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WILLIAM PEPPER LABORATORY
OF CLINICAL MEDICINE

DEAR DOCTOR:

It gives me pleasure to send you a copy of *Contributions* (No. 6) *of the Laboratory.*

ALFRED STENGEL
Director

University of Pennsylvania
Philadelphia, April 12, 1909

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TWO CASES OF STREPTOCOCCUS INFECTION WHICH GAVE A TYPICAL WIDAL REACTION.

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and
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(From the William Pepper Laboratory of Clinical Medicine.)

These cases are deemed worth reporting because they were thoroughly studied, and in the course of such study the blood responded so completely to the Widal reaction, that they were placed in the medical wards of the Hospital of the University of Pennsylvania, with the belief that they were cases of typhoid fever. While displaying this most essential reaction they exhibited no other distinctive sign of typhoid unless the copious nasal hemorrhage in one case be considered such. Enlargement of the spleen which was present in both cases, is so common in infectious diseases that it dare not be allowed any diagnostic value.

The cases also prove conclusively that the blood culture affords the only reliable means of making a thoroughly accurate diagnosis of typhoid fever.

Case I.—Andrew C., aged thirty-six years, white, single, American; laborer; admitted to the University Hospital to the service of Dr. Tyson, November 6, 1906. Died, March 22, 1907.

Family History. Negative except for fatal Bright's disease in one brother.

Previous Personal History. Also unimportant except for hard manual labor as fireman, an attack of gonorrhea and considerable use of alcohol and tobacco. In April, 1906, he was operated upon successfully for strangulated hernia, and never felt strong since his discharge from the hospital, May 18, 1906. He was, moreover, unable to do hard work on account of shortness of breath, weakness, and later on, swelling of feet and ankles. He also had pain in both legs and at the shoulder with "neuralgic" twitches in the right side of the face, and some cardiac palpitation. Slight cough developed with slight expectoration, and on October 30, 1907, he says that he lost about a pint of *blood from the nose* with another attack of less severity since. He lost twenty pounds between April and November, although he had been regularly taking milk and eggs, the latter of which, however, he had trouble in retaining for a day or two prior to his admission. He also complained of night sweats for a week before coming to the hospital.

Examination on November 6, 1906, revealed a poorly developed man of about 140 pounds, with slight amount of subcutaneous fat, flushed face, and pale mucous membranes; teeth are poor, tongue coated, and breath foul. There was no glandular enlargement and skin was clear, but there was violent pulsation in the vessels of the neck. Chest was well shaped but of deficient expansion. Lungs were essentially negative, and the apex beat was strong in the fifth interspace, one inch outside the nipple line, whence a diffuse wave-line impulse passed down and across the epigastrium. The heart extended from the upper border of the third rib to the right border of the sternum and one inch inside the anterior axillary line. A soft systolic murmur was heard at the apex and in the axilla, and at the aortic area a double murmur was heard, the systolic the louder of the two and transmitted into the vessels of the neck. The second aortic and pulmonic sounds were both accentuated. The pulse was full and Corrigan in character and Traube's and Duroziez's signs were both present. The liver was tender and enlarged to two inches below the costal border; the spleen was also enlarged to percussion, vaguely palpable and tender, but the abdomen was otherwise negative except for herniotomy scars. There was slight edema over the ankles.

Examination found the urine practically normal and blood showed hemoglobin, 70 per cent.; red blood corpuscles, 4,970,000; white blood corpuscles, 10,000. Blood pressure, systolic, 130.

His condition remained about the same for several days after admission with a rise of temperature in the evening up to 100° to 101½°. He complained of joint pains which yielded to salicylates, and he was comfortable while in bed. Pulse tracings taken were typically those of aortic regurgitation, though systolic pressure remained low, at 120 with diastolic at 60.

His temperature continued to vary, he felt alternately better and

worse, and on November 22 examination showed impairment of percussion resonance with increased vocal resonance at the right apex, both of which signs were doubtfully present on admission. A few fine dry rales were heard at the right base also. No rose spots were to be seen. A Widal taken on November 23 was positive and the patient was put on typhoid treatment.

On November 27 the Widal was again positive in the 1 to 100 dilution. A blood culture of the same date showed a pure growth of streptococci in three out of four flasks. For some days the patient remained in statu quo, quite comfortable with no other signs of typhoid.

On December 4 the rheumatic pains returned in the left shoulder, temperature continued high, and blood pressure fell to 100 and 60.

5*th*. A ward note states: Rheumatic pains have disappeared. Blood pressure systolic, 85; diastolic not obtainable.

6*th*. Widal positive again in one hour, up to 1 to 200 dilution. This dilution gave a slight reaction. Temperature lower, patient comfortable, and blood pressure very low, systolic, 85; diastolic, 60.

7*th*. Blood count gave red blood corpuscles, 3,640,000; white blood corpuscles, 5680; hemoglobin, 70 per cent.

16*th*. A second blood culture shows streptococci in pure culture.

29*th*. Trace of albumin in urine with some granular casts and leukocytes. When salicylates are stopped for more than a few days, joint pains return.

January 11, 1907. Blood culture showed streptococci again in pure culture.

22*d*. The patient had a sharp pain in splenic region which radiated across abdomen and left him very prostrated, with some local tenderness. Spleen questionably palpable.

23*d*. Blood count gave red blood corpuscles, 3,050,000; white blood corpuscles, 10,000; hemoglobin, 54 per cent. Blood pressure, 85 to 70. Patient given Blaud's pill, gr. v, arsenic, gr. $\frac{1}{60}$, and tr. digitalis ♏ x, three times a day.

31*st*. Patient apparently somewhat stronger, and felt well, but there is much edema of feet and legs when he sits up in a chair long.

February 4, 1907. Murmur at apex of heart unchanged; murmur at base weaker and the diastolic element hard to hear. Small purpuric patches on legs and feet.

10*th*. Has remained in bed for some days and purpuric patches have almost disappeared. Edema also gone, but patient is very weak.

13*th*. Allowed to be up when purpuric patches of feet and legs returned by night.

16*th*. Rest in bed again caused the disappearance of the purpura.

22*d*. Red blood corpuscles, 2,000,000; white blood corpuscles, 8000; hemoglobin, 40 per cent.

24*th*. Nausea and vomiting occur at night and dyspnea remains about the same.

March 14. Has felt better for a week past than at any time since admission. Temperature normal, but his feet still swell when he gets out of bed and the purpuric spots then again reappear. Hemoglobin, 50 per cent.; red blood corpuscles, 2,220,000; white blood corpuscles, 6200. No tubercle bacilli or elastic tissue in sputum.

19*th*. Weaker and more dyspneic for some days past. Urine as before.

20*th*. Several attacks of nose bleed last night, one quite severe. Very weak today and has air hunger.

21*st*. Blood culture showed short thick bacilli; Widal positive in 1 to 100 dilution.

22*d*. Severe attack of dyspnea and general distress today. He became very noisy and after about an hour of this discomfort, died.

No autopsy was secured.

Case II.—Dora P., aged eighteen years, white; primipara. Admitted to the maternity on November 19, 1906, seven days after delivery, with vaginal discharge, severe headache, and temperature of 105⅘°. She was treated as a case of puerperal sepsis, and the discharge decreased, but the high temperature and headache persisted and a Widal reaction was positive on November 23 and November 26, 1906. On the latter date a blood culture showed streptococci. Transferred to the service of Dr. Tyson on November 30, 1906. Died June 1, 1907.

Her family and previous personal history were uneventful, the present condition dating from her confinement, for the first three days after which she did well; her uterus was then curetted and she developed high fever.

On admission to the service of Dr. Tyson, temperature, pulse, and respiration were 104°, 120, and 40. She was evidently very sick and was much exhausted, but complained of nothing more than a headache.

Examination shows a young, slight woman, fairly well developed, with moderate amount of subcutaneous fat. Her face was pale and red in spots. Lips were dry, tongue heavily coated, and breath foul. Chest was symmetrical, of poor expansion, breasts long and pendulous and not lactating. Chest clear; to percussion heart extended from third rib to middle of sternum and one inch inside midclavicular line. The first sound at the apex lacked muscular tone, but there were no murmurs. At the base both valvular sounds were weak. Abdomen was marked with white striæ, but shows no tenderness or distention. Liver is apparently normal in size.

December 1, 1906. The urine shows mucus, many leukocytes and epithelium, but no albumin or casts. Blood gives a count of red blood corpuscles, 2,250,000; white blood corpuscles, 9890; hemoglobin, 52 per cent. Widal positive. Blood culture shows streptococci. The temperature keeps high and the patient is repeatedly sponged. No rose spots or abdominal symptoms of any kind.

7*th*. She shows some tendency to tympanites today for the first time,

and a day or two ago developed a profuse vaginal discharge. There are no rose spots but the spleen is enlarged to percussion and in other respects her condition suggests typhoid.

9*th*. 80 c.c. anti-streptococcic serum given today every six hours until 320 c.c. were administered. Patient's condition seems worse and she shows some tendency to delirium.

12*th*. Blood culture again shows streptococci in pure culture. Patient's appetite is good. She takes large quantities of milk, but she is very restless.

16*th*. Profuse diarrhea developed today and vaginal discharge persists, but in other respects her condition remains much the same.

21*st*. Appetite is failing and she vomited today for the first time.

26*th*. Anti-streptococcic serum (60 c.c.) again given today. Urine shows albumin, medium sized, pale granular and small granular casts, many small and large leukocytic casts. Blood: red blood corpuscles, 1,680,000; white blood corpuscles, 12,400; hemoglobin, 28 per cent.

28*th*. Urine shows albumin to mark 1 (by Esbach); casts, and other features as before.

January 3, 1907. Legs and feet have become edematous.

7*th*. She has had pain in her left arm, but it is now much better. There was also a purpuric eruption over the left leg and sacrum which has now disappeared, but over the site of this there are sinuses under the skin. Urine about the same.

9*th*. A blood culture today was sterile.

18*th*. Seems to be improving. Diarrhea gone, mind clear, temperature lower and edema has disappeared and sinuses are healing.

February 1. Condition continues to improve except that she has some pain in her right hip

5*th*. Temperature normal for some days.

14*th*. Bacillus diphtheriæ found in throat today in routine examination of all patients who were exposed to a case occurring in the ward. No clinical signs of the disease, however. Pain in the left hip is increasing, and appetite failing, with a rise in temperature every evening.

23*d*. For a week past condition has been unsatisfactory, with high fever, excruciating pain in the left hip and edema of whole of left leg. Pulse good and mind clear. Presence of B. diphtheriæ in throat evidently only transitory as no organisms are found today.

March 3. Patient remains in about statu quo. Left leg presents a distinct phlebitis.

22*d*. Condition persists without much change, with irregular temperature and leg now shows an area of redness in middle of thigh.

25*th*. Leg opened and (℥xxiv) pus removed. Patient feels better tonight.

26*th*. Temperature fell to normal and she feels vastly improved.

30*th*. Temperature elevated again without evident local cause. Wound draining freely.

April 6. Temperature slowly fell and she now seems better again.

15*th*. Patient has been better and worse alternately, holding her own fairly well, though she has several broken-down areas on her back and elsewhere. Today, however, temperature rose to 103°, after having been normal for about nine days.

16*th*. Temperature today 105.5°. A red rash appears over left thigh.

25*th*. Blood count gives white blood corpuscles, 22,000; hemoglobin, 32 per cent.

May 6. Temperature septic now and right knee opened because of swelling and fluctuation. Streptococci reported in pus obtained.

15*th*. Condition has been poor and a fluctuating abscess on left shoulder opened and drained. Joint not involved.

June 1. She is growing steadily worse; condition of back undescribably bad, and patient is much weaker and extremely emaciated. Eats nothing and is delirious most of the time.

