gradual; this, however, depends upon the thoroughness with which the diseased focus is isolated from the healthy tissues. A normal leucocytic count, with a relative increase in the polymorphonuclear leucocytes or an absolutely normal count, may be seen in chronic inflammatory cases; however, counts ranging from 9000 to 12,000 leucocytes per cubic millimetre are usually to be encountered in this class of cases. The erythrocytes in chronic pus cases generally show more or less marked changes either in their number or in degenerations of these cells, depending upon the chronicity of the process and the drain on the general system.

In fact, scarcely any disease has greater direct

[1] The cases from which these counts are taken were in the ward of Dr. Charles B. Penrose during the session of 1896–97. The counts were made twenty-four hours before the operation, within five hours after the operation, and then every twenty-four hours until the count returned to normal limits. No attempt was made at that time to complete the daily blood examination; consequently only the erythrocytic and leucocytic counts, estimation of the hæmoglobin, cover-glass spreads, and notes of the cases, were made. Later the differential counts were made and the daily notes compared with the findings in the blood. Since the publication of these cases similar work has been completed by Drs. Frazier and Holloway, with results similar to my own. From these cases the value of comparing the blood findings with what actually takes place in the patient is at once apparent.

action on the blood as a whole than long-standing septic cases.

Complications. During the course of a disease the occurrence of a secondary infection may completely alter the blood findings. How much these superimposed conditions counterbalance the blood changes in one class and exaggerate them in another is a very difficult matter to state. The blood changes in these conditions may be very different, even when the same type of a secondary infection is ingrafted upon dissimilar primary diseases. In tuberculosis the blood findings are only slightly changed from the normal as long as the process remains simple. As soon as a "mixed infection" complicates the original process, however, the blood findings immediately change, and the changes here follow more or less the type which is usually seen in septic conditions. A diverse reaction to a secondary septic infection has been noted in a marked degree in leukæmia. Kormoczi reports a case of splenomyelogenous leukæmia, which, when first observed, showed 100,000 leucocytes and marked degenerations and reduction in the number of erythrocytes. During the observation of the case a septic condition of the nasal cavity developed. The blood examination during the septic infection showed a reduction of the leucocytes to 7300 cells per cubic millimetre (from 100,000) and an absolute disappearance of the degenerations in the erythrocytes, with the exception of a microcytosis.

In typhoid fever the value of the blood examination as an aid to the diagnosis, and during the course of the fever as a help in the diagnosis of complications, is of the utmost value. As an aid in the diagnosis of complications in this disease some knowledge of the previous condition of the blood should be known, for cases are reported with a leucocytosis running throughout the whole course of the fever and without discoverable cause. However, in typhoid fever the occurrence of a leucocytosis is generally assignable to some complication; therefore, before a leucocytosis which may occur during the course of a typhoid fever case can be of any value in the graver forms of complications in this disease all the causes for a leucocytosis in the case *must be considered*. In intestinal perforation a leucocytosis is the rule if the patient is reacting; no leucocytosis, or a decrease in the number of these cells (in the great majority of cases) points to a severe asthenic condition of the patient, and therefore suggests a grave prognosis.

The hourly study of the leucocytes in typhoid fever, to endeavor to foretell a perforation, scarcely seems to be warranted by our present knowledge of the reactions of the leucocytes, during the course of this disease, to treatment and to other complications. It is true that in probably the majority of cases some change in the leucocytic count may precede all other signs or symptoms of a perforation. This change may not be in numbers only, but simply a change in the relative proportions of the different forms of the leucocytes, as in other cases cited above; but it must not be forgotten that the method of treating typhoid fever may play a very important part in increasing the number of leucocytes. The cold bath almost always produces a transient increase in the number of leucocytes, and hemorrhage and phlebitis usually produce a leucocytosis. I do not mean to say that a careful blood examination would not indicate in some way—probably very early—the occurrence of this condition, and therefore be of great value in directing treatment; but the necessity for absolute rest in these cases seems to me of more importance and of greater value in preventing these complications than are the early leucocytic counts, alone, in directing treatment—for the blood changes are only one of the signs which lead in each case to a diagnosis of this complication.

Finally, it must not be forgotten that physiological influences produce definite changes in the blood, and should always be considered and excluded before the possible pathological influences are given serious thought. Important among these are the time of day the examination is made; the influence of muscular exercises; the influence of profuse sweating; the effects of digestion, etc. The therapeutic action of drugs on the blood, as a whole, is more or less important, according to the class of drugs considered. In the individual case a drug may be a prime factor in causing the blood change, or it may lead to ambiguous results if not considered in the individual blood examination.

In conclusion: I have endeavored in discussing the rôle which the blood plays in the diagnosis of disease to present absolute facts, not hypotheses. Certain typical conditions almost invariably produce changes in the blood. These changes may be of a positive or of a negative value in the diagnosis of the disease. In some conditions the blood changes may absolutely clinch the evidence pointing to the diagnosis; in other cases, with our present knowledge, the blood offers absolutely nothing as an aid in the diagnosis. This, however, can be said of any branch of medical or surgical methods of examinations, of which blood examinations are only a part. In any case, blood analyses to be of

any value must be considered *only* in connection with the findings of other methods of examination, the history of the illness, and in the presence of complications.

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THE RELATION OF THE TUBERCLE BACILLUS TO PSEUDOLEUKEMIA [STERNBERG'S DISEASE].*

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The etiology of Hodgkin's disease, or malignant lymphoma, is one of the most elusive problems in medicine; in fact, there are now included under this term a number of conditions most of which are struggling, with slight success, for recognition as disease entities. That certain of the cases are due to a peculiar form of tuberculosis of the lymphatic apparatus has been recognized for a considerable length of time, chiefly as a result of the brilliant article of Sternberg; but such cases have been considered rather as pathological curiosities than as clinically recognizable. The majority of cases have been diagnosed pseudoleukemia, and only the autopsy has revealed the true condition. Indeed, it has required an histological examination, and even careful inoculation experiments (Brentano and Tangl. Sabrazés) before the etiology was clear. In some cases (Kosler, Freudweiler) tuberculosis of some of the other organs has been recognized as a complication, but has not been supposed to be the cause of the pseudoleukemic manifestations.

I have, in a comparatively brief period, had the opportunity of observing four cases of lymphatic tuberculosis that resembled pseudoleukemia, on all of which autopsies were obtained confirming the diagnosis, and all presenting certain common clinical features.

CASE 1.—M. S., white, male, single, an Austrian by birth, and a laundrer by occupation, was admitted to the wards of Dr. William E. Hughes, at the Philadelphia Hospital, April 4, 1901. As he spoke only Polish, a history was obtained with great difficulty. Through an interpreter it was learned that his father and one sister had died of some unknown cause. His mother had died of pneumonia, after having been sick for 7 days; another sister had died at the age of 4. His present sickness commenced 4 months before admission, the first symptoms being a severe cough with expectoration, followed by progressive weakness and loss of weight. A month later he suffered from pain in the back and abdomen, that at times was sharp. He was constantly thirsty, but drinking water increased the pain. He had also had chills. For 3 months he had been on an absolute milk diet. He stated that he had not noticed any enlargement of the abdomen, nor any change in the character of the urine. When admitted it was noted that he was a fairly well developed man. The tongue was moist and slightly coated in the centre. The pulse was regular, rapid, full, and of good force. The peripheral arteries were slightly sclerosed; the pupils reacted normally; the muscles of the eyes showed no alterations, and the mucous membranes were pale. The thorax was slightly flattened; the abdomen bulged slightly in the upper part, especially on the right side. The left lung was normal. The right lung anteriorly showed dulness at the apex gradually diminishing toward the base to a normal note. The respiratory sounds were harsh, especially at the apex. Posteriorly there was also dulness at the apex, diminishing toward the base; some crepitation heard everywhere, and moist, almost bubbling rales at the apex. The heart was normal. The liver could be distinctly palpated, extending a hand's breadth below the costal margin. Its surface was smooth. Pressure caused pain. The extremities were negative.

April 5 the following notes were made: There is profuse expectoration streaked with blood; the eyes are sunken; the skin is an olive color. The right side of the thorax moves less than the left during respiration. Tactile fremitus and vocal resonance are greatly increased at the right apex, and there are numerous crackling rales, The liver extends from the 5th rib to 2 inches below the costal margin, and is quite tender. The spleen is greatly enlarged and extends 6 inches below the costal margin. The sputum was examined and diplococci and staphylococci were found, but no tubercle bacilli. The urine was red, the specific gravity was 1026, a considerable amount of albumin was present, and there were numerous red bloodcells in the sediment. The blood showed: Hemoglobin, 47%; red bloodcells, 4,010,000; white bloodcells, 6000. The differential count gave polymorphonuclears, 74%; eosinophiles, 3%.

April 6. Blood examination gave: Hemoglobin, 50%; red bloodcells, 3,050,000; white bloodcells, 7,200; polymorphonuclear 63%; transitional, 15%; mononuclear 17%; eosinophile, 5%.

April 7. The urine contained albumin in considerable quantity, and blood casts. Specific gravity, 1022.

April 10. Patient is stronger and out of bed; he is greatly emaciated and his expression is dull; he complains of pain in the apices of both lungs. The sputum is copious and rusty, but does not contain tubercle bacilli.

April 11. Patient complains of great weakness.

April 12. A very few tubercle bacilli were found in the sputum for the first time. Patient is weaker than yesterday and complains of great tenderness in the region of the liver.

April 27. The liver and spleen are increasing in size; there is movable dulness in the flanks and fluctuation in the abdomen. The sputum contains numerous tubercle bacilli.

April 29. The ascites has increased enormously and it is impossible to palpate the liver and spleen. There is no dyspnea, but the respirations are very slow (12 to 16). Edema of the lungs developed rapidly and the patient died at 8.30 P. M.