8*th*. Died today, after lying unconscious for twenty-four hours. No autopsy obtained.

The cases are reported without further comment because none is needed for the purpose which is simply to show conclusively the occasional association of clumping by other than typhoid bacilli.

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CRYPTOGENETIC STREPTOCOCCUS INFECTION WITH PERSISTENT CUTANEOUS ERUPTION, ENLARGEMENT OF THE LYMPHATIC GLANDS AND FEVER SUGGESTING SYPHILIS.

By Alfred Stengel, M.D., J. William White, M.D.,

and

Joseph S. Evans, M.D.

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

The report of the case which is the basis of this paper was prompted by the unusual clinical features and the results of bacteriologic study. The patient, a physician, had consulted a number of physicians, dermatologists, and syphilographers before consulting one of us (S). Various opinions had been expressed for and against syphilis. Our own belief in the non-syphilitic character of the disease seems to be confirmed by our bacteriologic studies, which appear sufficiently conclusive to justify publication. We are indebted to Professor James C. Wilson for the photographs of the case, which were taken when the patient consulted him, and to Professor Henry W. Stelwagon for photographs and a statement of the clinical features observed by him.

L. D. J., aged twenty-six years, does not remember having diseases of childhood and was in good health until fourteen years of age. At that time he had some form of gastrointestinal disorder with marked nervous symptoms and disturbances of vision. The nervous symptoms were attributed to a muscular disorder of the eyes and astigmatism. About the same time he developed a fissure in ano. After correction of the eyes and cure of the fissure his general health improved and he was practically well. At eighteen he began to prepare for his medical studies and finally graduated at twenty-five. He was a resident physician in one of the hospitals and while there was perfectly well until June 1, 1905.

The following account of his condition from the onset of that trouble until he first consulted me (S) was prepared by a medical friend who was constantly associated with him during the time.

History of Present Illness. In the latter part of May, 1905, the patient began to complain of digestive disturbances, sore throat, and lassitude. He being slightly jaundiced, vomited occasionally, and had no desire for food. He also complained of an intense itching of the skin. At this time an eruption which looked exactly like seborrhœic eczema made its appearance upon the ankles, thighs, buttocks, back, and elbows. This eruption appeared in fairly well-defined patches.

Examination of the throat, made upon several occasions, showed the posterior pharyngeal wall to be dry and congested, with an enlarged follicle here and there over its surface. The tonsils were also somewhat inflamed and slightly enlarged.

The patient was placed on a reduced diet, given sodium phosphate internally, and ordered a warm alkaline bath at bedtime. Slight improvement followed the treatment. In the middle of June he went to the country for two weeks. Upon his return he stated that he felt no better.

From July to the middle of September his condition varied from week to week, although during this period he never felt

in his normal condition. The eczematous rash faded markedly and in some places disappeared entirely. Slight jaundice was noticeable at times, nausea was experienced, and on several occasions vomiting occurring immediately after eating.

FIG. 1.—The eruption in its earlier stages. (From a photograph taken for Dr. J. C. Wilson.)

The patient was nervous, irritable, and suffering from insomnia. In the latter part of September he complained of feeling much worse, "sick all over," as he himself expressed it, and about the first of October left again for the country, where he remained until November. During the month of

October he became steadily worse, losing weight and strength, and suffering more and more from insomnia. The axillary lymphatic glands began to enlarge and were painful and sensitive to touch, there was more or less pain under the

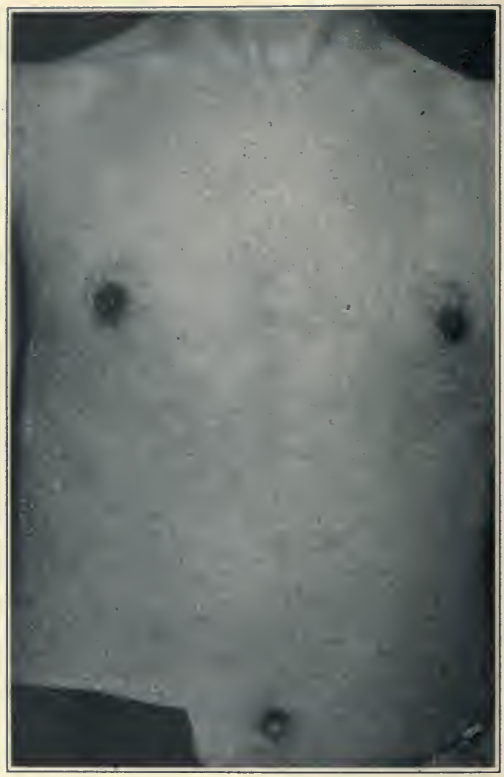

FIG. 2.—The eruption in the later stages. (From a photograph taken by Dr. H. W. Stelwagon.)

sternum, and dyspnœa, which became worse upon exertion, developed. The patient states that at this time he had several sharp chills followed by free sweating. In the meantime an erythematous rash broke out on the arms, thorax and abdomen, and later invaded the lower extremities. After

the patient returned to Philadelphia early in November his condition became constantly worse. The pain in the region of the sternum extended over the entire anterior thoracic region, the dyspnœa became severe, the axillary glands continued to enlarge and become more and more painful. The other lymphatic glands, notably the inguinal group, likewise became affected. The patient had an evening temperature of 100° to 102° F., with profuse sweating at night, and was distressed by the constantly increasing dyspnœa and the severe substernal pain. In short, he presented the appearance of one seriously ill. A blood count showed a leukocytosis of over 21,000. The rash which had become more and more marked assumed a multiform character, papules alternating with macules, etc.

The patient consulted several physicians, surgeons, and dermatologists in Philadelphia and New York, and finally entered a hospital, where he received the so-called mercurial therapeutic test in the form of hypodermic injections, there being a question as to whether his illness might not be the result of syphilitic infection. This treatment seemed to produce a slight fading of the rash, although the change was not at all decided, and he himself doubted the occurrence of any noticeable alteration. Only a few injections were administered.

November 26, 1905. The patient first consulted me (S) on this date, when he gave substantially the history as above and in addition told me that he had had numerous attacks of tonsillitis. He also reported that in October, 1905, he began to have intense headaches after eating. After this he developed rheumatoid pains in his left shoulder, and on one occasion, after having drunk cold water at a mineral spring, he had a heavy shaking chill and continued chilly for about three days. It was after this that he first developed substernal pain and enlargement of the gland in his left axilla. There was also a constant aching sensation in his jaws followed by a swelling of the glands at the angle of the

maxilla on the right side. The rash which he presented on first consulting me appeared about this time, first covering the abdomen and chest. There was none then on legs. He reported hyperæsthesia at various points but had no itching. There was a distinct tendency, however, to urticaria.

After the original chill there was some fever and this continued more or less steadily for three weeks; then subsided, the rash at the same time becoming marked. Subsequently each recurrence of the fever was attended with a distinct increase in the rash.

The glandular enlargement when I first saw him involved the post-auricular groups on both sides, the anterior cervical and both axillary groups, especially the axillary glands on the left side; both inguinal groups slightly and the supra-clavicular on the left side.

The rash found at his first visit was a blotchy erythema and folliculitis, most marked over the abdomen and chest, some on the forehead, none on the arms or legs. He reported that there had been papules and miliarial vesicles but these were not present when I saw him. Physical examination at this time and subsequently disclosed no evidence of any visceral lesion. The thoracic and abdominal organs all appeared normal. Repeated palpation of the spleen failed to show any enlargement. The only pathological conditions discoverable were the pharyngitis and tonsillitis, the cutaneous eruption and the enlargement of the superficial lymphatic glands.

January 7, 1906. He presented himself on this day with a fresh outbreak of eruption, much of which was papular and minutely vesicular.

17*th.* The rash has subsided distinctly, apparently under the influence of salicylates.

27*th.* The rash is of dusky color but still quite evident. Glands remain about the same. He has been taking guaiacol carbonate and salicylates since January 7th.

The following clinical examinations were made under our direction:

Urine: Specific gravity, 1020; reaction, acid; no albumin; no sugar; microscopic examination, negative. Subsequent examinations gave similarly negative results.

Blood: The patient reported that there had been leukocytosis (21,000 and 17,000 per c.mm.) before he consulted us.

November 27, 1905. Leukocytes, 8880; polymorphonuclear, 73 per cent.; large mononuclear, 5 per cent.; transitional 2 per cent.; lymphocytes, 14.5 per cent.; eosinophiles, 4 per cent.; basophiles, 1.5 per cent.

January 17, 1906. Red corpuscles, 5,090,000; leukocytes, 8320; hæmoglobin, 65 per cent.; polymorphonuclear, 67.4 per cent.; large mononuclear, 4.4 per cent.; transitional, 5.6 per cent.; lymphocytes, 18.6 per cent.; eosinophiles, 1.8 per cent.; basophiles, 2.2 per cent.

March 26*th.* Red corpuscles, 5,730,000; leukocytes, 10,320; hæmoglobin, 95 per cent.; polymorphonuclear, 69 per cent.; transitional, 2.4 per cent.; lymphocytes, 19.8 per cent.; eosinophiles, 2.4 per cent.; basophiles, 0.8 per cent.

April 19*th.* Red corpuscles, 5,720,000; leukocytes, 6080; hæmoglobin, 90 per cent.

The patient reported that several examinations had previously been made to determine the presence or absence of the Spirochæta pallida. One observer had failed to find this organism either in the serum taken from the skin over the eruption or in one of the lymphatic glands which was excised for the purpose of examination. Another observer had reported the finding of a single spirochæta in the examination of a number of slides prepared from the serum obtained from the skin over the eruption. The slide in which this supposed spirochæta was found had been lost and the finding could not, therefore, be subsequently verified. Without such verification we think it permissible to question the finding in view of the previous negative report on the serum and juice of an excised gland and our own subsequent failure to find the organism in the serum drawn from the skin or in the juice drawn from a thoroughly kneaded lymphatic gland.

Stomach Contents, November 28, 1905. Total acidity, 25; free HCl, 18; no lactic acid.

Dr. Evans' bacteriological studies were as follows:

On January 23d a cultural examination of the patient's blood was made. Five cubic centimeters of blood were taken from a vein at the flexure of the elbow-joint, a point free from the cutaneous lesions being selected. Twenty tubes of melted agar cooled to 45° C. were inoculated and plates poured. At the end of twenty-four hours there was such marked evidence of contamination that the culture was discarded.

A second examination was made January 29th; ten cubic centimeters of blood were taken with the same precaution to avoid skin lesions. Five cubic centimeters of this were divided equally among five flasks of bouillon, each containing 200 cubic centimeters; the remaining blood was divided among tubes of litmus milk for anaërobic cultures by the pyrogallic acid and sodium hydroxide method. The cultures were incubated in 37.5° C., and at the end of twenty-four hours there was a slight acidity in the milk. Sub-cultures were made from the flasks on slant agar, and twenty-four hours later a growth was found to have occurred in four of the flasks, the remaining one being sterile.

The organism in all four tubes was identical and proved to be a Gram-positive coccus, oval in shape occurring mostly in diplococcic forms but also found in chains of four and six. Division occurred in only one plane. A further description will be given later.

At the time the blood culture was made, smears were taken from the serum of the cutaneous lesions with the end in view of examining for the Spirochæta pallida, since previously there had been both a positive and negative report as to the presence of this organism. Our findings were negative.

The next day an enlarged axillary gland was massaged and a small quantity of the glandular juice withdrawn by a syringe. Artificial sodium hydroxide blisters were also made. Specimens of the glandular fluid and the serum of the blisters failed to reveal the presence of the Spirochæta pallida.

On March 27th a second blood culture was taken. At this time the patient was practically free from the cutaneous lesions. The only glandular enlargement was in the anterior cervical chains. The flask method was employed and subcultures showed growth in all five. Morphologically the organism was identical with the one isolated by previous culture.