During the stay of the patient in the hospital I had the oportunity, through the kindness of Dr. William E. Hughes, to demonstrate him repeatedly to my ward classes. The diagnosis that at first seemed most likely was pseudoleukemia. Afterwards, when the nature of the process in the lungs was recognized, it was changed to pulmonary tuberculosis with amyloid disease, although later I recognized the

*The tuberculous form of pseudoleukemia deserves to be called Sternberg's disease, because Sternberg was the first to regard it as more than a pathological curiosity, and to attempt to establish its importance by systematic studies.

case as pseudoleukemia associated with the lung condition. I was not at this time thoroughly familiar with Sternberg's article.

The autopsy was performed April 30, 1901, at 12.30 P. M., by Dr. F. J. Kalteyer. The pathological diagnosis was as follows: Tuberculosis of the lungs; chronic pleurisy with adhesions; cirrhosis of the liver; congestion of the spleen and kidneys; tuberculosis of the intestines, and ascites. I quote the following from the notes:

The peritoneal cavity contained 2500 cc. of straw colored fluid, specific gravity 1015. The lower margin of the liver extended 3 cm. below the costal margin; the heart was normal. The left lung was studded with miliary tubercles from the apex to the base. The right lung was densely studded with tubercles, varying in size, the larger ones 3 to 4 mm. in diameter and usually caseous in the centre. The spleen was greatly enlarged, measuring 18x13.5x3.5 cm. It weighed 680 gm. The capsule was thickened and the tissues congested. The kidneys were large, dark, and friable, but showed no gross lesions. The liver was enlarged, measuring 26x21x6.5 cm., and weighing 1990 gm. It was granular, firm, and contained numerous yellow tubercles surrounded by yellowish red liver substance. The small and large intestines contained a number of tubercular ulcers of various sizes. The tissues were unfortunately lost, and microscopical studies could not be made. The condition of the lymph glands was not noted.

CASE 2.—G. G., a negro, 28, a driver by occupation, was admitted to Dr. Musser's wards at the University Hospital on the 24th of May, 1901. He had always worked hard, and his appetite had been good. He indulged moderately in alcohol, and used tobacco to excess. His mother had died at the age of 80; his father is living and well at the age of 70. One sister died at the age of 18 from a "bad cold." One sister and three brothers are living and well as far as he knew. There was no history of tuberculosis, and only an indefinite history of tumor in an aunt. Up to the time of the beginning of his sickness he had always been well and exceptionally strong. About five years ago he had had an attack of pain in the right hip. He had never had any venereal disease, nor any of the ordinary diseases of childhood. Two years ago, while lifting a barrel of oysters, he had felt a sensation of something giving way in the sternum, and 2 days later a tumor appeared near the xiphoid which grew rapidly for a month and then remained stationary in size. It had never been painful, and had never given him any trouble, whatever. A few days later he noticed that the right side of the abdomen was full, and he felt a mass there, which he supposed was a tumor. This also had never been painful, nor given him any discomfort. About a month before admission he noticed some swelling of the feet, and more pain in the back and hip. He had also cough with expectoration, and the day before admission profuse nose-bleeding. On two occasions he had had night sweats and had felt feverish for several days. His physical condition was as follows.

The arteries pulsated vigorously. The superficial lymph glands were not enlarged. A hemispherical tumor covered the lower part of the sternum, extending from the level of the 4th interspace to below the xiphoid cartilage, and from 2 inches to the left, to 1.5 inches to the right of the sternum. It fluctuated, but did not pulsate, and was not affected by respiration or by coughing. It could not be reduced by pressure. It was neither painful nor tender. It was surrounded by a zone of absolute dulness about ½ an inch broad. The upper portion of the thorax was fuller on the right than on the left side, and moved more during respiration. The percussion note was slightly impaired at the right apex. Tactile fremitus and vocal resonance were increased at this place, and there was slight pectoriloquy. Inspiration was slightly harsh and interrupted synchronously with the heart beat; expiration was harsh and as long as inspiration. The left lung was normal. Posteriorly the respiratory sounds were vesicular, more distinct on the left than on the right side. There was a distinct cardiac impulse over the precordium. The apex beat was in the 5th interspace, inside the nipple line, powerful and diffuse. The area of cardiac dulness commenced at the 5th rib in the nipple line, and merged into the dulness of the tumor. There was a systolic murmur heard best at the pulmonic cartilage, and reduplication and accentuation of the second

solute liver dulness commenced at the 6th interspace. T lower border of the liver extended from the anterior s perior spine of the ilium to the junction of the ribs and t left anterior axillary line. It was firm, the surface smoo and not tender. It moved with respiration. The sple was not distinctly palpable, but percussion indicated th it was enlarged. There was slight general anasarca a edema of the legs extending to the knees. The knee jer could not be elicited, but otherwise the nervous system w negative.

The subsequent course of the case was quite uniform. T temperature was very irregular: there was nose-ble almost daily, and this was usually severe and difficult

control. Emaciation progressed steadily, but very slowl The liver gradually decreased in size; on the 5th June it was one inch below the umbilicus, and on the 20t it was barely below. The spleen remained enlarged b auscultatory percussion, and the lower edge was distinct palpable. By the 1st of July the edema of the legs had b come quite severe; on the 14th there was a distinct accum lation of fluid in the peritoneal cavity, and on the 16t pronounced general anasarca. This persisted until deat The stomach was not enlarged. On the 19th of July h became slightly delirious and had a convulsion beginnin in the hands and arms. After this he remained unconsc ous for some time. The muscles were spastic, but the was no paralysis. The pupils were equal and contracte On the 20th he was partially conscious, and able to tak nourishment, although still very restless. On the 21st the was a slight tremor of the hands and some doubtful pares of the left side of the face. When spoken to he answere only in monosyllables. Toward midnight he lapsed in complete unconsciousness, the pulse grew weaker, and h died at 2 A. M. on the 22nd of July.

Throughout the case the urine was examined, at first a most daily and afterward at frequent intervals. On th 25th of June the specific gravity was 1020; albumin, suga and indican were absent; the diazo reaction was neg tive; the sediment contained a few leukocytes, but n casts. Subsequently there was occasionally a faint tra of albumin, constant toward the end; granular casts rare intervals, and faint traces of bile twice. On the 28

the urea was found to be 228 grains in 24 hours (0.9%). On the 24th of May the blood count was as follows: Hemoglobin 50%; red bloodcells 2,300,000; white bloodcells 4080. The leukocytes were counted at frequent intervals, and ranged between 3060 and 4380, with the exception of June 23rd, when they reached 11,400 for some unexplained reason. The hemoglobin decreased at first slowly; on the 20th the blood count was 45%, and 3,500,000. Later the anemia was more severe, and on the 8th of July the count was 20%, and 2,800,000. The differential count on the 28th of June was: Polymorphonuclear cells 81%; eosinophile cells absent; large mononuclear cells 9%; small mononuclear cells 10%. On the 25th of June careful search failed to show the plasmodium of malaria. On the 26th of May the Widal reaction was reported positive, and, on the 3rd of June, negative. On the 29th of May the Justi test for syphilis was negative. As it is of little value in the tertiary stage, this was not considered significant. The sputum contained staphylococci and streptococci, but never any tubercle bacilli. The stomach contents showed diminished acidity (18%); lactic acid was not present. On June 1st the cyst was aspirated and a thick yellow fluid withdrawn, containing some cheesy masses. It also contained numerous compound granule cells, but no bacteria. The chemical examination gave: Reaction, alkaline; specific gravity 1030; albumin 7%; albumoses present; evidently an inflammatory exudate. Tubercle bacilli in particular were not found. Cultures on various media remained sterile. Two guinea-pigs were subcutaneously injected, one of them dying ten weeks later of generalized tuberculosis, the other remaining healthy. On the 20th of June 5 mg. of tuberculin were injected, and the temperature was lower than usual during the following 24 hours. On the 29th Professor Edward Martin incised the cyst, and found it to consist of a cavity filled with cheesy masses, surrounded by a dense fibrous wall. It communicated by a narrow opening with a substernal sinus that was apparently closed. Smears, cultures and inoculations with this fluid, made by Dr. Kneass, were all negative.

The diagnosis of this case presented many difficulties. It presented the syndrome of progressive anemia, enlargement of the spleen and liver, and fever of an extremely irregular type. After typhoid fever and malaria have been excluded, and the negative Justi test and failure to react to antispecific treatment had rendered a diagnosis of syphilis improbable, it appeared that the case must be either one of pseudoleukemia with irregular temperature, or a case of lymphatic tuberculosis, that is, Sternberg's disease. The latter supposition was slightly strengthened by the presence of a symptom of mediastinal tumor described by Smith, which consists of the development of a harsh murmur over the base of the heart, when the patient arches his back. This murmur, distinct from the hemic murmur, constantly heard, was easily elicited. In view of the frequency with which cases of pseudoleukemia prove to be tuberculous, and particularly on account of the irregular temperature, and the extrathoracic abscess (a symptom of lymphatic tuberculosis first described by Askanazy) a positive diagnosis of lymphatic tuberculosis was finally made, before Professor Martin's operation. The autopsy was obtained with great difficulty, and not until 44 hours after death. It was made by Dr. Hendrickson, to whose kindness I am indebted for the following notes:

Intense edema throughout the body. Post-mortem decomposition well advanced. The abdominal cavity contained 800 cc. of blood-stained fluid. The liver extended 10 cm. below costal border, in the median line. The pericardial cavity was obliterated by firm adhesions. The weight of the heart was 420 gm. The walls were moderately hypertrophied, but post-mortem degeneration was so far advanced that it was impossible to determine anything further. The glands about the base of the heart were enlarged and caseous. The pleural cavities were obliterated by firm adhesions. The lungs contained numerous recent white miliary tubercles. The bronchial glands were enlarged and pigmented but not caseous. The spleen was enlarged; it weighed 270 gm. and had undergone considerable post-mortem change, but numerous yellow conglomerate tubercles could be distinguished. The kidneys contained no tubercles. Both lateral lobes of the prostate contained caseous areas, the right side being greater. The liver weighed 2720 gm.: the surface was smooth; the lobules well defined, suggesting cirrhosis, and a few bile-stained conglomerate tubercles were scattered throughout its substance. The gastrohepatic and retroperitoneal lymph-glands were greatly enlarged and caseous, but not all to the same extent. The aorta was the seat of slight sclerosis. The brain, stomach, intestines and pancreas were normal.

In view of these findings Dr. Hendrickson made the following diagnosis: General tuberculous adenitis; chronic tuberculosis of the prostate (probably the initial lesion); subacute disseminated tuberculosis of the liver and spleen; acute disseminated tuberculosis of the lungs; chronic obliterative pleuritis and pericarditis; chronic subcutaneous tubercular abscess. He has also informed me that the histological examination of the tissues has confirmed in all respects the macroscopic diagnosis, although he was unsuccessful in staining the tissues for tubercle bacilli.

CASE 3.—J. B., male, negro, 36, laborer, was admitted to my service at the Philadelphia Hospital, July 30th, 1901. He was desperately sick and very unintelligent. He stated that his father and mother had died of asthma, and that three brothers had died in infancy of unknown causes. He had had most of the diseases of childhood and gonorrhea. Otherwise his health had been good. His present sickness commenced at Christmas, 1900, when he was thrown from a wagon and fractured two ribs. From this time he had had pain in the chest and abdomen. During the month of June he commenced to cough and to expectorate a mucopurulent material that was never mixed with blood. He suffered from diarrhea for several weeks. He had lost considerable weight, had grown very weak, his appetite was poor and his digestion disturbed. For a week he had had only whisper speech. When admitted it was noticed that he was greatly emaciated, his expression was anxious, the pulse was rapid, weak, compressible, and regular. The tongue was slightly coated: the pupils reacted normally; there was complete aphonia; no pareses: the thorax was well formed, and expanded equally on both sides. The percussion note was impaired over the right apex, and over the left base posteriorly. Tactile fremitus and vocal resonance were slightly increased at the right apex. Fine crepitant rales were heard in both lungs anteriorly and posteriorly. The outline of cardiac dulness extended from the 4th rib downward, and from the left border of the sternum to the left parasternal line. The apex beat was weak and circumscribed, and situated in the 5th interspace inside the nipple line. The sounds were clear but very faint and distant. Liver dulness extended from the 6th rib to a line 3 inches below the costal border, and to the left as far as the nipple line. The surface of the liver was smooth and pressure upon it produced pain. The spleen was distinctly palpable as a large rounded mass in the left hypochondrium.

July 31. The urine continued albumin and granular and hyaline casts. The specific gravity was 1025. The sputum contained numerous tubercle bacilli.

August 2. The blood examination gave: Hemoglobin 60%: red bloodcells 4,190,000; white bloodcells 13,900. A differential count was not made.

August 8. The patient grew gradually weaker and died at 8 A. M.

In view of the physical signs a diagnosis was made of miliary tuberculosis of the lungs, tuberculosis of the liver and spleen: general tuberculous involvement of the lym-

phatic system, and myocarditis. It was strongly suspected that the lymphatic involvement was primary on account of the marked enlargement of the liver and spleen. The autopsy was performed by Professor Joseph McFarland, who has kindly permitted me to use his notes.

Autopsy performed 8 hours after death. The pathological diagnosis was: General tuberculosis, most pronounced in the lymphatic apparatus and spleen; miliary tuberculosis of all the organs; tuberculous ulcers of the stomach and intestines. Acute hemorrhagic myocarditis. The pleural and pericardial cavities were obliterated by adhesions, and everywhere studded with yellow tubercles. Firm tumors the size of lima beans were found on the inner surfaces of the pleura. The base of the heart was surrounded by a large mass of tuberculous lymphatic glands. At the root of the aorta there was a single gland about the size of a hen's egg, firm in consistency and resembling a fibroma upon section. It was encapsulated, and after section the cut surfaces became convex. The smaller glands were filled with yellow tubercles. Both lungs were filled with gray tubercles. The heart weighed 620 gm. The epicardium was greatly thickened and gelatinous. The muscle was soft, yellowish in color, and everywhere studded with petechial hemorrhages. The spleen was enlarged, measuring 16x11x7 cm., and weighing 590 gm. It was firmly attached to all the surrounding surfaces by adhesions that included several cheesy lymphatic glands, and a number of dark colored hemolymph glands. The substance was dark red in color, firm and thickly studded with gray tuberculous areas varying in size from a shot to a pigeon's egg. These were firm in consistency. The kidneys showed some parenchymatous degeneration and a few tubercles. The bladder and prostate were normal. The peritoneum was everywhere studded with miliary tubercles. The mesenteric glands were enlarged and tuberculous. About the celiac axis they were as large as pigeon's eggs, and for the most part dense and hard. The liver was firmly attached to the diaphragm; it was enlarged, weighing 1690 gm. The section was nutmeg and showed everywhere numerous miliary tubercles and a few bile cysts containing inspissated bile. The gall bladder was thickened and small as a result of a chronic pericholecystitis. The pancreas was normal. The stomach showed numerous hemorrhagic erosions and a large ulcer near the pylorus. A few tuberculous ulcers were found in the intestines. There was slight tuberculous erosion of the 7th rib on the left side, and of the bodies of several vertebræ. The larynx was tuberculous. I am indebted to Professor McFarland for the following note:

Concerning the specimens taken from the body of J. B., who came to section on August 8th, I beg to report that the disease of the organs and lymphatic apparatus was tuberculosis. The large fibrous lymph-nodes of the mediastinum, when examined miscroscopically, showed a chronic fibrosis with scattered foci of cellular infiltration and coagulation necrosis. There were no typical tubercles present. The lymphatic tissue itself had disappeared. Except for the associated conditions it would have been very difficult to recognize the true nature of the lesion. The lungs contained scattered miliary tubercles with cheesy centres and giant-cells. There were similar tubercles in the liver. The heart muscle showed marked fatty degeneration with interstitial hemorrhages, the microscope fully confirming the naked-eye-appearance of the heart-muscle.

CASE 4.—J. K., white, 49, stevedore, was admitted to the Philadelphia Hospital on the 29th of July, 1901, complaining of pain in the stomach, fever, and loss of appetite. His family history was too indefinite to be of value. His own previous medical history was also very unsatisfactory. He admitted gonorrheal infection 30 years ago: had been a moderate drinker, and 3 years ago he had fractured his collar bone. The ends of the bone had been wired together, but union had not occurred, and the sternal end of the outer fragment had penetrated the skin. His present disease began, according to his own account, about 6 months before admission with an attack of jaundice. He was admitted to St. Mary's Hospital and treated for some time and apparently recovered. After leaving the hospital, however, he had chills and fever, and from time to time severe hemorrhages from the nose and mouth. He rapidly grew weaker, his appetite was impaired, and he lost 42 pounds in weight. When admitted to Dr. Stengel's wards at the Philadelphia Hospital, his physical condition was as follows: A poorly nourished, well formed man, with a subicteroid tint of the skin; the pupils were normal; the tongue a good color, coated and slightly fissured. There was a large scar below the right clavicle at the sternal end and at its upper end a small necrotic mass of bone penetrated the skin. In the end of this bone several wire sutures could be seen. The skin around it was slightly discolored. There was a slight pulsation of the veins at the base of the neck; the cervical glands were not enlarged; the pulse was of moderate force, quick and receding; the vessels were soft; there was a distinct capillary pulse. The thorax was well formed; the expiratory movement was greater on the right side; respiration was vesicular; expiration was prolonged. On the left side inspiration was slightly diminished in intensity, and there was friction in the left axillary region. The apex was in the 6th interspace, 1 inch outside the nipple line. The deep area of cardiac dulness extended from the right parasternal line to the left anterior axillary region horizontally, and from the 3rd rib above. At the apex the 1st sound was loud and sharp; the second sound was of moderate intensity. At the base both sounds were clear. The aortic second was louder than the pulmonic second. The liver extended from the 6th rib to a line one inch above the umbilicus; the left lobe could be felt extending as far as the left nipple line; the surface was smooth and the liver slightly tender. The spleen was not palpable, but appeared enlarged to auscultatory percussion. In the right lumbar region a smooth regular mass could be felt which seemed to be the right kidney. There was considerable gurgling in the abdomen upon deep palpation. The chest and abdomen showed some whitish areas. On the 1st of August a blood count was made and showed 4,530,000 red bloodcells, and 11,300 white bloodcells. On the 12th of August the physical signs were as follows: On the right side inspiration was harsh, expiration was harsh and prolonged. On the left side inspiration was accompanied by a creaking friction; expiration was soft and prolonged. The cardiac dulness extended horizontally from the midsternal to the left nipple line, and from the 3rd rib downward. The apex was in the 5th interspace 1 inch to the left of the nipple line. The heart sounds were clear; the pulmonic second was slightly accentuated. The liver extended from the 6th rib downward to the left of the umbilicus; it moved slightly with respiration and was still distinctly tender. The spleen was not palpable but was enlarged to auscultatory percussion. The abdomen was not distended.

Throughout the course of the case the patient had an extremely irregular temperature, but as a result of rest and feeding he improved slightly in his general condition. On the 21st he requested and was given his discharge.

In view of the irregular temperature, the enlargement and tenderness of the liver, the rapid loss of weight, the history of hemorrhage, and the fact that nutrition must have been impaired as much as 3 years ago, all indicating a slowly progressive and very chronic condition, a diagnosis was made of lymphatic tuberculosis, although I felt at the time that there was a possibility that it was not correct. On September 15th the patient was readmitted to the hospital to the service of Dr. Riesman, suffering from cough and expectoration. The latter was examined and tubercle bacilli readily found.