On March 29th a culture was made from the depths of a large crypt in the tonsil. A mixed growth occurred, but one of the organisms was identical with that isolated from the blood. A systematic study of the cultural characteristics of the three organisms revealed only one difference. Culture No. 1 (isolated January 29th) produced slight acidity of litmus milk lasting for twenty-four hours, followed by an alkaline change, whereas culture No. 2 (isolated March 27th) and culture No. 3 (throat) produced permanent acidity. This difference, however, was thought to be due to the different ages of the three strains.

April 24th culture No. 1 (then three months old) and culture No. 2 (one month old) were again studied on the various media and exhibited identical characteristics. Culture No. 3 unfortunately became contaminated and was lost.

The following are the characteristics of this organism:

Morphology. Cocci, oval in form, occurring as diplococci and in chains of four and six. Division takes place in one plane and the elongation which precedes it sometimes is indistinguishable from a rod. There is a capsule especially when grown on blood serum. Involution forms are numerous.

Motility. None.

Temperature Requirements. Grows well at 37.5° on ordinary culture media; better on glycerin agar, blood serum and glycose agar; no growth at 20° or 28°.

Oxygen Requirements. Facultative anaërobe.

Gelatin. No growth either in plate or stab culture.

Glycerin Agar Plate. Superficial colonies are flat with an abrupt border and a deep dark central nucleus. They are homogeneous, translucent, grayish in color, and dew-like in appearance. Under the low power they appear irregularly round with rough edges, coarsely granular and light yellow in color. A short distance within the edge there is a greater degree of growth, from which ring it decreases both toward the centre and the true periphery (cross-section). The deep colonies are pin-head in size, irregularly round or whetstone shape with margins at first sharply defined but later showing irregular prolongations.

Stroke. Small, pale grayish, dew-like colonies. Marked growth in the water of condensation as a thick, white flaky sediment. In this sediment the cocci occur in longer chains and the capsule is more readily demonstrated.

Stab. Growth occurs along the entire length of the puncture as minute grayish, translucent colonies.

Potato. No visible growth occurs.

Blood Serum. Small grayish irregular colonies with slight tendency to confluence. A flaky cloudiness in the water of condensation.

Gas Production. None produced on glucose, saccharose or lactose media. Growth abundant along the entire length of the stab.

Litmus Milk. Slight acidity for twenty-four hours, then progressively increasing alkalinity. No coagulation.

Bouillon. The organism grows as a whitish, flocculent sediment, the medium remaining clear. Later the sediment becomes confluent and when the medium is shaken rises up from the bottom as a thread.

Staining. Stains by ordinary aniline dyes and by Gram's method. Optimum growth occurs on glycerin agar, glucose agar, and blood serum.

Pathogenesis. Was non-pathogenic to rabbits and guinea-pigs when inoculated in large doses intravenous, intraperitoneal and intrapleural. Slight temporary inflammation took

place at the site of subcutaneous injection. White mice inoculated subcutaneously sickened and lost weight, an abscess forming at the side of inoculation. When given plenty of sunlight and fresh air the animals recovered in two to three weeks. 2 c.c. of a suspension of the culture having a cloudiness equal to a twenty-four-hour typhoid bouillon culture injection into the inner surface of the right thigh of a ring-tail monkey produced in twenty-four hours an inflammatory reaction at the site of injection which continued for five days without producing suppuration. Three days after inoculation the right inguinal glands became slightly enlarged. Six days later they became markedly enlarged and there was noticed some enlargement of the left inguinal and right axillary glands. Four days later the left axillary glands could be palpated. The monkey did not apparently sicken. This glandular enlargement began to lessen at the end of four weeks and entirely disappeared at the end of twelve weeks.

We believe this organism to be one of the streptococcus group, because it divides in one plan and occurs in encapsulated chains. Notwithstanding the present tendency on the part of many observers to look upon the various streptococci found in different pathological conditions as being in reality the same organism modified in some of its characteristics we consider that this organism is distinct from the pyogenes variety or from the Streptococcus pneumoniæ. It resembles the latter because of the predominance of the diplococcic forms, but the character of the growth on agar and the size, shape, and consistence of the colonies are entirely different. The appearance of the colonies under the low power of the microscope, *e. g.*, the sharply defined edge and the concave centre, the production of an alkaline reaction and the absence of coagulation in milk, even in the first sub-culture, distinguishes it rather sharply from the pyogenes variety. The characters of the organism isolated by Schütz, Saud, Jensen and others from horses suffering with contagious coryza and glandular enlarge-

ment agree most closely with those found in the examination of our organism. We make this comparison, however, not to identify the organism isolated from our case with that of Schütz, but merely to state our belief that we are dealing with a peculiar form of the streptococcus.

Dr. J. William White, to whom the case was referred on account of the suspicion of syphilis, made the following report:

"The patient in question came to me on December 4, 1905. At that time he had a small papular, punctate, miliary eruption, irregularly grouped, profuse on the trunk, slight on the limbs. There was occasional itching. The inguinal, axillary, cervical, and supraclavicular group of lymph nodes were all enlarged. He gave me the following history:

"He had been well up to June, 1905. He then had urticaria lasting for three months, and very profuse. During this time he lost weight noticeably. In September his general health was poor but he had no local symptoms. In October, after drinking much mineral spring water, his general health improved, due, he thought, to the eliminative action of the fluid that he took in such large quantities, but toward the end of the month he had a heavy rigor, followed with fever (100° to 102°) and sweating, followed at once by palpable enlargement of the axillary lymph nodes and by sternal and substernal pain. After this a macular rash appeared, and his general condition became worse. The sternal pain extended; the sweats were profuse; there was marked dyspnœa; and about the end of October a distinct leukocytosis (21,000) was noted.

"He gave no history of any form of primary sore, or of any lesion, dry or ulcerative, that remotely resembled a chancre."

My expressed opinion was that he was suffering from some unusual form of toxemia, probably of tonsillar or gastrointestinal origin, and associated with a certain degree of toxic neuritis. I was then told of a slight development of jaundice that had accompanied his early symptoms, and of the ap-

pearance at about the same time of an eruption of an eczematous type which had affected the back, elbows, buttocks, and the posterior surfaces of the thighs. Still later, I learned that an examination of the blood, made at Dr. Stengel's request, had shown the presence of streptococci, and that the same organism had been found in cultures taken from the tonsils; all of which was, of course, evidence strongly confirmatory of the opinion I had given.

"Apart from the improbability that an intelligent, well-trained, and obviously intensely interested medical man would overlook or deny the existence of an initial lesion, and the comparative rarity with which such lesions remain undiscovered in the male, I was satisfied that the character and distribution of the eruption; the "intense" itching said to have been associated with certain of its early outbreaks; the urticarial character indicating a degree of nerve irritation unusual in syphilis, but in this case noticeable throughout (as a welt, bright red in color, could always be raised by slight friction of the skin); the degree of the fever and of the leukocytosis; the unusual enlargement of the lymph nodes (which much exceeded in size that of typical syphilitic glands); the direct associations of the symptoms with tonsillar and gastro-intestinal phenomena, which seemed to indicate the probable channels of infection; the severity of the sternal, substernal, and general thoracic pain, easily explainable by an enlargement of the mediastinal nodes, comparable to that noticed in those that were more superficial and palpable, but most unusual in syphilis; all led me to believe that the theory above mentioned was probably correct. At any rate, I was quite unwilling to join in a diagnosis of syphilis or to give my approval to any anti-syphilitic treatment which could only confuse the diagnosis or perhaps make a positive diagnosis impossible.

"I next saw the patient on May 27, 1906, and found that in the interval the eruption had largely faded, but without the development of any deeper lesions, the formation of scales,

the occurrence of mucous patches, or the appearance of alopecia. In other words, the intervening period was thoroughly atypical as regarded from the syphilitic standpoint. Furthermore, he reported to me that he had had several mild attacks of tonsillitis, on each of which occasions the eruption grew worse, and this was followed by the occurrence of articular pains jumping from joint to joint, and sometimes severe enough to be quite troublesome. His leukocytosis in the meantime had dropped to from 8000 to 10,000. This seemed to me to warrant persistence in my original opinion, which at this date (May 11th) I still hold."

Dr. Henry W. Stelwagon saw the patient several times prior to and after our connection with the case and has kindly given us an account of his observations:

"When I first saw the eruption about November 1st, it had already lasted about one or two weeks. It consisted of discrete but rather numerous rosy-red macules, with but slight, if any, elevation; the color was not a bright red, nor could it be said to be dull. The eruption could be seen over trunk, upper parts of the arms and upper parts of the legs, but was for the most part upon the trunk. The lesions increased in number for a week or more, and then began to show in their central portions the development of pin-point to a pin-head sized papules, which finally increased slightly in size, but the papule was never as large as a small pea, holding mostly to the size of a medium-sized pin-head. The papule was of the same color as the macule upon which it developed. Some new macules continued to appear and some of the older lesions became less distinct, and probably some disappeared. There was, however, no capriciousness, as there was more or less persistence in all lesions; but there was a variable amount of change in their depth of coloring, the eruption as a whole being much more hyperæmic or red some times than at other times. There was no marked crowding together nor grouping of the macules. At this time there was no scaliness, but later the small papules were here and there capped with a

minute scale. Upon pressure the new lesions seemed to disappear entirely, the older ones left a slight stain. Before the central papulation took place, the eruption was strongly suggestive of a macular syphiloderm, but the lesions were of a much brighter tint than was to be expected in this eruption, and could have been well considered as possibly a toxic macular erythema; but the individual lesions were much more persistent than one would expect in the latter rash. About the same time that the central papulation was developing, some macules appeared upon the forehead, and some upon the chin, and some near the nose and near the mouth, and later some of these showed slight scaliness, suggesting a patchy seborrhœa. Later, probably about three to four weeks after my first seeing the eruption, new small papules began to form in the neighborhood of the other papules, especially here and there in places, and the eruption became of a sluggish hue with a brownish tinge. When this condition had fully developed, the eruption consisted of some scattered macules, many with central papulation and irregular groups of brownish-red papules, the whole suggestive of a macular syphiloderm which had developed into an ill-defined and abortive miliary papular syphiloderm. As before, the rash showed some variation in its hyperæmic tinge from day to day, on some days being of a much brighter hue and of a puzzling character—too bright in hue for a syphilide; on other days, when the hyperæmic element was less marked, the diagnosis of a syphilide seemed the only permissible one. The eruption thus persisted with slight fluctuation for three or four months, gradually disappearing, having lasted in all about four to five months. The patient had a rather irritable skin and red lines and streaks could be easily provoked by rubbing, and it was due to this irritability of the skin, as it seems to me, that the eruption varied in its depth and brightness of coloring from time to time. There could scarcely be said to have been any distinct subjective symptoms."

In view of the confessedly atypical character of the eruption,

the complete absence of syphilitic history and the negative result of the clinical examinations our thoughts were directed to other possible explanations of the curious clinical picture and especially the cutaneous and glandular features. From the beginning there was a strong presumption of some form of toxic or infectious disease and, in view of the long continuance of the symptoms, more decidedly that of an infection. The onset with gastrointestinal symptoms and tonsillitis, chills, and jaundice, and the successive development of fever a skin eruption and glandular enlargement, of vague general pains and more localized pains under the sternum and in the joints all suggest a systemic infection. The occurrence of leukocytosis and anemia strongly corroborates this view and the bacteriologic examination confirmed it, though not in itself wholly excluding the possibility of another infection, such as syphilis, not certainly demonstrable to cultural methods.