On the 23rd of September the patient stated that about the middle of the month he had had a severe hemorrhage from the nose which had been repeated several times since. His present condition was as follows: He was poorly nourished; there was marked pigmentation of the chest and back, with irregular areas of leukoderma. The right lung showed slight impairment of resonance at the apex; respiration was harsh and vesicular; expiration was prolonged. In the left lung the respiration was slightly impaired at the apex during inspiration. The heart was enlarged: the apex was in the 6th interspace 1 inch outside the nipple line, feeble and diffuse. Dulness commenced above at the 4th rib and extended laterally from the left border of the sternum to 1 inch to left of the nipple line. The heart sounds were clear; the pulmonic and aortic second sounds were clear. The liver dulness commenced at the 6th rib and there was slight respiratory movement. The lower border could be palpated at the level of the um-

bilicus, and the lower lobe as far as the left nipple line. There was considerable tenderness over the liver. The spleen could be palpated during deep inspiration. By auscultatory percussion it appeared to be considerably enlarged. The axillary and inguinal lymph glands were palpable but small. The cervical lymph glands could not be felt. The pulse was medium full, normal volume; the arteries soft. Knee jerks were normal, and there was no disturbance of sensation. The patient had cough and expectoration and tubercle bacilli were readily found in the sputum.

The patient continued to grow worse. The physical examination showed very little change excepting that the skin grew noticeably darker over the whole body. On the 9th of November the presence of a considerable quantity of fluid in the abdominal cavity was recognized. The liver and spleen were both palpable and the patient was very weak. On the 17th of November he died. The only examination of the urine made during his last stay at the hospital showed a specific gravity of 1010, no albumin and no sugar. The autopsy was made by Dr. Buckley on the day of death. The pathological diagnosis was miliary tuberculosis of both lungs, pleurisy with an effusion on the left side, tuberculous ulcers of the intestines, cirrhosis and fatty infiltration of the liver, parenchymatous nephritis and a tape-worm. The weight of the spleen was 250 gm. and of the liver 1570 gm. There was fluid in the left pleural cavity: the spleen contained numerous tubercles: the glands of the mesentery and mediastinum were only slightly enlarged. Otherwise nothing of importance was found.

Dr. M. P. Ravenel very kindly consented to make cultures from the glands which at the time of autopsy were not as greatly enlarged as I had expected to find them. No tubercle bacilli were found upon staining, but guinea-pigs inoculated with the glandular substance died with generalized tuberculosis, and Dr. Ravenel states that there is some reason to believe that this bacillus is more virulent than the variety ordinarily obtained from human beings. The cultures have not yet been completed.

These four cases have so many clinical and pathological features in common that they may properly be considered as belonging to the same group. In all there was moderate anemia, progressive cachexia terminating in death, and enlargement of the liver and spleen. In the case longest under observation (II) the temperature was unusually irregular. In the other three cases it was not taken continuously, but was quite irregular for periods of several days. In two cases (I and II) there was almost constant edema, and in three (I, II and IV) a terminal ascites. In three cases (I, III and IV) the liver was exquisitely tender, and in the other it had been enlarged for two years and was almost painless. In three cases (I, III and IV) tubercle bacilli were found in the sputum before death, and in the other a lesion, probably, but not certainly, tubercular, existed. The post-mortem findings in three cases were very similar. There was enlargement of the deep lymphatic glands, miliary tuberculosis of the lungs, subacute tuberculosis of the liver and spleen, and in one case tuberculous erosions of the bones. The subcutaneous densely encapsulated sterile abscess in case II was similar to the fluctuating tumors situated close to the spinal column observed by Askanazy in a woman of 37, who was suffering from anemia. These contained a sterile, partly cheesy material that could only be drawn through an incision, and communicated with the thoracic cavity by a narrow sinus. Case III had a huge fibrous encapsulated tumor at the base of the heart that resembled very closely the tumor described by Claessen, occurring in a boy of 19, who had chronic passive congestion of all the organs, enlargement of the liver and spleen, and symptoms of chronic obliterative pericarditis. This tumor resembled a fibroma and showed no areas of necrosis, but tubercle bacilli were found in its substance. The bronchial glands were caseous and miliary tubercles were found in the pleuræ and pericardium, but the lungs and other organs were free. Testi, Bradbury, Witthower, Scott and others have also reported tumors of the mediastinum. Testi's and Bradbury's cases had enlargement of the cervical glands; Witthower's, diagnosed sarcoma, had the Pel-Ebstein type of recurrent fever, and Scott's case was undoubtedly tuberculous.

In case IV the findings were rather atypical inasmuch as the deep lymph glands were not greatly enlarged. There was, however, a subacute tuberculosis of the spleen and miliary tuberculosis of the lungs and, in addition, tuberculous ulceration of the intestines. Fortunately, the inoculation experiments by Dr. Ravenel prove conclusively the tuberculous nature of the process in the lymph glands.

Summaries of the Four Cases.

1. The disease commenced with cough and expectoration followed by weakness and loss of weight; then pain in the back, chills and thirst. Four months later the liver and spleen were found to be enlarged; there were signs of catarrhal disease of the right apex, and a slight anemia. The urine contained albumin and blood casts. In the course of a few weeks tubercle bacilli were found in the sputum, ascites developed and the patient died of pulmonary edema. At the necropsy there was found miliary tuberculosis of the lungs and liver, and tuberculous ulcers in the intestines.

2. A man, 28 years of age, as a result of a severe strain developed a fluctuating tumor over the sternum. Shortly after this he noticed enlargement of the liver. Two years later he had pain in the back, cough and expectoration, profuse epistaxis and fever. When admitted, an abscess containing sterile pus covered the lower parts of the sternum. The liver and spleen were enlarged; the resonance of the right apex was slightly impaired; a hemic murmur was heard at the base of the heart; the temperature was irregular; the blood showed moderate anemia, and the urine contained a slight amount of albumin. He finally developed general edema and ascites, had a slight apoplectiform attack and died. At the necropsy there were found an adherent pericardium, caseous mediastinal and abdominal lymph glands, recent miliary tuberculosis of the lungs, conglomerate tubercles of the spleen and liver, and old tuberculosis of the prostate.

3. Six months after an injury to the chest the patient developed cough and expectoration. He had diarrhea, was emaciated and slept poorly. When admitted he had aphonia, impaired resonance at the right apex, a feeble heart beat, enlargement of the liver and spleen, albuminuria and moderate anemia. The sputum contained tubercle bacilli. At the necropsy there was found general tuberculosis, most pronounced in the lymph glands and spleen, miliary tuberculosis of all the organs, tuberculous ul-

cers of all the organs, obliterative pericarditis and pleuritis, and hemorrhagic myocarditis.

4. Man of 46, fractured his clavicle and, in spite of wiring, union did not occur. Two years and a half later he had an attack of jaundice, then chills and fever, and hemorrhages from the mouth and nose. The liver became enlarged and tender; the spleen was moderatly enlarged, and there was moderate anemia without leukocytosis. The temperature was irregular. From time to time he had a hemorrhage from the nose. The liver increased in size, the superficial lymph glands were palpable but small; he developed the typical signs of pulmonary tuberculosis and tubercle bacilli were found in the sputum. Finally there was a severe ascites and death. At the autopsy the abdominal and thoracic lymph glands were found moderately enlarged; there was subacute miliary tuberculosis of the spleen, and fatty degeneration but no tuberculosis of the liver. There was miliary tuberculosis of the lungs and tuberculous ulcers in the intestines. Dr. Ravenel made cultures from the lymph glands and obtained an actively virulent tubercle bacillus.

It may be said to be the prevailing opinion among pathologists of the present day that there are three forms of disease of the lymph glands that may give rise to the syndrome characteristic of pseudo-leukemia. These are lymphosarcomatosis, tuberculosis, and a peculiar infectious process whose cause has not yet been discovered, but which by some (Reed) is regarded as the only true form of Hodgkin's disease. The relation of the tubercle bacillus to Hodgkin's disease has been a subject of interest for many years. Billroth long ago suggested that the hard fibrous form of polyadenitis was really a tuberculous infection of the lymph glands. In 1875 Winiwarter wrote that "some have endeavored to find in syphilis and tuberculosis an etiological factor for malignant lymphoma; at present there is nothing to prove this;" and in 1891 Dreschfeld called attention to the analogy of some of the changes in the lymph glands with those of chronic tuberculosis. Of late years a considerable amount of proof has been furnished, although the opinions of the authorities are much at variance. With the possible exception of Sternberg I have been able to find no authority who declares himself unqualifiedly in favor of the theory that pseudoleukemia is always produced by infection of the lymphatic apparatus with tubercle bacilli. But even Sternberg is not dogmatic, although he regards this view with considerable favor. That the glands in many instances contain tubercle bacilli is no longer a matter of question, and that these bacilli are capable of infecting susceptible animals has been conclusively proven. Moreover, it has been shown that in many cases with the characteristic histological picture of lymphoma tuberculosis exists, and the tubercle bacilli may be numerous and virulent. It does not necessarily follow that they are the cause of the pseudoleukemia, because, as many authors have suggested, they may exist either as a secondary or as an associated infection. That is to say, there is no reason why lymph glands, the seat of tuberculosis, might not take on the changes and produce the symptoms of pseudoleukemia, or tha lymph glands characterized by the morbid altera tions of pseudoleukemia and associated with symp toms of that disease, might not become infecte with tubercle bacilli. The latter view is held b Liebmann, Dietrich, Schmalz, Koster, Fischer an others. Some of these authorities also believe tha tuberculous infection of the lymph glands may, un der certain circumstances, produce morbid change somewhat similar to those of pseudoleukemia, an that the symptoms of the diseases may be indis tinguishable. Stengel, Frolich, Liebmann, Diet rich, Finzi, Combemaole and others, who hav written within the last decade, admit the tuberculou nature of some cases of pseudoleukemia. Howeve they insist that it can also be produced by othe hitherto undiscovered causes. Weiss and Reed, believe, are the only authors who assert that al though lymph glands may be infected with the tu bercle bacilli and may give rise to the symptom of pseudoleukemia, nevertheless all such case should be considered as merely instances of lymph atic tuberculosis, not belonging to the pseudoleu kemic group. In fact, they believe that they dif fer essentially from this group in their morbid ana tomy and in their etiology. Pinkus, one of th most recent writers on the subject, after a brief sum mary of the facts at hand, states, very fairly I think, that "the question whether tuberculosis is invariably present in those glands which show changes of pseudoleukemia, can only be decided by a considerable increase of the available material. The fact that the more carefully the investigations are conducted with all the aids of modern knowledge, the more frequently has the tuberculous nature of the process been proven, argues strongly for the influence of tuberculosis in these cases."