It must, of course, be admitted that practically all of the symptoms referred to may occur in the early stages of syphilis. Thus the repetition of tonsillitis, the development of early jaundice, the appearance and persistence of fever, the recurring eruption in the skin and the pains and leukocytosis, all are possible manifestations of syphilis, but it is noteworthy that each of these occurred in a manner or degree quite unusual in syphilis. Placing those facts alongside of the denial of venereal or other syphilitic infection and the positive and identical results of culture from the tonsils and blood on several widely separated occasions the presumption seems to us a very strong one that the whole condition was one due to a form of streptococcus infection of unusual character.

The presence in the tonsils and in the blood on two occasions separated by one or two months of a streptococcus of peculiar character and properties establishes the existence of such an infection. The organism was certainly not of the pyogenes group and differed both culturally and morphologically from any of the streptococci usually encountered in human pathology. Though not in every respect identical

with the descriptions of the Streptococcus equi found by Schütz and others in epidemic coryza and glandular enlargement of horses, the correspondence was suggestive.

The association of cutaneous lesions with mild or severe forms of septicopyæmia and with rheumatic polyarthritis has been recognized for a long time. The so-called surgical scarlatina (Thomas, Riedinger) is a simple form of this condition. It may present itself as an ordinary erythema or an erythema associated with urticaria and vesicles (Gussenbauer). Brunner has recently called attention to this condition and determined its relation to streptococcus infection. In a series of thirty-five cases of septic infection Litten found skin lesions in 80 per cent. Among the manifestations were multiple hemorrhages, jaundice, macular erythema, pemphigoid lesions, scarlatinous and morbilliform erythema with urticaria, hemorrhagic vesicles, hemorrhagic herpes, phlegmons, and erysipelas. Leube described herpes, hemorrhagic vesicles, and urticaria as associate cutaneous manifestations of cryptogenetic septicæmia. Deenig reports the dermal lesions of sepsis as of the type of erythema multiforme.

Kaposi, in calling the attention to the association of joint manifestations with erythema multiforme, suggests that this relationship suggests an etiological kinship or identity. A similar view has been put forward by Sir Dyce Duckworth, Smith, and other English authors. Boeck, Fowler, Garrod, Stewart, and Lasegue have referred to the occurrence of erythema nodosum or multiforme, or rheumatism and endocarditis as consequences of tonsillitis, and Gerhardt, Osler, and Lewin have emphasized the association of erythema multiforme with endocarditis and other grave visceral lesions.

If, as we believe, our patient's illness was due to a peculiar form of streptococcic infection it is probable that the tonsils were the original seat of the infection and portal of entrance of the organisms. The early occurrence of distinct pharyngitis and tonsillitis and the subsequent repetition of attacks as

well as the appearance of the tonsils strongly indicated a local condition of the throat as the course of the continuous infection. However, as this is a matter of uncertainty we have used the title cryptogenetic infection, though we are impressed with the probable tonsillar origin of the disease.

The Attitude of the Clinician in Regard to Exposing Patients to the X-Ray.

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Assistant Professor of Medicine, University of Pennsylvania; Woodward Fellowship in Clinical Chemistry, William Pepper Laboratory of Clinical Medicine.

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In its relation to medical practice, one of the most remarkable things about the *x*-ray is the tardiness with which there was any realization of its power of producing very marked changes in other tissues than those superficially situated. So large a number of persons have for years been exposed to the action of the *x*-ray that it seems strange, indeed, that, while it is now known to have very decided and sometimes profound constitutional effects, the recognition of such effects by clinicians has come only after years of use, and chiefly because of purely empirical and even haphazard clinical observations. In fact, for some time after it became reasonably evident that it influences the general organism, many persons persistently doubted whether the general effects were actually due to the *x*-ray.

X-RAY AND METABOLISM.

At present this doubt is thoroughly dispelled, for more extended trial with patients and with animals of the clinical effects of exposures, histologic studies of the tissues of human beings and of animals that have been exposed, and investigations of the influence of the *x*-ray on metabolism have all shown that it has in some instances, and particularly on some tissues, a most energetic and powerful effect. In spite of the continued and already extremely impressive accumulation of facts re-

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lating to this point, there is as yet, it appears to me, an insufficient appreciation of its importance to clinicians. With agents that are introduced nowadays for diagnostic or therapeutic purposes, it is customary, as a rule, to study the manner of action, to reflect carefully on the character of the cases in which the effects are likely to be useful and those in which they may be harmful, and particularly to determine all these points, as far as possible, by purposeful experiments before such agents are used freely with human beings. With the *x*-ray, on the contrary, the method that has been adopted has been to try its effect for both diagnostic and therapeutic purposes on all manner of conditions, and only gradually, largely by painful experience, to learn that it may have dangerous effects, and seems usually to have noteworthy general effects if the organs active in metabolism are exposed to its influence; while, at the same time, in this somewhat hazardous way, it has been empirically or by lucky chance learned that some general affections are benefited, some are not in any noteworthy degree altered, and some perhaps are harmed.

Partial justification for the risks that have been run may be found in the novel power of the *x*-ray to picture many conditions of the internal organs, when this, of course, had previously been wholly impossible. The manifestly great value of this from a diagnostic standpoint, and the fact that profoundly dangerous effects are unusual and other less dangerous but nevertheless deplorable results of its use are often unnoticed for a long time or have but an inconspicuous relation to the exposure to the *x*-ray, led to a rather natural and wholly humane desire to determine as widely as possible its value in diagnosis; and an empirical study of its therapeutic relations somewhat naturally followed this. It is not surprising that some of the evil results, sterility, for example, were long overlooked, for this effect is not one that becomes apparent readily; and it could with difficulty have been decisively attributed to the *x*-ray, were it not that, the possibility having once arisen, experiment readily demonstrated conclusively that exposures may produce it. The same is true to a less marked degree of nephritis, for this affection may run so silent a course as to have little evident relation to its cause; and, likewise, late toxic reactions, as well as mild and rather indefinite early toxic reactions, are difficult to attribute

clearly to the *x*-ray unless attention is carefully directed toward proving this point. Nevertheless, it can hardly be said, I think, that, because its manner of action was unknown, the empirical method of determining which cases were suited and which were unsuited to *x*-ray exposures was necessary, if an agent so evidently valuable was to be used at all. We are not, as a rule, in haste to experiment with human beings in regard to the effects of new drugs until we have determined whether or not they have noteworthy constitutional effects, and, if they have such effects, which tissues in particular they influence; but in the case of the *x*-ray no extensive attempt was made to determine that it had general effects until remarkable results of its empirical use, partly favorable and partly disquieting, demonstrated that it actually has.

That the empirical and not the experimental method of study was first used with the *x*-ray is, I believe, much more largely the fault of those of us who are medical and surgical clinicians than of those who are specialists in the use of the *x*-ray; for, in the first place, the latter, in a large proportion of instances, receive their patients from clinicians for the single purpose of having them exposed to the *x*-ray, the clinician being responsible for its use, while the *x*-ray specialist merely carries out the clinician's orders in a skilful manner, and, in the second place, it is essentially the duty of the clinician, before any measures are recommended by him, no matter who conducts them, to determine or to have determined the main features of its good or bad general effects.

As has already been stated, we now have sufficient evidence of decided general effects, and there is no longer any question that we should, as far as possible, decide on its use in the same manner as we determine with other agents whether they shall or shall not be employed. It appears to me, therefore, to be of much importance to determine, as far as we may, the general nature of its action, in order that an agent that has already become so valuable, especially in diagnosis, may not have further discredit thrown on it through encountering dangers in its use that might have been avoided by proper study, and in order that its usefulness may be rationally extended into proper channels. A somewhat extensive series of studies of the effect of the *x*-ray on metabolism in various medical conditions that I have made in the last eighteen months, part of which I have

described, part remaining as yet unreported, together with some investigations of others on the same point, have shown that the influence on metabolism is, in some instances, most violent; that it occurs even in normal persons, and that apparently when a general influence is clinically evident it is always associated with decided changes in metabolism. These changes in metabolism are due largely, if not entirely, to tissue destruction that occurs chiefly in those tissues rich in nucleoprotein, and they are evidenced most particularly by an increase in the total nitrogen output, with ordinarily a relatively large output of uric acid, purin bases and phosphates, the substances that indicate the degree of nucleoprotein destruction. Extensive histologic studies by various authors, among whom Warthin is most conspicuous in this country, show that the special tissues most severely affected are the bone-marrow, spleen and lymphoid tissues; the effect on these tissues being, indeed, so much more marked than on any others as to be almost specific.

My studies in metabolism have further pointed out some facts that were previously less clear or not at all evident and that are of very considerable clinical interest and importance. For example, they have shown that at times a single exposure of ordinary severity may have a most profound influence on metabolism and one that may show itself for many days afterward. The effect of an ordinary dose may, in fact, be more severe than the effect of a similar dose of any other therapeutic agent with which I am acquainted, and may either be extremely useful clinically or so dangerously violent as to hasten death, and perhaps even to cause it when it would otherwise have been avoided. I would note, also, that in one instance an exposure for an *x*-ray picture, only eight seconds in duration, although actually a moderately severe exposure, produced so striking an effect in one patient (a case of unresolved pneumonia) that he excreted more than double the amount of nitrogen and nearly double the amount of chlorids that he had passed in equal periods previously; the effect in this case having been highly beneficial, but so violent that in some disorders it might evidently have been most dangerous. This point is of interest and importance, in that it demonstrates the possibility of occasional dangerous effects from the mere diagnostic use of the *x*-ray.

Further, I would direct especial attention to the sug-

gestiveness of an observation that I made when studying the metabolism of a case in which a severe toxic reaction occurred. I have the records of three cases in which, after one exposure, there was a reaction so severe as to make the patient profoundly ill, and in two of these cases death occurred, while the third patient had a narrow escape. In only one instance was I personally responsible for the use of the *x*-ray. In two of these cases I was studying the condition of metabolism before the reaction occurred, and I continued the observations afterward, and was thereby enabled to determine that with the reaction certain marked changes occur that had not previously been noted and that help, I think, to make clearer the nature of this disturbance. The special features of metabolism in these cases I have described elsewhere and need not repeat, but the point that I wish to emphasize here is that in one of these cases it was clinically not clearly evident that the *x*-ray exposure produced the severe illness that followed it. Indeed, the careful clinician that had charge of the patient had not considered the probability that it was due to that cause; for the man had been more or less ill for some time, and it was rather naturally supposed that the increased illness was merely an accentuation of the previous condition and that it occurred at the time it did through pure coincidence. But the patient's metabolism showed the same peculiar changes as those seen in another case during what was clearly a severe and almost fatal reaction to an *x*-ray exposure, and I think, therefore, that there is little, if any, doubt that the added symptoms in the man under particular discussion were due to the *x*-ray.

I would also particularly note that this man received an intentional and direct exposure only over one arm from the elbow down; though the trunk was not screened, and hence he undoubtedly got a general exposure which, while distant, was nevertheless an exposure to the deeply penetrating rays. It was, however, mild and was of but five minutes' duration, the intensity of the general exposure having certainly been less than is commonly used in their diagnostic or therapeutic exposures. In addition to this, I would draw attention to the fact that the other patient whose metabolism I studied at the time of the toxic reaction, and who showed profound clinical symptoms and violent disturbance of

metabolism, received what Dr. Pancoast tells me was the mildest exposure he had ever given.

It seems to me that the moral to be drawn from these cases is that we must be on the watch for mild or moderate symptoms, as well as for severe ones, after *x*-ray exposures; and must be prepared to determine fairly and justly whether unfavorable symptoms of some degree are not much more commonly due to the *x*-ray than we have hitherto believed and whether their relation to the *x*-ray has not been obscured by pre-existing disorders, which, instead of the *x*-ray, have been held responsible for the increased symptoms. I think most conscientious and conservative *x*-ray specialists already believe that, at least to some extent, this is true, and it appears to me to be highly probable, for, as I have said, even extremely mild exposures may produce very great alterations in metabolism, and it is but natural that this might not uncommonly cause unfavorable symptoms in persons that already had serious disease.

CARE NEEDED IN USE OF X-RAY.

In consideration, then, of the various facts that we have learned in recent years I believe that we should recast our attitude in regard to the use of the *x*-ray even more decidedly than we have done. As far as I am able to judge, the great majority of clinicians look on the *x*-ray, first of all, as an agent that makes valuable pictures and that does good in some diseases; and only secondarily and somewhat distinctly as an agent that has powers for harm and has been known to do harm. The attitude that appeals to me as a suitable one for the careful clinician to assume is that the *x*-ray is, first of all, an agent that has as active an effect on the organism as has a powerful dose of medicine; that it is not to be used at all, therefore, unless there is some reasonably evident useful purpose in view; that with those that are seriously out of health it is to be used at first tentatively and with brief and mild exposures; that in case fairly definite contraindications can be found to exist persons that present such contraindications shall not be exposed at all, unless cogent reasons for doing so seem to outweigh those to the contrary; and, finally, that the clinician should not order a patient to be exposed to the *x*-ray unless he has taken measures of a simple and reasonable character to determine that there are no easily rec-

ognizable conditions present that appear to contraindicate its use, or, if such are present and he still desires to use it, he should acquaint the *x*-ray specialist of the fact of their presence, in order that especial caution may be exercised. Furthermore, the clinician should know that the individual *x*-ray specialist to whom he refers patients protects habitually, as far as this can be done, all parts except those that require exposure, by properly screening them.

These rules may appear somewhat severe, in contrast with the easy freedom with which the *x*-ray has long been used, but I am sure that most thoughtful *x*-ray specialists will agree with me that they are, in the main, proper, and I know that a limited number of clinicians do nearly all these things already. I may seem extreme in having purposely constructed my statements so that they mean that a physician or surgeon should not lightly and without considerable knowledge of his patient have him exposed to the *x*-ray for either diagnostic or therapeutic purposes. I believe that this is a proper attitude, but I would hasten to explain that I do not wish to exhibit or to excite in others an hysterical fearfulness of the *x*-ray or the feeling that the dangers are imminent and ever present. I shall perhaps make myself clearer through an analogy with the use of anesthetics: There are dangers associated with their use, and no one thinks of recommending that they be used unless he has a clearly defined purpose in doing so. Even with persons apparently well, it is a general custom to determine first that the patient is not the subject of any disease that renders the use of an anesthetic possibly or certainly dangerous to a degree that makes one question the wisdom of using it at all with him individually, and if such disease be found and it is still decided to be best to proceed both surgeon and anesthetizer do so with particular caution. Such precautions are taken almost automatically nowadays and no one considers them unreasonably burdensome.

What I have said in regard to the use of the *x*-ray amounts to much the same thing, merely modified somewhat to suit the different conditions. I would not urge that the *x*-ray be used, each time that it is employed, with ponderous and fearful thought of its dangers and that it be used only when one unwillingly feels that he can not escape it; but I would urge that its unnecessary

use be discarded, and particularly its repeated use, when one exposure has given all the information that is likely to be gained and when further exposures are undertaken largely from restless diagnostic curiosity. With cases in which rapid diagnosis of fractures or the like is desired, or when a small area is to be treated for epithelioma or other superficial disease, I would not advise hesitation in its use or recommend any especial precautions, except the extremely important precaution of limiting the exposure as carefully as possible to the area that is intentionally exposed. It is, I think, part of the clinician's duty to his patient to determine that the *x*-ray specialist that does the work recognizes the necessity for habitually doing this. Even with robust persons it is desirable, simply because it is always unwise to administer to any one an unnecessary dose that has an active and ill-understood effect on metabolism, and this is still more true if repeated exposures are given. With persons that are already seriously out of health it is even more urgently desirable, as is emphatically illustrated by the case that I have noted, in which a severe reaction followed an exposure of the lower part of one arm, and in which this could probably have been largely or entirely avoided had the other portions of his person been protected.

In cases that require extensive exposures, even though these be only over the extremities, and even though the trunk can be protected, we are treading on somewhat more dangerous ground and should go somewhat more cautiously. I have seen one case of pernicious anemia in which an exposure over the thighs produced a reaction that was the cause of a violent access of symptoms soon ending in death. The bone marrow is known to be one of those tissues that exhibit peculiar sensitiveness to the *x*-ray. Hence, when large areas of marrow are exposed, bad results may readily follow. In healthy persons, the possibilities of harm are so distant that they probably do not deserve very serious thought, but it is desirable that before exposure an examination of the patient, which should include an ordinary examination of the urine and some consideration of the general features of his case, should have furnished evidence that he is reasonably healthy. If he is distinctly out of health, I think that the indications for the use of the *x*-ray, even for diagnostic purposes, should be definite and

at least moderately forcible before it is used over extensive areas. If he presents certain forms of disease that I shall mention soon, I think the *x*-ray should be avoided, if possible, and, if it is employed at all, it should be used with great caution and under the stress of urgent indications.

In the case of exposures of the trunk, all I have just said may be applied with some added emphasis. Healthy or moderately healthy persons are not at all likely to be harmed by them, but patients should not have them given in the first instance or have them repeated, unless there is good occasion for doing so, and unless it has actually been determined that these persons are not seriously out of health. With persons whose health is decidedly disturbed, there should be serious consideration of the propriety of extensive exposures before they are undertaken; there should be a tendency to avoid them unless they are very distinctly indicated; and one should have as clear a knowledge as possible of the patient's general condition before ordering the exposure. I have some doubt, even, of the propriety and safety of the use of plates and the fluoroscope in the diagnosis of cardiac and pulmonary disease, in case the patient has much circulatory incompetence or a noteworthy degree of infectious toxemia; and in such conditions I especially question the wisdom of the frequent and often rather regardless use of this method that has not uncommonly been adopted in recent times by enthusiasts. Personally, I use the *x*-ray for diagnosis in both cardiac and pulmonary disease, but I use it only when it seems especially desirable because other methods are insufficient, and in employing it I try to use well-considered caution.

In bringing together the limitations to be placed on the use of any measure, one escapes with difficulty, if at all, the danger of over-emphasizing the evils. I have tried to avoid this, but, lest I have not succeeded in doing so, I would again insist that my purpose has not been to urge a general restriction of the use of the *x*-ray in all sorts of cases, but rather to plead for its use in a manner that guards, as far as possible, against dangers that are, in occasional instances, known to be great and that are probably not uncommonly encountered in milder and less evident forms. I have, further, desired to urge that occasionally, in cases that past or future experience

may lead one to think especially unsuitable, its use should be discarded altogether or should be undertaken only with caution and after a just balancing of the good and evil chances has made the latter appear to be the lesser. I have insisted on caution with all those that are seriously out of health, unless the exposure is limited to a narrow area, and I think reasonable conservatism justifies this view. A certain degree of freedom must necessarily be exercised in deciding which cases require especial caution and much more knowledge and experience will be needed before we can be generally accurate in this regard.

DISEASES THAT SUGGEST SPECIAL DANGERS IN USE OF X-RAY.

There are at present, however, certain points in our knowledge that indicate that the most noteworthy dangers are to be expected in those diseases in which there would be particular difficulty in completely disintegrating and in excreting the products of the tissue breakdown that the *x*-ray causes; and two groups of disorders seem to deserve more careful consideration in this respect than any others with which we are as yet familiar.

One of these has become pretty well known. Clinical and pathologic observation has shown that nephritis may follow *x*-ray exposures, and the enormous increase in excretion that sometimes follows exposure makes it evident that the kidneys are likely to suffer. From the occasional occurrence of nephritis, therefore, as well as from observations on metabolism, we must conclude that with those patients who already have nephritis or those whose kidneys are under especial strain *x*-ray exposures should be guardedly used or excluded.

The other group has been suggested to my mind by the fact that all the cases in which I have seen evidently serious results were already subjects of a considerable degree of toxemia. It would seem highly probable that a person already struggling with a toxemia would be more likely than a normal person to suffer ill effects to his organs of metabolism, as well as to his kidneys, if, in addition to his previous burdens, he were suddenly required to complete the disintegration and excretion of a large mass of broken-down tissues. It appears to me, therefore, that those who are to any noteworthy degree toxic from metabolic disorder or infectious dis-

ease should not be exposed without great caution and without urgent reasons.

It is probable that a third group with which we should proceed very cautiously is constituted by those cases that are very anemic. The tissue-destroying effect of the *x*-ray is so largely exerted on the blood-building organs that it might readily cause serious embarrassment if these organs are already insufficient, and I have notes of two patients with pernicious anemia who became profoundly, indeed, fatally, ill after one exposure. On the contrary, I know two patients with the same disease that were benefited, one very greatly and rapidly benefited, by *x*-ray treatment, and it is possible that in some circumstances ordinary doses may destroy or at least seriously damage large portions of the blood-building organs, while in other circumstances the same dose may influence them favorably. It is possible, too, that toxemias may at times be favorably influenced, and it must likewise be admitted that the effect is not damaging in every case of nephritis. Nevertheless, in our present limited state of knowledge, it seems wise to be exceedingly cautious with cases of nephritis, of marked toxemia, and of decided anemia, and particularly with those cases in which there is pronounced anemia in association with a distinctly toxic state. I believe that further clinical, metabolic and other accurate studies of the contraindications, as well as of the indications, for the use of the *x*-ray constitute a valuable field of investigation, and it seems to me to be extremely desirable that clinicians make it a general custom to observe patients very carefully after *x*-ray exposures, in order to determine whether noteworthy after-symptoms seem to be common. even though the patients appear to be doing well under the exposures, and particularly to make careful studies of the urine in a large number of cases. The result of such observation would not be to throw further discredit on the *x*-ray, but to make it possible to use it more rationally and with more logical judgment.

I may not improbably be met with the objection from various sources that as yet there are but a limited number of dangers known to be associated with the use of the *x*-ray and that the number of cases known to have been seriously damaged is small. I think this objection may be met with sufficient force by the statement that the dangers of the *x*-ray have been recognized for only a

comparatively short time, and that there has consequently been relatively little opportunity to determine how great and how numerous they are; and that, in spite of this, a very considerable number of cases that have been injured have been described. The histologic studies and the studies of metabolism that have thus far been made make it wholly rational to expect that the dangers are more frequent than we yet know, and the standpoint that appears to me to be wise and proper is not to belittle the dangers and attempt blindly to escape them, but to determine in whatever ways are open to use what they are and how they may be avoided.

THERAPEUTIC VALUE OF THE X-RAY.

I have thus far dealt almost entirely with the points that should limit or discourage the use of the *x*-ray and I have done this purposely because, while these points are still hazy, they are, nevertheless, more definite and demand more immediate attention than those that relate to new indications for its use. Still, as I said earlier, one should have in mind not only the determination and restriction of the dangers, but also the discovery of new channels of usefulness. An agent that has a profound effect on metabolism is not likely to exercise this effect solely in an evil way if proper opportunities for doing good with it are sought out. It is evident already that in leukemia and in some other general disorders metabolism may be stirred up by the *x*-ray to the accomplishing of at least transitory good, and it appears to me probable that some other disorders of metabolism not yet known to be benefited by the *x*-ray might be improved through its use. Up to the present my observations in this direction, which have been limited in number and have been undertaken only in cases that seemed to be proper to subject to exposures, have remained of little or no therapeutic value, except in one condition, in which they have been quite encouraging.