When we sift the mass of clinical and pathological material that has been accumulated in the literature, we find that the greater proportion of it furnishes merely presumptive and not decisive evidence. In the majority of cases that have been reported no effort has been made to find tubercle bacilli unless certain characteristic lesions were present. On the other hand, in many instances what were apparently miliary tubercles have been regarded as the metastases of lymphosarcoma and described as such without the exclusion of tuberculosis by histological examinations, cultures or inoculations. It must be stated, however, that a considerable number of these cases were observed before the discovery of the tubercle bacillus, and therefore before it was possible to identify the nature of the lesions. Among these are the cases reported by Winiwarter, Langhans, Kuhnhern, Desmos, Barié, Arkmann, Wendt, Rosenstein, Perret, Morrison, Pantoppidan and Schmidt, and many of the cases collected by Crocq. In other cases, although the prevailing views of the nature of the process, and the belief that the cause was unknown, led to the neglect of careful investigations, the reasons to suspect the existence of tuberculosis was very strong. For example, there has been cheesy degeneration in the glands, as in the cases of Brauneck and Winiwarter; amyloid disease of the organs, as in the

cases of Buchanan and Pantoppidan; necrosis and softening of the glands, as in the cases of Winiwarter, Mosler, and Brigidi and Piccoli Other cases have been recorded in which the clinical course resembled in many respects that which we believe is typical of lymphatic tuberculosis, but in which the autopsy is either lacking or so inadequately reported that it is impossible to draw any conclusions from it. Among these are the cases of Mosler, Liebmann, Türk, Sippi and Russel.

In addition to these cases there are now a number of references in the literature to a peculiar form of disease, first described by Pel and Ebstein, and given by the latter the name of "recurrent fever" (Rückfall-Fieber). A number of cases have been reported by Pel, Ebstein, Murchison, Renvers, Hanser, Völckers, Klein, Fiedler, Hammer, Seebohm, Van der Scheer, Hampel, Gowers, Puritz, Barbrock, Henoch, Mosler, Fischer, Kast, Kosler, Witthower, Askanazy, Sternberg and Musser. Of these, certain cases, particularly those of Puritz, Henoch, Kosler, Sternberg and Askanazy, were certainly due to tuberculous infection. In other cases, those of Renvers, Völckers, Hammer, Seebohn, Puritz, Henoch and Witthower, were apparently due to sarcoma, although in none of these cases was the tubercle bacillus certainly excluded. Fischer and Klein obtained cultures of the staphylococcus from the glands, and Hampeln's case was apparently one of carcinoma of the stomach. Sternberg is strongly of the opinion that all these cases are tuberculous.

The cases that have been sufficiently well studied so that they furnish direct evidence upon this question are few in number. They include those in which tuberculosis of the lymph glands and possibly of other organs existed and was positively demonstrated by inoculations, or by staining the tubercle bacilli. Second, those in which careful histological and bacteriological examinations excluded the existence of the tubercle bacillus. Among the earliest cases of the first group was that of Delafield. His patient, a woman of 23 years, had enlargement of the cervical lymph glands, an irregular and often high fever, progressive emaciation and death. At the necropsy there was found calcification of the mesenteric glands, evidently a chronic process, and miliary tuberculosis of the lungs. The next case, reported by Waetzold, was of the utmost importance, because it was the first in which tubercle bacilli were demonstrated in glands which failed to show the characteristic histological changes, and therefore called attention to a form of tuberculous infection hitherto unrecognized. A woman of 30 years had had glandular swellings in childhood; these reappeared 3½ years before death and were extirpated. Immediately afterward the patient developed anorexia, diarrhea, cough, and progressive weakness. One and one-half years before death the glands were again extirpated and histologically appeared to be pure lymphomata. After this the emaciation became extreme; there was complete insomnia; the cough was worse and not controlled by drugs, although there were no signs of pulmonary disease. The temperature showed irregluar elevations and there were chills and epileptoid attacks that apparently improved upon quinine. Dry pleurisy, ascites, and albuminuria developed and the inferior maxillary glands underwent softening just before death. The necropsy revealed enlargement of the spleen; the retroperitoneal and mesenteric glands were enlarged; there were amyloid kidneys, a normal liver and miliary tuberculosis of the lungs. The mediastinal and bronchial lymph glands were also enlarged and contained hyaline areas in which were numerous tubercle bacilli.

A still more remarkable case was reported the following year by Brentano and Tangl. A woman, 57 years of age, had swelling of the inguinal and cervical lymph glands; irregular fever with evening rise; ascites; pleural exudate; progressive anemia and cachexia and death. The necropsy showed enlargement of the mediastinal, mesenteric and retroperitoneal lymph glands; chronic peritonitis, tuberculosis and ulceration of the intestines. The liver was not enlarged. The lymph glands were not necrotic, and presented none of the histological characteristics of tuberculosis, but inoculation of a guinea-pig with the glandular substance caused death from tuberculosis. The authors contend this case proved that negative histological evidence is insufficient to exclude tuberculosis, although it must be admitted that a single inoculation experiment is not absolutely conclusive.

In 1893 Cordua described some glands removed from a woman of 22 years, who was supposed to be suffering from Hodgkin's disease. The clinical history is incomplete. The glands, upon histological examination, presented the appearance ascribed to Hodgkin's disease, but Cordua was able to demonstrate the presence of tubercle bacilli in their substance. He calls the disease malignant aleukemic lymphoma, apparently not regarding the presence of the tubercle bacilli as excluding Hodgkin's disease. A similar case was reported by Sabrazés in 1891, who, however, only proved the tubercular infection of the glands by inoculation.

In 1894 and later, Askanazy reported 3 cases. The first was a woman of 30 years, who had enlarged glands in the neck, an enlarged liver, and recurrent fever. At the necropsy the mediastinal and bronchial lymph glands were enlarged, but the spleen and retroperitoneal glands were normal. Tubercle bacilli were found in the lymph glands. The second case, a woman, 37 years of age, complained of pain in the left side of the chest. There was severe anemia and fluctuating tumors arising from the ribs on the left side. These were incised and found to contain a sterile cheesy material, and to communicate with the thoracic cavity by narrow sinuses. Tubercle bacilli were not found in the sputum. At the necropsy the mediastinal glands were found to be enlarged and partly necrosed, and showed marked tendency to fibroid induration. The liver was enlarged and contained numerous tubercles. The retroperitoneal lymph glands were greatly enlarged, and guinea-pigs inoculated with the glandular tissue developed tuberculosis. Microscopically the glands exhibited the characteristic picture of tuberculosis. The third case, a woman of 30 years, com-

plained of chills, night sweats, and expectoration. There was moderate anemia, and fever of an irregular type. She developed hydrothorax and later a hard, immovable tumor appeared in the neck. Tubercle bacilli were found in the sputum. At the necropsy all the glands were found to be enlarged and firm but not necrotic. The liver was enlarged and contained yellow nodules. The costal pleura was greatly thickened and dense. All the organs presented the characteristic histological changes of tuberculosis, and tubercle bacilli were found in the tissues. Askanazy calls attention to the many features of resemblance between this case and pearl disease in cattle, a valuable suggestion which I shall discuss more thoroughly later.

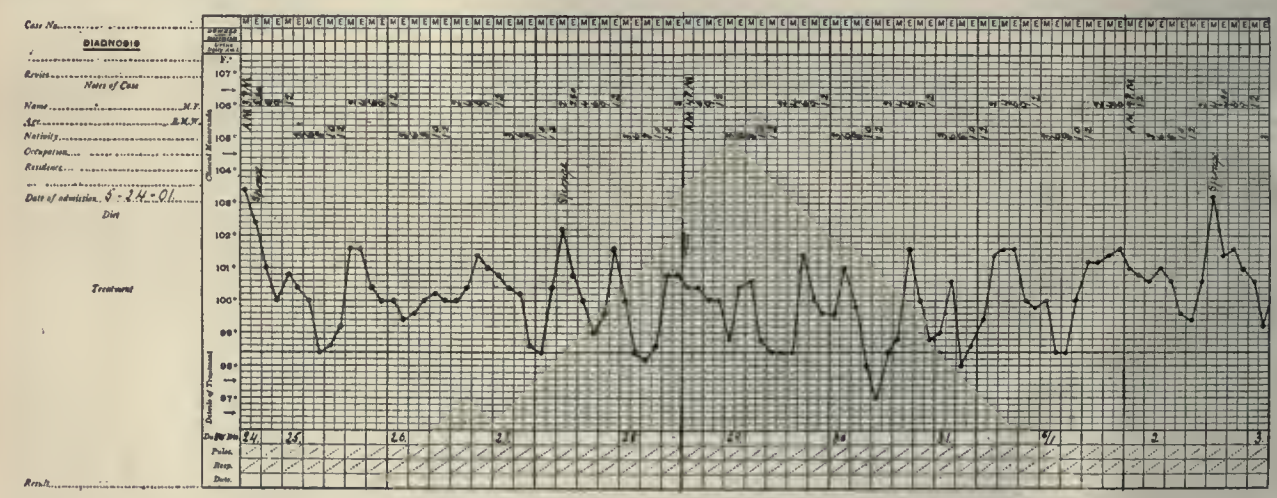
In 1896 Brosch reported the case of a man, 25 years of age, who had pain in the limbs, a petechial eruption, fever, icterus, enlargement of the spleen, albuminuria, and death. At the necropsy tuberculosis of the lymph glands was diagnosed.