I have had the *x*-ray used in two cases of gout, a disease that has repeatedly been treated in this way. The clinical results in other instances, as well as in these two cases, have, I think, been doubtful or discouraging. The studies of metabolism that I made with Dr. Fife in these two cases, during the time that they were under treatment, showed that the exposures had no influence in stopping or warding off the disturbances of metabolism

that are associated with the attacks. Likewise, in two cases of diabetes that were subjected to this treatment no changes of consequence could be demonstrated in the clinical condition or in the excretion of sugar and acetone bodies. I tried the effect of the *x*-ray, also, on a case of persistent headache associated with a deposit of oxalates in the urine, and, while the increase in general metabolism that has usually been observed was noted in this case, there was no change in the amount of oxalic acid that was determined to be present and the clinical condition was not altered.

In several cases of unresolved pneumonia I have had promising results. I used the *x*-ray in these cases because I believe that it probably acts chiefly through increasing the velocity of some ferment processes and because in unresolved pneumonia it is probable that the ferment processes that should and ordinarily do dissolve the exudate are ineffectual. In three such cases the clinical effect was a rapid clearing up of most or all the signs, and in two of these cases in which Dr. Pemberton and I studied the metabolism we observed a tremendous influence that was coincident with the improvement in the physical signs, the metabolic alterations having been of much the same quality and degree as those that are seen at the time of an ordinary successful crisis. These latter results are, then, encouraging. While the others mentioned are not so, I believe that there is certainly constructive work to be done in searching out the therapeutic relations of the *x*-ray, and not simply the more destructive type of work that I have chiefly discussed earlier. I think this is particularly true if the work be planned with the view that this agent has a lively influence on metabolic processes, particularly on those that occur in the spleen, the lymphatic tissues, and the bone marrow, and if it be carried out with a calm but definite appreciation of the restrictions that should be placed on any such experiments in therapeutics.

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OBSERVATIONS RELATING TO THE NATURE OF ATROPHY OF INTESTINAL ORIGIN.

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General atrophy that is associated with, and apparently stands in direct relation to, a greater or lesser degree of preceding intestinal disturbances occupies a position of profound importance in the pathology of infancy. Marasmus is, indeed, so common and often so intractable that the laity are almost as familiar with its general features as are physicians. Much less commonly, but still occasionally, a condition that is, in its chief clinical features, apparently the same as the atrophy of infancy, appears in early childhood. In later life, typical cases of this kind are rare; there are, however, very many instances of serious disturbance of general nutrition that seem to bear a direct relation to intestinal trouble, but are too pronounced in their general features to be satisfactorily explained by the mere loss of nutriment that occurs through lack of digestion and absorption—for these patients may still be absorbing an amount sufficient to maintain or improve nutrition, and yet they emaciate or remain about stationary in a condition of more or less profoundly depraved general nutrition. Cases of this kind have recently been studied by Roehl, who decides that the disturbance of nitrogen absorption does not suffice to explain the tissue loss; and the general absorption is at times quite sufficient to cover their needs.

THEORIES REGARDING ATHREPSIA.

An immense amount of work has been devoted to the study of the pathogenesis of infantile atrophy, particularly, but no satisfactory explanation of the nature of

the condition has been furnished. It has been shown that digestion and absorption are impaired in most or all atrophic infants, but the degree of impairment is often by no means enough to explain the atrophy. I have myself, with Dr. Caspar Miller, studied the absorption in several such cases, and while it was below normal, it was not exceedingly bad and the infants still absorbed an amount sufficient to have made most of their contemporaries gain in weight and health.

The lesions found at autopsy are, too, insufficient to explain the condition. There is still a somewhat general belief that an extensive primary atrophy of the intestine occurs in these cases; but while this has repeatedly been described and has been considered the cause of the general emaciation, it has been shown by Heubner, Gerlach and Habel that the appearances on which so much stress has been laid are really due to the manner in which the intestinal wall is prepared and cut for microscopic examination. Wentworth's recent able review of the pathology of the condition leaves only a single fact undisproved—Bloch found in several cases an absence of the granules that are normally present in Paneth's cells.

The hypothesis has also been put forward (Escherich) that the disorder may depend on the ferments and other obscure biologic elements in human and animal milk. This, however, could not explain the matter, for it leaves out of consideration the fact that athrepsia occurs in only a portion of artificially fed infants and not in all.

Recently a suggestion of another kind regarding the nature of the condition has been put forward. Since the injection of animals with protein of foreign species is followed by the development, in the blood serum of the animal injected, of substances capable of precipitating the protein that was introduced, Moro and Hamburger have attempted to show that the serum of atrophic infants contains a precipitin for cows' milk—thinking that they could in this manner demonstrate that foreign protein (namely, bovine casein) reaches the circulation in such cases. If this were the case, it might be conceived that this foreign protein produces chronic toxic symptoms that lead to emaciation, even though sufficient food be absorbed. They were not successful in their work, but Moro has recently found such a pre-

cipitin in one case. He declines, however, to draw any conclusions from this as to the nature of infantile atrophy. Even if such a precipitin is frequently to be found its presence may, I think, be quite as properly, if not more properly, applied in another way, in support of my own working hypothesis regarding the nature of infantile atrophy, which hypothesis I shall describe.

RECENT VIEWS OF PROTEIN DIGESTION.

I shall first, however, in order to make the character of my conception clear, find it necessary to refer very briefly to some of the recent transformations of view concerning the nature of protein, and the manner in which it is digested and utilized by the tissues, and shall refer also to some points in regard to ferments. All these matters are well known to those that have had particular interest in such questions, but are not yet generally appreciated.

The comparatively simple teaching of a few years ago, when put into its briefest form, was that the digestion of protein consists essentially of hydrolysis into albumoses and peptones, and the formation of small amounts of some simpler bodies—chiefly amino-acids, such as leucin and tyrosin; and that the albumoses and peptones are absorbed and, in the process of absorption or very soon after this, built up again into native protein. The process as conceived at that time was, therefore, in the main part merely hydrolysis of higher protein to lower forms of protein—the major portion of the substance remaining protein all the time, and the chief apparent purpose of digestion being to transform the ingested protein into substances that are relatively very soluble and that easily pass animal membranes; that is, to get them into a form in which they can readily reach the circulation.

Throughout recent years, however, it has become increasingly evident that the change is much more fundamental than this; and the key to the understanding of the main purpose of digestion seems to have been furnished by more elaborate study of the products of digestion, and particularly by a more intimate knowledge of the composition of protein. That is, it has been shown that a protein consists of a union of numerous crystalline substances which are relatively simple in their structure as compared with protein, but still somewhat

complex; these are chiefly or entirely so-called amino-acids, among the many of which leucin and tyrosin are the most popularly known representatives. Protein substances of different kinds contain varying amounts of the various amino-acids, but they differ quite as much in the quantity as in the quality of the component substances. Some forms of protein do contain some kinds of amino-acids that other protein substances do not, but the distinction between different protein substances seems to lie quite as much, if not more, in the fact that this one contains more of certain amino-acids, that one contains less of these amino-acids but more of others. To use the picturesque simile employed by the Germans to describe the matter, proteins are constructed of "buildings stones," and stones of many shapes are used in building any protein; but the ultimate structures differ in their architecture, and in giving them their proper form, sometimes more stones of one shape are employed, sometimes more of another.

Concurrently with the development of the above mentioned knowledge, it has been shown that the digestive breakdown of protein is much more complete than was previously taught. Even pepsin can carry a large part beyond the peptone stage, and trypsin does this much more quickly and extensively than pepsin. Trypsin, indeed, is capable, even in laboratory experiments, in some circumstances, of carrying the whole amount of protein beyond the peptone stage; and, hence, under the more favorable conditions that exist in the animal organism, it probably carries most, possibly nearly all, beyond that stage.

At the same time, it has been made apparent that the intestinal mucous membrane contains a proteolytic ferment which has been given the name erepsin. Whether this has the characteristics attributed to it by Cohnheim—namely, inability to attack native protein, but active powers of further fragmenting albumoses and peptones—or whether, like trypsin, it can carry on the process from the beginning, is a question that is still *sub judice*. Of the existence of a proteolytic ferment in the intestinal mucous membrane, there is, however, no question; and there is every probability that it is produced there, and is not simply pancreatic trypsin that has lodged there.

It seems at present that the purpose of digestion is to

fragment the protein complex thoroughly into its constituent amino-acids, or building stones; and that the protein falls first into the hands of pepsin, then trypsin, and next the ferment of the intestinal mucous membrane, in order that with each attack the fragmentation may be made more complete. It is not yet clearly determined whether these ferments actually differ, as they have been supposed to do, in the nature of the end products that they produce. The progressive action of one after the other may be intended simply to permit each succeeding ferment to put finishing touches on the portions of unfragmented or partially fragmented protein that have escaped the preceding ferments. The prime object of this breaking-up process appears to be to yield the amino-acids themselves; in order that they may be available in free form and in proper quantities, for a complete reconstruction, which will yield protein homologous with the individual to be nourished. It is not necessary to fragment all portions completely as certain fractions will be obtained that can be reconstructed into homologous forms without complete fragmentation, but except for such fractions it must be complete. That the digestive process, together with the subsequent reconstruction process, does accomplish this transformation—that is, that it does change protein of foreign species, containing certain amino-acids in quantities peculiar to this protein, into another form of protein, apparently containing the same amino-acids in quantities peculiar to the individual that has digested and absorbed the protein—has been shown experimentally with almost final positiveness; and it has likewise been shown that the reconstructive process occurs before the absorbed digestive products reach the general circulation, almost certainly, indeed, in the intestinal wall itself.

Furthermore, physical chemists consider it to be theoretically well nigh certain that the same ferment that accomplishes fragmentation also causes the reconstruction—that the direction in which a ferment acts, whether toward the production of simpler products or toward the formation of more complex substances is determined, not by the nature of the ferment, but by the physical and chemical conditions of the medium in which it acts and by the concentration of the products of digestion. If conditions favorable to disintegration

are present, the ferment hastens this; but if the conditions favor synthesis, the same ferment hastens this. This has actually been shown to occur with some ferments that act on carbohydrates and fats; and similar observations that are suggestive, though not yet conclusive, have been made regarding proteolytic ferments, the conditions of such experimentation with the latter ferments being much more difficult than those attached to carbohydrate and fat ferments. If this view that ferments are capable of reversed action is correct, as a general principle, and this now appears most probable, the same ferment in the intestinal wall that continues the process of fragmentation of the protein food also carries on the process of reconstruction of homologous protein.

This cursory statement of some of the main aspects of the present day teaching of the physiology of digestion will, I trust, suffice to make clear the hypothesis that led to the observations I am about to report. My results have not yet been sufficiently extensive or elaborate to justify, of themselves, quite so formidable a preamble as I have given, were it not that the explanation is necessary in order to make their bearing clear. So far as they go, however, they offer some support to the following hypothesis:

THE AUTHOR'S HYPOTHESIS.

Clinically, it is quite clear that most atrophic infants do well, provided they are not already far advanced toward death, if human milk can be given them; while with even the most capably conducted artificial feeding, they usually have, at best, a precarious and long struggle for existence, and very often go slowly, but persistently, toward death. It seems, then, that the difficulty consists in making use of milk of foreign species. The difficulty does not lie simply in acomplishing the absorption of the elements of the heterologous milk; for, as I have already noted, sufficient is absorbed in many of these instances to produce a gain in other infants.

It has seemed to me that the disturbance may be the result of disorder of the ferment function of the intestine. That is, when the protein of the food is progressing in the course of its breakdown the final attack by the ferment of the intestine does not occur or is ineffectual; that the protein complex is torn apart more or

less completely by the pepsin and trypsin, but that fragmentation sufficiently complete, in order that the structure may be rebuilt in a new form entirely homologous with the patient's tissues, does not take place.

Granting the absence or serious reduction of this ferment in cases of atrophy, one of two things may be conceived of as occurring as a consequence: in the first place, it might be that the protein would be fragmented to various stages short of absolute completeness—to albumoses, peptones, simpler non-protein amino-acid complexes (heptides) and in more or less considerable extent, to free amino-acids—and that these would then be reconstructed; but the synthesis taking place without sufficient preceding fragmentation, the product of synthesis is not the normal one, but is more or less hybrid in character. To use again, for clearness of conception, the building stones simile, it would be like taking away the upper structure of a building, while leaving the foundation unaltered, and then making the new structure conform to the old foundation, instead of tearing out the latter completely and building anew from the start. The infant would, in such a case, have his circulation and tissues supplied with more or less markedly foreign protein, while normal infants receive homologous protein. The infant nourished with mother's milk, even though he absorbs all his protein food wholly unfragmented or only half fragmented, would not so far as we know, be crippled by this, for his food protein is already homologous. The artificially fed infant that I have postulated, however, who receives imperfectly broken down, and hence improperly reconstructed protein, has manifest difficulties in his way in carrying out metabolic processes; and the most evident difficulty would be in tissue construction. He would be able to use much, at least, of the more or less completely foreign protein in obtaining energy, that is, he would be able to disintegrate it, for it is known that animals can thus utilize considerable amounts of foreign protein when introduced subcutaneously or into the circulation. In attempting to use it to construct tissue, however, he would be obliged to go through the difficult task of disintegrating again, and then completely reconstructing it; while, when the tissues are, as is normally the case, served with homologous protein, it would seem evident that the process of construction and repair of the tis-

sues would be comparatively easy. We have, indeed, no knowledge that the tissues are capable of building new tissue from foreign or partly foreign protein served thus directly to them, and it may readily be that they are more or less completely incapable of it. They can undoubtedly secure energy from it and can transform one variety of homologous protein into another variety of homologous protein, but this is very different from transforming a foreign protein into a homologous protein. Even if they could do the latter, to impose on them the necessity for carrying it out would be to make entirely unnatural demands of them, and they would doubtless be likely often to fall under the extra burden.

The second idea conceivable as the result of absence of the intestinal proteolytic ferment is dependent on complete acceptance of the theory of reversibility of ferment action. While this theory now appears to be probably susceptible of general application, this has not been actually demonstrated to the same extent as have the other matters that I have so far used in constructing my hypothesis. Therefore, although this theory will probably be shown to be correct, I mention its relation to the subject under discussion in only a secondary place. In case it applies in this instance, the effect would appear to be that, the intestinal ferment being reduced or absent, not only would disintegration of the protein suffer, but the especial agent that carries out the reconstruction of protein being decreased or absent, the reconstruction also would be more or less completely absent. Instead, therefore, of entering the circulation as hybrid reconstruction products, the more or less completely fragmented products would themselves go into the circulation, and use of them by the tissues, in the synthesis of new tissue, would be much the same difficult process as in case they had been made into hybrid protein.

Either of these ideas would be in harmony with the repeatedly mentioned fact that absorption in many of these cases is sufficiently good to maintain nutrition; for incomplete fragmentation would not prevent absorption, since digestion products, all the way from albumoses on, are readily capable of absorption—and indeed, this occurs with many unchanged albumins. The hypothesis would in either case, also, be in harmony with—indeed, it is dependent on and, if correct, explanatory of—the fact that the difficulty lies in the utilization

of milk of foreign species. There is no good evidence that infants ever fail to assimilate human milk, unless they are already desperately ill; provided that the milk is not so rich in some of its constituents as to upset digestion or so poor as to be insufficient; and provided, also, that the mother or nurse supplying the milk is not the subject of physical or emotional disturbances that presumably cause the quality of the milk to be disordered. In other words, there is no evidence that an infant, not desperately ill, that is taking normal human milk of such composition that it does not disturb digestion, ever fails to be able to utilize this milk on account of the character of its constituents. On the other hand, large numbers of infants, when fed on foreign (that is, usually cows') milk, even when the constituents are of wholly normal quality, do badly or die, however one may vary the proportion of the constituents in deference to difficulties in digestion; often, indeed, even when no noteworthy difficulties in digestion are present. The experience of Westcott, Holt and others, shows that many malnourished or even severely atrophic infants that do badly on cows' milk mixtures exhibit remarkable improvement if, while their diet still consists chiefly of the same mixture, small quantities of human milk are added. This suggests strongly that they can secure from the artificial food the energy that they need, if only the essential moiety absolutely demanded for tissue-building and repair is given them in normal form.

The hypothesis also conforms with the fact that infantile atrophy, as well as the malnutrition of older children and adults, is not a clearly delimitable condition. There is no definite boundary line on one side of which cases are simply malnourished, while on the other side they are the subjects of persistently progressive atrophy; nor are there any cases that can be labeled essentially fatal. The worst of them almost may get well if only one can secure a food that is especially suitable in the particular case. If in such cases human milk is used improvement is often remarkably rapid, while on other foods it is, as a rule, slow and laborious at best. The hypothesis that I have described does not conflict with these facts, but is rather supported by them. Such variations in the severity of atrophy may be chiefly a question of a larger or smaller degree of reduction of the ferment action of the intestine. It is not to be expected

that the ferment or ferments would often be entirely and persistently absent; it is rather to be expected that various degrees of reduction of the amount or the activity of the ferments would occur in different cases, and that there would correspondingly be more or less severe results. Since there would be no essential structural change in the intestine, but simply more or less complete failure of a function—a function, however, that would seem to occupy a critically important position in the process of homologizing protein—any little increments added to the powers of the patient to carry on functions properly (such increments as would be secured through better feeding and better hygiene, and the consequent better general nutrition) would improve the manufacture of ferments, as well as other functions, except in cases so badly damaged that the recuperative powers were lost.

The general line of thought that I have indicated, whether my hypothesis is correct or not, would also offer a reasonable explanation of the fact that extreme grades of atrophy are so much more common in very early life than in older persons. After growth is completed, synthesis of tissues is necessary only in so far as repair is required; while in the young not only is repair required also, but there is, in addition to this, a relatively enormous amount of synthesis necessary in manufacturing new tissue. Any disorder that makes synthesis of tissue more difficult would consequently fall particularly heavily on the young.

I would likewise note that the one point regarding the pathology of infantile atrophy that is as yet unassailed (Bloch's observation that granules are absent from Paneth's cells) seems to me to suggest of itself that the ferment functions of the intestine may be at fault. Similar granulations are observed in other digestive organs, when they functionate normally, at those times when they are preparing their digestive secretions; while after the secretions are discharged the granules become much reduced in number or entirely absent. Lack of granules from the cells in the intestines of atrophic infants may, therefore, readily mean that these cells are not producing digestive secretions, while the same cells do produce them in other infants.

I have previously mentioned the possible presence of precipitins for bovine casein in the blood serum of

atrophic infants. This matter is not of much importance in this connection, as there is little evidence as yet that such precipitins exist. If they do exist it is apparent that their presence is quite as directly in conformity with the view that I have outlined as with the suggestion that a chronic toxic state results from the presence of the foreign casein in the circulation. Those that have experimented on the effect of subcutaneous injections of unaltered foreign protein differ in their conclusions; but it may, I think, be said fairly, so far as this concerns the question immediately under discussion, that atrophic infants show absolutely no clinical evidences of any such actively toxic state as has been described by some authors as consequent on the subcutaneous administration of very small amounts of foreign protein. Yet if such infants do have casein-precipitins in their blood, they must absorb directly quite as large amounts of casein as are used in injection experiments. This point seems to me to rob the theory of a foreign-protein intoxication of its chief established basis, so far as infantile atrophy is concerned; although I, of course, do not deny the possibility that such an intoxication may have something to do with the condition.

CASES STUDIED.

Up to the present, my studies regarding the defensibility of my hypothesis have consisted of investigation of the proteolytic power of the intestines obtained at autopsy in eight cases. Three of these cases were characteristic instances of progressively fatal atrophy (two in infants and one in a child of two years); three were cases of advanced emaciation that was known to be due to other causes than simple atrophy, these cases serving as controls; and the other two cases were instances in older persons of continuous and finally extreme emaciation for which autopsy showed no cause.

Although I have been working on the question, as opportunity offered, for a year past, the number of cases that I have to report is small, because I have, in order to avoid confusion, limited my observations relating to the atrophic cases carefully to those in which the clinical conditions and the autopsy findings showed an entire absence of evidence of infection of the digestive tract, and in which, also, there was absence of evidence of poor absorption or of a noteworthy degree of gastroenteritis.

I have found it difficult to secure such material from entirely reliable sources. The three cases of infantile atrophy that I report were, however, of this kind. All showed at autopsy merely the lesions of simple, uncomplicated atrophy, and clinically, all had shown merely progressive wasting, with no gastric symptoms. Intestinal symptoms, also, were absent in all except Cases 2 and 3, in which two or three bowel movements occurred at times in the 24 hours. The movements, however, were not large, appeared well digested, were of good color, and did not contain visible mucus.

Case 1 was under the care of Dr. Howard Hill, who did the autopsy. Cases 2 and 3 were under Dr. J. P. Crozer Griffith's care at the Children's Hospital, and Dr. C. Y. White and Dr. Howard Carpenter made the pathologic studies in them. For the material from the other cases, I am indebted to Dr. Longcope and Dr. Lavenson. I wish, also, to acknowledge my especial indebtedness to Dr. Ralph Pemberton for aiding me in the studies of the cases. The details of the methods used will be given later with the figures obtained. Meanwhile, I shall briefly discuss the results.

In the first of the three cases of infantile atrophy, the proteolytic ferment in the intestinal mucous membrane was present in extremely small amount, if at all; in the second it was greatly reduced as compared with the three control cases; in the third case, which was the most rapid in its progress, the infant dying at five months, no ferment-action was demonstrable. In the first of the two cases of emaciation of undetermined cause in older persons, ferment-action was exceedingly slight, in the second of these cases it practically could not be demonstrated at all. Indeed, in the whole group of five atrophic cases, all those that show slight ferment-action provide, to indicate this, figures so small as to be almost or quite within the range of error. Since, however, in all instances, two nitrogen-estimations were, as is usual, made for the purpose of controlling the results; and since, in all instances (except case 5, in which the control was lost), the two estimations corresponded practically exactly, I think that the figures are accurate, and do not indicate slight ferment-action.

The figures from the three control cases that had not simple atrophy do not, to be sure, indicate the digestion of large absolute amounts of protein; but they do show

relatively large amounts as compared with the atrophic cases, and it must be remembered that I was dealing with small figures in all cases, since, as may be seen in the protocols of the experiments, only 10 c. c. of milk was introduced in each instance for the ferment to act upon, in addition to the small amount of protein present in the extract which contained the ferment; and the amount of milk mentioned represents only about 0.05 grams of nitrogen. Considering that the period of digestion was purposely made short (only four hours), in order to be more certain of excluding bacterial action, the figures in the non-atrophic cases really show a very considerable degree of digestion, while the atrophic cases, at best, show almost none.

The objection may be offered that the differences were due to bacterial action. Toluol was used freely, however; the experiments were made so short that there was little opportunity for bacteria to act; and, more important than this, there are no irregularities in the results to suggest that bacteria had been active. It is, perhaps, impossible in experiments carried out as these were with an extract of the mucous membrane, to exclude bacterial action absolutely. I used this method, however, instead of attempting to isolate the ferment by means of precipitation and dialysis, because I believe that it is possible only by means of the method followed to secure quantitative comparisons in different cases; and bacterial action cannot be said to have produced the results obtained, unless one assumes the rather strained position of considering that bacterial proteolysis occurred regularly in the non-atrophic cases, while it was regularly absent or almost absent in the atrophic.