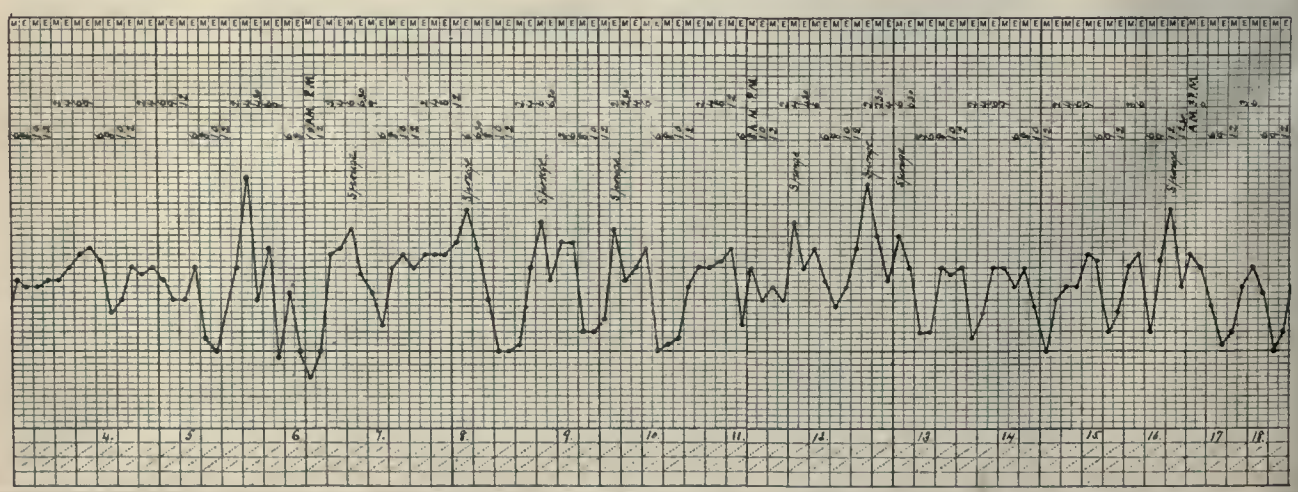
In 1898 Sternberg published a paper that he had evidently had in preparation for a considerable time. In view of the occasional discovery of tubercle bacilli, or of the evidence of tuberculous infection in a number of cases that clinically resembled pseudoleukemia, he determined to study the tissues from a considerable number of cases in order to determine whether the micro-organisms bore any actual relation to the disease or not. For this purpose he obtained specimens from 18 cases of pseudoleukemia, of which he says fifteen in their anatomical changes, and usually in their clinical course, resembled the peculiar cases of pseudoleukemia which had attracted his attention. For reasons that Sternberg does not explain, the clinical histories of his fifteen cases are not given; in fact, in some even the clinical diagnosis is lacking, and it is not, even when given, always pseudoleukemia. But it is not improbable that in all cases pseudoleukemia was suspected at some time in the course of the disease.

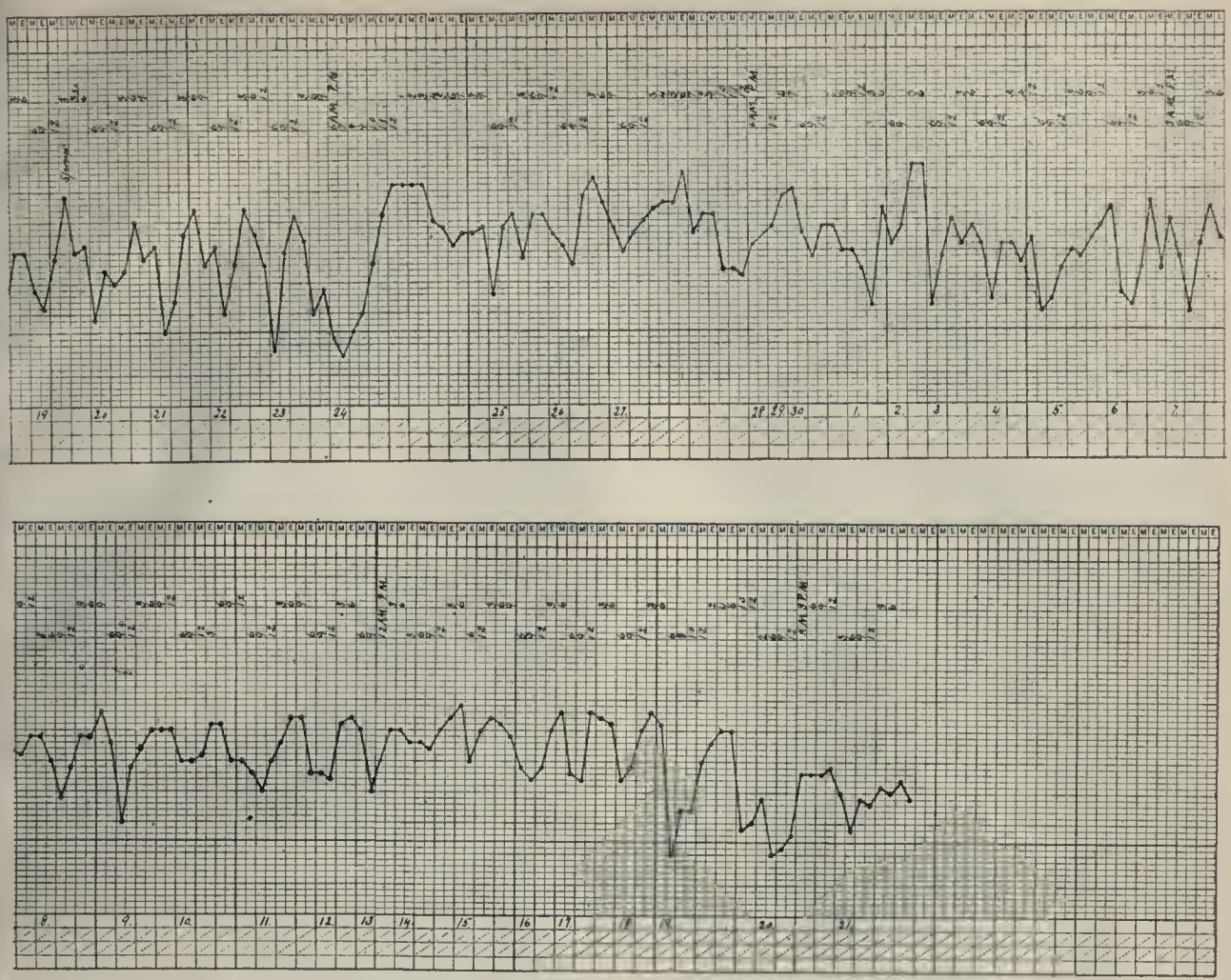
Briefly epitomized the cases are as follows:

CASE 1.—Clinical diagnosis, pseudoleukemia, bilateral pleuritis sicca, miliary tuberculosis which was doubtful, and splenic tumor. The lymph glands were generally enlarged and formed tumor-like masses in the mediastinum and retroperitoneal space. The spleen was enlarged and contained numerous white nodules. The right pleural cavity was obliterated by adhesions, and the left contained clear fluid. The right lung was filled with grayish nodules. There was clear fluid in the abdominal cavity. The nodules sometimes showed necrosis and in some of them a few tubercle bacilli could be demonstrated.

CASE 2.—Clinical diagnosis, pseudoleukemia. The lymph glands had enlarged and several had suppurated, or showed caseous degeneration. The liver and spleen were enlarged and contained numerous tubercles; the bone marrow was embryonal. The histological picture was in general that of tuberculosis, but tubercle bacilli could not be found.







CASE 3.—No clinical diagnosis. The lymph glands were enlarged and in part caseous. The spleen was enormously enlarged and contained numerous miliary tubercles. There was general icterus. The tissues contained necrotic areas with giant cells, but tubercle bacilli were not found. There was general arteriosclerosis.

CASE 4.—Clinical diagnosis, pulmonary tuberculosis, cirrhosis of the liver, considered doubtful, and degeneration of the myocardium. There was enlargement of the lymph glands and of the liver and spleen, and the latter contained miliary tubercles. The histological changes were those of atypical tuberculosis; tubercle bacilli were not found.

CASE 5.—No clinical diagnosis. The lymph glands were enlarged; the spleen and liver were enlarged and contained numerous tubercles. The tissues showed atypical tuberculous lesions and these contained numerous tubercle bacilli.

The tissues from cases 2, 3, 4 and 5 had been preserved for many years.

CASE 6.—Clinical diagnosis, pseudoleukemia; icterus due to compression of the common duct by swollen lymphatic glands. The lymph glands were generally enlarged and necrotic; there was chronic tuberculosis of the right lung. The spleen was enlarged and contained numerous miliary tubercles. Ulcers in the cecum. The histological changes indicated tuberculosis, but tubercle bacilli were not found.

CASE 7.—Clinical diagnosis: chronic tuberculosis of the lymph glands and serous membranes. There was universal edema, profound anemia; enlargement of the lymph glands and spleen; subacute nephritis and hypertrophy of the left ventricle. Cheesy areas, giant cells, and tubercle bacilli were not found in the tissues. The spleen showed considerable amyloid degeneration.

CASE 8.—Clinical diagnosis, pseudoleukemia with recurrent fever. There was tuberculous infiltration of the apices of both lungs; the lymph glands were enlarged and firm; the liver and spleen were greatly enlarged and contained white masses and miliary tubercles. The tubercles were composed of cellular aggregations and necrotic areas containing giant cells and a few tubercle bacilli.

CASE 9.—Clinical diagnosis, tuberculosis pseudoleukemia, tuberculous infiltration of the right lung, compression of the common duct by enlarged glands. There was enlargement of the lymph glands with caseous degeneration. The liver and spleen were enlarged, the bone marrow contained numerous nodules. The nodules showed cellular proliferation and some necrosis that was not caseous. Tubercle bacilli are not mentioned.

CASE 10.—A boy of 10 years with typical pseudoleukemia; an extirpated gland showed the cellular proliferation with necrotic areas; tubercle bacilli were not found.

CASE 11.—No clinical diagnosis. The anatomical diagnosis was pseudoleukemia and tuberculosis of the retroperitoneal lymph glands. The liver and spleen were enlarged and contained numerous nodules. The retroperitoneal glands were also greatly enlarged and consisted of fibrous tissue containing spindle cells, lymphocytes and giant cells. The borders of the glands were very red.

CASE 12.—Clinical diagnosis, tuberculous pseudoleukemia, tuberculosis of the lung and lymphatic glands, and enteritis. Anatomical diagnosis, lymphosarcoma of the lymphatic tissues and chronic tuberculosis of the glands. The lymph glands contained a large amount of fibrous tissue, groups of spindle cells and giant cells, or proliferated endothelial cells and erythrocytes. In some cases cheesy degeneration was present, and tubercle bacilli were found in the lymph glands.

CASE 13.—Clinical diagnosis, pseudoleukemia. Anatomical diagnosis, pseudoleukemia with general enlargement of the lymph glands and spleen, hydrothorax, and ascites. The lymph glands and spleen showed fibrous alterations, enlargement of the capillaries and desquamation of the epithelium.

CASE 14.—Clinical diagnosis, tuberculous lymphadenitis. Marked tuberculosis of the lungs; spleen greatly enlarged. Lymph glands were enlarged and contained necrotic areas and foci of epithelioid and giant cells. Tubercle bacilli could be demonstrated in the serous membranes. The liver contained numerous nodules.

CASE 15.—Clinical diagnosis, pseudoleukemia and tuberculosis of the lungs. Anatomical diagnosis, miliary tuberculosis of the lungs; cirrhosis of the liver; tumor of the spleen, and marked tuberculosis of the lymph glands. The lymph glands showed caseous degeneration and tubercle bacilli were found in them, and in the spleen. The liver contained numerous nodules.

The critical examination of these cases is not entirely as favorable to the relation between tuberculosis and pseudoleukemia as the enumeration appears to prove. In Delafield's case the clinical symptoms of pseudoleukemia were not distinct enough to enable a diagnosis to be made. In Waetzold's case the long course of the disease renders secondary infection with tubercle bacilli possible, and the same may be said of the case reported by Brentano and Tangl. The cases of Cordua and Sabrazés appear to be more certain. The clinical course and the histological changes in the glands were identical with pseudoleukemia; there were no evidences of tuberculosis in other parts of the body, or of tuberculous cachexia, nevertheless tubercle bacilli were demonstrated in the glands removed by operation. Askanazy's first case also appears to be very conclusive, but the second and third cases may merely have represented diffuse tuberculosis of the lymphatic glands and not pseudoleukemia. The 15 cases of Sternberg are not all of such a character as to prove his contention regarding the relation of the two conditions. It will be noted that the clinical diagnosis of uncomplicated pseudoleukemia was made in only three cases, and that of recurrent fever, that is, Ebstein-Pel's disease, in two others. In two cases the diagnosis was pseudoleukemia complicated by tuberculosis, and in a third tuberculous complication was considered probable. In four cases a diagnosis was made of lymphatic tuberculosis simulating pseudoleukemia; and in one the diagnosis was pulmonary tuberculosis and cirrhosis of the liver, a condition which, it appears, is difficult to differentiate from pseudoleukemia due to tuberculous infection. In three cases no diagnosis is given. In these 15 cases no inoculation experiments were made; no cultures were made, and tubercle bacilli were found in only 5. Therefore Sternberg's diagnosis of tuberculosis was made in the remaining cases because of the presence of lesions resembling those found in the tissues of the cases in which tubercle bacilli were demonstrated, but not resembling the lesions ordinarily found in tuberculosis of the lymph glands, and therefore not certainly the result of the activity of the tubercle bacillus. If it were not for the cases that have been already reported, we should be obliged to regard the work of Sternberg as doubtful. It is only the fact that this work confirms the results obtained by other men who have made careful examinations of the lymph glands in cases of pseudoleukemia that we are justified in considering it as establishing his contention that in a large proportion of the cases supposed to be pseudoleukemia the tubercle bacillus is present either as a causative or as an associated factor.

The negative evidence is even more scanty, and in view of the incomplete studies made in the majority of cases, far less satisfactory. In 1891 Czerny reported the case of a boy, 4 years of age, who had a tumor on the right side of the neck. There was continuous fever, moderate leukocytosis, progressive anemia, enlargement of the liver and spleen, pain in the abdomen, and emaciation. Shortly before death there was epistaxis and anasarca. At the autopsy a purulent exudate was found in the abdomen; the liver and spleen were enlarged and contained miliary nodules. The histological appearances were not characteristic of tuberculosis, and tubercle bacilli could not be found. Five years later Dietrich reported 3 cases with enlargement of the cervical and axillary glands. In one of these there was considerable fever, emaciation, and edema; the spleen and liver were enlarged and contained necrotic areas in which giant cells were found. The lymph glands were enormously enlarged.

In another case the cervical and axillary glands were enlarged and contained necrotic areas, but tubercle bacilli were not found. But as the tissues had been hardened in Müller's fluid, it is possible that they had lost their staining power. Inoculations were not made, and for that reason the evidence must be regarded as doubtful. In 1897, Fischer, stimulated by Dietrich's paper, attempted an experimental investigation of the whole subject. Unfortunately, this has only been published in the form of a lecture, and the details of the individual cases were not given. His general results, though, are stated very clearly. In all he studied 12 cases, 10 men and 2 women. In none of them was there leukocytosis, and cultures and inoculations made from the blood were without success, with the exception of one case of recurrent fever, in which the inoculations were positive during the febrile periods and negative during the intervals. He does not state the nature of the organism found, but merely calls it "secondary infection." Four of the cases died, and in all there was general involvement of the lymphatic structures in the lymphomatous change. One of these cases had in addition tuberculosis of the lungs and mesenteric glands, and the other, tuberculosis of the lungs, spleen and liver. In both the process was recent, and must therefore be regarded as a secondary infection. In all the cases the glands were extirpated, and from these glands inoculations, cultures and histological examinations of the tissues were made. The guinea-pigs inoculated were killed 2 or 3 months later, and only one showed any tuberculous change, and this was not in either of the cases complicated by tuberculosis. Cultures were negative and histological examination was negative, and eosinophile cells were found in great numbers in the glandular substance. According to Kanter, who has made a careful study of the changes in lympho-

matous and tuberculous lymph glands, and has reached the conclusion that they are essentially independent diseases, although they may co-exist, eosinophile cells are strongly against the existence of tuberculosis. Fischer does not share this view. The positive case was a girl of 16, who had enlarged cervical lymph glands. They were removed and found to contain numerous eosinophile cells, but no areas of necrosis, and no giant cells. Tubercle bacilli could not be stained, but fragments of the glands inoculated into two rabbits caused their death in 7 or 8 weeks, and both presented typical tuberculous lesions. Later the patient developed tuberculosis of the lungs, and the tubercle bacilli could be demonstrated in the sputum, and the scar of the operation by which the glands had been removed re-opened and suppurated. This case seems particularly valuable for the purpose of proving that in the absence of characteristic histological changes of tuberculosis, or of the ability to stain the tubercle bacilli in the tissues, what appears to be certain tuberculous infection may have existed. Since Fischer's paper no important article has been written excepting that of Freudweiler. He reports the case of a woman, 31 years of age, who at the age of 30 had swelling of the cervical lymph glands, then pain in the abdomen followed by swelling and finally ascites. She became cachectic and there was profuse diarrhea. She then developed a large abscess in the wall of the abdomen, which ruptured spontaneously. The pus was sterile. Animals inoculated with this pus did not develop tuberculosis. At the autopsy the cervical and mesenteric lymph glands were enlarged, and the latter were cheesy. There were ulcers in the gastro-intestinal tract, but there were no nodules in the spleen and liver. The glands showed the characteristic changes of sarcoma and in the cervical glands there were, added to these, the changes characteristic of tuberculosis. The diagnosis, therefore, is one of lymphosarcoma, which he believes developed in the tuberculous glands.

In this series of cases the only ones of any value are those of Fischer, and even they appear to be insufficient to establish the conclusion that pseudoleukemia is sometimes due to other lesions than tuberculosis. It is almost unnecessary to call attention to the valuelessness of the inability to discover the tubercle bacillus in the glandular tissues as a proof that tubercles do not exist, for in the case of Sabrazés and in that of Brentano and Tangl tubercle bacilli were not found, and yet the inoculations were positive, and the same thing was true of case IV in my series. Inoculations, too, can only be regarded as satisfactory evidence, if they are made in sufficient number, or if the results are positive. In case II of my series the presternal abscess was unquestionably tuberculous, and yet only one of several guinea-pigs inoculated with a large quantity of the pus developed tuberculosis. Nevertheless, it must be admitted that Fischer's paper furnishes the strongest evidence, and practically the only absolute evidence that we have at present against the tuberculous theory of Hodgkin's disease. Excepting it therefore, we are obliged to consider two possibilities; either the etiology of Hodgkin's disease, so-called, is multiple, that is to say, there are a variety of factors that can cause it, or that there is some other single etiological factor, and that the tubercle bacillus, when it does occur in a gland, must be regarded as an accidental or mixed infection. There is no particular reason why the first of these possibilities should not be so, because in other conditions with similar clinical course, such as cerebrospinal meningitis, the variety of etiological factors is considerable. If, however, this is not the case, we must assume either that tuberculosis is the invariable cause, but for some unaccountable reason was not detected in any of Fischer's cases, or that the tuberculous infection in some cases is secondary. If this latter supposition were correct, we should expect to find tuberculous infection not so infrequent in cases of leukemia, and also occasionally in other forms of tumor. It is of course well known that cases of pseudoleukemia may develop a terminal leukocytosis (Fleischer and Penzoldt) and present before death the characteristic picture of leukemia. In 1892, Francksen, whose original paper I have been unable to procure, was able to collect a few cases in which leukemia and tuberculosis apparently co-existed. In 1900, Junger reported an additional case in a man, 25 years of age, who had a sudden swelling of the tongue, which was relieved by a copious discharge of pus, edema of the hands and feet, enlargement of the cervical, axillary and inguinal glands and of the spleen. There was bronzing of the skin. The leukocytes were at first 40-and later 125.000. The fever was intermittent and the temperature often fell below 35°. The patient died, and at the autopsy miliary tubercles were found in all the serous membranes and in the liver and spleen. The hyperplastic lymph glands were also tuberculous. In the blood from the hemorrhagic lymph glands tubercle bacilli could readily be demonstrated. The lungs were free. He supposes that the case was one of latent tuberculosis awakened by the development of the leukemic process. The following year Sturmdorf reported an additional case occurring in a woman, 35 years of age, who at the age of 33 developed enlargement of the spleen. Two years later she awoke one morning with pain in the throat, cough and hoarseness. She lost weight; there was moderate fever, tuberculosis of the larynx, and the characteristic blood picture of leukemia, the leukocytes being 156,000. The fever was irregular and it was found that the myelocytes varied inversely with it. Tubercle bacilli were readily demonstrated in the sputum. This case can easily have been a tuberculous infection of the larynx complicating leukemia. Brückmann has also reported a case of myelogenous leukemia in a boy of 13 years. At the necropsy the lymph glands showed old tuberculosis and there was recent miliary tuberculosis of the pleura and peritoneum.

In regard to the infection of other forms of tumor with tuberculosis, the evidence derived from a study of the literature would seem to indicate that it is of the rarest occurrence. In 1895, Ricker reported two extraordinary cases. A woman was operated

on for sarcoma of the breast. Two years later there was recurrence with the symptoms of general sarcomatosis followed by death. The necropsy showed miliary tuberculosis of the lungs which contained hard nodules without caseation or giant cells, and great enlargement of the spleen, which contained miliary tubercles. In the breast there were two tumors, one caseous, the other resembling the metastases in the lungs, but containing giant cells. Tubercle bacilli were found in both tumors. Ricker admits that this was possibly a secondary infection of the tumor from tuberculous lesions that already existed in other parts of the body. He argues against this, however, that there is no other case on record in which a tumor has become infected in this manner, or in which a wound has become infected during operation, nor is there any case on record in which a wound has become infected as a result of tuberculosis in other parts of the body; leaving the impression that it is his belief that either sarcoma and tuberculosis co-existed, or that the process was tuberculous from the beginning. The second patient was a boy, who at the age of 10 years had some swollen lymph glands removed from the neck. These recurred, and at the age of 15 years the boy was brought to the hospital emaciated, pale and complaining of severe pain in the lumbar region. A diagnosis of lymphosarcoma was made. Subsequently paraplegia developed and the patient died. At the necropsy large tumors were found in the neck, in the mediastinum, in the lungs and in the bodies of the vertebræ. These tumors showed the structures of lymph glands. Scattered throughout the lymphoid tissue there were groups of six or seven endothelial cells, but typical giant cells were absent. Great numbers of tubercle bacilli were found in the sections. Ricker regards the tubercle bacilli as undoubtedly the cause of the tumors in this case, although he admits that further investigations are necessary in order to determine what relation the tubercle bacillus bears to malignant lymphoma or lymphosarcoma. He is convinced that when it involves the lymphatic tissues it can produce a clinical type of disease that differs greatly from the ordinary pulmonary form. In 1899 Whartin reported two cases of carcinoma of the breast; the first, in a woman of 42, appeared, three years after the organ had ceased to functionate, as a small lump that grew rapidly. At the same time there was enlargement of the glands in the axilla. The breast softened and an abscess was found in it, and after a partial amputation the patient made a perfect recovery. Histologically, it showed the characteristic picture of carcinoma simplex associated with tuberculosis, and tubercle bacilli were found in the pus. The other, a woman of 39, had carcinoma of the breast with metastasis to the axilla. Carcinoma associated with tuberculosis was found both in the breast tissue and in the involved glands. But on account of the hardening fluid (Müller's) tubercle bacilli could not be stained. He accepts Lubarsch's classification of these structures.

I am inclined to believe that these cases are analogous to the cases which have been reported of [illegible] and tuberculosis

and carcinoma of the esophagus. Of the latter a number of cases are now on record, particularly those of Cordua, Letulle, Michaux, Zenker, and Pepper and Edsall. These cases are characterized usually by the presence of old tubercular lesions in the lungs and the absence of metastases to the glands surrounding the structures, although Michaux states that in his case some of the glands were softened and some firm and white, as in glands affected by carcinomatous metastases. As no histological examination was made, his statement must be received with reservation.

I think there is considerable doubt regarding the nature of these so-called carcinomatous tumors. Ribbert has shown that epithelium separated from its basement membrane by pathological processes may proliferate, and he attempts to find in this an explanation for the cause of carcinoma. It is possible that in these circumstances, however, the proliferation, although morphologically similar, is etiologically distinct from that characteristic of the true carcinomatous growth. The long history of some of these cases seems to be strongly against a malignant proliferative process.

The evidence regarding the tuberculous nature of pseudoleukemia, aside from that which we have quoted, is so scanty and inconclusive as to be almost worthless. Delbet inoculated a dog with bacilli, whose nature is not mentioned, from a case of lymphadenoma and produced chronic abscesses with enlargement of the lymph glands. Galasso has observed improvement in cases of tuberculous lymphoma after the use of Maragliano's serum. Jaccoud, Mosler and Birch-Hirschfeld have observed infectious adenitis following infectious diseases. Tuberculosis, of course, often follows infectious disease, but there is no other reason for supposing the two processes the same. Liebmann has observed miliary tuberculosis as a complication of adenitis. He supposes that it may be a true complication, or else either assume the appearance of adenitis or actually cause it. Phillipart calls attention to the similarity between a case of cutaneous lymphomata and leprosy.

Assuming the tuberculous nature of these conditions, the question naturally arises, why tuberculosis of the lymph glands sometimes produces such extraordinary symptoms. In 1894 Askanazy suggested that the lesions in one of his cases resembled pearl disease in cattle. In 1898 the careful studies of Theobald Smith proved that there was more than one variety of the tubercle bacillus. He believed at that time that the chief distinction lay between the bovine and human tubercle bacillus, and that the greatest difference existed in the degree of virulence of these two organisms. His paper has since been amply confirmed by Koch, Ravenel and others; Koch even going so far as to claim that the human tubercle bacilli were not pathogenic for cattle, nor the bovine tubercle bacilli for human beings, a statement that has been conclusively disproved by the work of Ravenel. In 1901 Lartigau showed that a considerable variation existed between specimens of tubercle bacilli obtained from different lesions in human beings, and Ravenel has found the same

thing to be true. It seemed possible, therefore, that perhaps in the pseudoleukemic forms of tuberculosis we had to deal with a variety of the tubercle bacillus that differed somewhat from the one ordinarily infecting human beings. Such a hypothesis could only be regarded as established if in a sufficient number of cases certain constant peculiarities were observed in the cultural and pathogenic character of the tubercle bacilli obtained from them, and it is needless to say that no such studies have as yet been made. In fact, case IV of my series is the only one, so far as I know, from which cultures have been made.

When I began to prepare this paper it was my object to find some common clinical features in these cases that would render possible during life their differentiation, on the one hand, from cases of true pseudoleukemia, if such actually exist, and, on the other, from cases of ordinary tuberculosis of the lymph glands. I now have great doubts whether any such clinical differentiation is possible. Yet, from the data at hand the following symptoms appear to be usually present in the forms which have certainly been determined to be tuberculous: Fever, continuous, irregular or recurrent; in fact, the forms described originally by Gowers, moderate anemia, more frequently associated with leukopenia than with leukocytosis; progressive emaciation; enlargement of the spleen and, less frequently, the liver; frequent enlargement of the superficial lymph glands, and, occasionally, the physical signs of enlargement of the thoracic and abdominal lymph glands; tenderness over the abdomen, especially in the right hypochondriac region, and hemorrhagic diathesis, or at least a very pronounced tendency to epistaxis; albuminuria, and, as terminal symptoms, anasarca and jaundice (probably due to pressure by the enlarged retroperitoneal glands.) Death apparently occurs in many cases as a result of the eruption of miliary tubercles. Not infrequently in these cases the following conditions occur and may be regarded as contributory evidence. The signs of pericardial adhesion and of myocardial involvement, the painless, fluctuating tumors arising from the thoracic cavity and lying between the skin and the ribs. Of course, the presence of tubercle bacilli in the sputum or other discharges must be regarded as highly significant. Excision of enlarged superficial glands with either histological examinations or inoculations into animals may confirm the diagnosis (von Noorden), and in some cases injections of tuberculin may give rise to the characteristic reaction, although in case II of my series 5 mg. of an active preparation produced rather a depression than an elevation in the temperature.

In conclusion, then, it can only be said that the time has not yet come for any dogmatic statement upon this question. None of the evidence hitherto presented can be regarded as decisive, and yet, as Pinkus says, the gradual accumulation of positive evidence, and the absence of entirely satisfactory negative evidence rather tends to confirm the supposition that the majority of cases of pseudoleukemia, if not all, will ultimately be recognized as tuberculous in nature.

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