Leaving aside the two cases in older persons for the present, the bearing of the results in the three of infantile atrophy seems to me to be the following: So far as these cases go, they harmonize with the hypothesis that I have stated, since they demonstrate that in these cases there was great reduction or entire loss of proteolytic power in the intestinal mucous membrane. It may readily be thought that this was a mere secondary effect of the profound emaciation, but this appears decidedly improbable, when one considers the three control cases, all of which were extremely emaciated, but as the result of definite causes other than simple atrophy. These cases show very much greater proteolytic action

than do the atrophic cases. It might be considered, also, that there was simply a general reduction in the ferments of the digestive tract. I attempted to exclude this objection by testing for pepsin in extracts of the gastric mucous membrane of the atrophic cases, and in all three instances I got a markedly positive result; hence pepsin was present in all.

Beyond what I have said, I do not think I can speak decidedly as to the meaning of my results. If continued studies shall show similar results consistently, this will demonstrate definitely a marked disturbance of the ferment-function of the intestine, and will indicate strongly that this has an important primary relation to the atrophy. Further studies are necessary, however, in order to show that this is a constant condition in atrophy, and a condition that is usually absent in other cases. Furthermore, in addition to the line of observation that I have been following, it is important to determine whether the intestine does or does not, in these cases, retain its power to produce secretin and enterokinase, and thereby to excite secretory activity in the pancreas and to activate the pancreatic trypsin. It is likewise important to determine, if possible, to what extent the pancreas retains its functional capacity in these cases; although this is extremely difficult to do satisfactorily with postmortem material, because in extracts of the pancreas the trypsin becomes, to some extent, activated, and it is difficult to determine to what extent this occurs, and therefore difficult to secure reliable results in comparing different cases.

In spite of the fact, which I have repeatedly mentioned, that absorption in these cases often does not suffer enough to explain the atrophy, it may be that the pancreas, as well as the intestine, shows reduction, and perhaps, entire loss of ferment-function. We know now quite clearly that fat-absorption is sometimes good in the entire absence of pancreatic secretion; and it is quite possible that this is more largely true of protein than we have thought. Indeed, in many cases, with severe lesions of the pancreas, the nitrogen-absorption is known to be not bad. This possibility of disordered pancreatic function is of particular interest in infants; for there is some testimony, though not based on very good evidence, that in the first three months or so of life the pancreas has only a subordinate rôle in carrying

on digestion and absorption, while after this it becomes increasingly important. Athrepsia in infants is particularly likely to begin about the third month of life; and, hence, if the above-mentioned view is correct, it becomes possible that the difficulty in athrepsia may be partly, at least, the result of failure of the pancreas to take up the large function that it should assume. If the pancreas fails to do its duty, fragmentation of the protein-molecule will be still more incomplete than if the intestinal ferment only were absent. In this case, pepsin alone would be left to digest the protein sufficiently for its absorption; but in infants, at any rate, with their simple milk diet, it is probable that pepsin is capable of doing at least a very large part of this. If there is any truth in the view that I have just noted concerning the development of the pancreatic function in early life, pepsin must, in even normal infants, in the very early weeks of their existence, do most of the work except that carried out by erepsin.

In addition to what I have mentioned, it is desirable to attempt to determine whether amino-acids or peptides do escape into the circulation in these cases; or whether, on the other hand, the circulating protein of atrophic cases shows differences from the circulating protein of other cases. These last points are very difficult to determine with our present methods, particularly with the paucity of material provided by the cadaver of an athreptic infant. They may be possible of solution in cases of atrophy that occur in older persons, perhaps even during life.

Furthermore, it is desirable to determine whether there are alterations in the ferments in the tissues that lie beyond the digestive tract.

Finally, I would, with an equal consideration of the criticisms that I have put upon my previously-mentioned results, refer to the two cases in older persons, as they need brief separate description. The first of these, Case 4 in the protocol, was an instance of dementia præcox in a man of 27, who was under the care of Dr. Charles W. Burr at the Philadelphia General Hospital. The only noteworthy points in his history were that, after prolonged overwork, he had developed delusions of persecution; and this had been followed by a stuporous state. He was admitted in the latter condition; and for eight months afterwards, remained in a state of

complete apathy, or negativism, physically and mentally. Throughout this time, he was unresponsive and practically motionless. He was fed continuously through a stomach-tube, on about three quarts of milk and eight eggs a day; but in spite of this he emaciated constantly and finally to an extreme degree. He then came out of his stupor rather suddenly, took an interest in his surroundings and ate with appetite. Though he then took no food beyond the ordinary ward diet (and this is certainly not more than what had been given him before, but rather less), and though he was in this period moving about and doing a little work, while previously he had been absolutely quiet, during the next three months, he gained flesh rapidly and became actually fat. He then went into stupor again, and remained so for two years and ten months, until he died. Throughout this entire time, he had been fed on the previously mentioned amounts of milk and eggs, through the stomach-tube, and during this period he again emaciated progressively, and ultimately to the last degree.

Case 5 was a patient of 25 years, who had meningitis followed by hydrocephalus, lasting seven weeks. During this time he was stuporous and during the last three weeks he was fed through a stomach tube. He emaciated rapidly and finally to an extreme degree, in spite of the subsidence of any evidences of infection.

Both these cases, as I have stated, had practically no evidence of the presence of proteolytic action in extracts of the intestinal mucous membrane. I would note also that in both, contrary to the conditions in the infantile-atrophy cases, there was but faint, if any, evidence of the presence of pepsin in the extracts from the gastric mucous membrane. Neither case had shown any digestive disturbance during life, and neither had any lesions of the alimentary tract at autopsy. There was no direct occasion, therefore, for considering that the intestine was at fault in any way in these cases, but I studied them in this connection for two reasons: First, because they were instances of unexplained progressive emaciation; and second, because Pawlow, in discussing his celebrated work on the influence of psychic factors upon the secretion of digestive juices, suggests that the more or less profound disturbances of nutrition often seen in depressive forms of insanity may be, to some

extent at least, due to the entire lack of psychic stimulus to the production of digestive ferments.

Two cases do not justify much comment. I would say only that they may, on the one hand, be evidence merely that my hypothesis is incorrect; that is, reduction or loss of the ferment functions of the intestine may occur in a variety of conditions and may have no primary relation to any disease or symptoms, and these cases are, perhaps, merely examples of that possibility. On the other hand, they may prove to have importance in explaining such conditions. In Case 4, especially, there was a striking succession of events, which appeared to show that the emaciation was closely related to the stupor. This may mean simply that some intoxication or other obscure condition was the cause of both stupor and emaciation, but it may be that the whole disorder was nutritional—that depraved nutrition from overwork produced psychic depression, and the latter so largely depressed physical functions, among which is the function of elaborating ferments, as to cause the progressive general atrophy. The sudden alterations in both mental and physical condition that occurred in this patient and are common in similar cases is certainly quite as much in harmony with this view as with the theory of intoxication, for every one is familiar with the extremely sudden changes in the gastric secretion that are known to occur at times in cases of purely neurotic achylia gastrica.

I believe, therefore, that the emaciation occurring in depressed and stuporous states, and also other obscure forms of emaciation, are suitable subjects of study from the standpoint that I have indicated. I do not, of course, mean to suggest in the most distant way that emaciation in general is dependent simply and solely upon failure of intestinal ferments. I mean merely that lack of these and of other ferments may be an important element in cases of this sort, and since the proteolytic ferment of the intestinal mucous membrane, according to prevailing views, seems to occupy a conspicuously important position in the process of utilizing protein, it is possible that more or less complete absence of this ferment, owing to the disordered chain of events that would probably ensue upon its absence, may be one of the important elements in explaining some instances of progressive emaciation, and, too, of chronic, but sta-

tionary, depraved nutrition. It is also possible that at times lack of this ferment is the chief and, indeed, of itself a sufficient, explanation of the nutritional disorder.

THE AUTHOR'S METHODS.

The methods used in my work were as follows: The whole of the stomach and small intestine was secured directly after the autopsy. This means from 12 to 18 hours after death, but a delay of this length appears from Vernon's observations to cause no decrease in the amount of erepsin. There was some difference in the time that elapsed in the individual cases between death and autopsy, but this was, at most, a few hours, and the average time in the atrophic and non-atrophic cases was just about the same. As soon as they had been secured, the stomachs and intestines were very thoroughly washed with running water. In obtaining the extracts the mucous membrane was scraped off the entire surface of the stomach or small intestine, whichever was being worked with; the whole amount obtained was thoroughly mixed and weighed portions were taken. Scrapings from the entire mucous membrane were used because the amounts of pepsin and erepsin, respectively, in different portions of the stomach and bowel differ largely; and in using organs from subjects of different ages and sizes, it would be impossible to be certain that exactly similar portions had been taken if one simply cut out especially chosen parts and took the scrapings from these.

Of these mixed scrapings from the intestine, a weighed portion was each time taken and ground for 10 minutes in a mortar with sand. The ground scrapings and sand were then washed into a flask with Ringer's solution, using always 30 parts of the solution to one part of the scrapings. Toluol was then added; and the flask was stood aside for four hours, shaking it every 20 minutes to half an hour. The contents were then strained, each time in the same manner, and 50 c. c. of the strained fluid was introduced into each of two flasks. That in one of these flasks was immediately boiled for a moment and then cooled, and to each flask was added 10 c. c. of previously-neutralized milk, the milk being from a supply that is constantly under chemical supervision, and that I know from a large number of personal estimations to vary extremely little in its

nitrogen-content. Toluol was then added to each flask and thoroughly shaken with the fluid, and both flasks were placed in the thermostat at body-temperature for four hours. Following Cohnheim's procedure, I then added 10 c. c. of saturated sodium chloride solution; boiled a moment; added 10 drops of acetic acid; boiled again; filtered and tested the filtrate to see that it was biuret-free. If it were not, or if it were not perfectly clear, it was filtered again, when it always became perfectly clear and biuret-free. The nitrogen in the filtrate was then estimated. The results gave the "uncoagulable" nitrogen, and the excess in the specimen that was not boiled in the beginning over that in the boiled specimen showed the amount digested. The figures given are for the whole amount in the flask.

At the same time that these flasks were prepared, two other flasks, each containing 25 c. c. of the extract from the intestinal mucous membrane (boiled in one; unboiled in the other) and 10 c. c. of a 1 per cent. solution of Witte's peptone, together with toluol, were placed in the thermostat for four hours, and afterwards coagulated in the manner mentioned, and the strength of the biuret-reaction in the filtrate was noted. The degree of reduction in the intensity of the biuret-reaction in the unboiled specimen, as compared with the boiled specimen, provided qualitative evidence of the activity with which the "peptone" had been digested beyond those bodies that yield a biuret-reaction.

I used cows' milk as the substance to be digested, because it is the food upon which artificially-fed infants depend. Even if Cohnheim be correct in claiming that erepsin can not digest most unchanged albumins, and that it is necessary that albumins be previously digested at least as far as the albumose-stage, casein is, nevertheless, an entirely appropriate substance to use in testing the activity of erepsin; for Cohnheim himself states that casein constitutes an exception to the above-mentioned rule, since, unlike most other undigested albumins, it is acted upon by erepsin. In case Cohnheim is right in stating that erepsin acts upon casein but not upon most other unchanged albumins, this of itself strongly suggests that the ferment may be especially important in infants whose diet is limited to milk. It was, indeed, this statement in Cohnheim's article that first brought to my mind the possible relation of this ferment to

infantile atrophy. I have not, however, considered that the proof that erepsin can not act upon other albumins is sufficiently definite to make it justifiable to use this point in my argument, in the earlier part of this paper, in favor of my hypothesis.

The pepsin tests were qualitative only. The scrapings of the gastric mucosa were placed in one-twentieth normal hydrochloric acid, in the proportion of three parts scrapings to 200 of hydrochloric-acid solution, and allowed to stand until the next day, when the fluid was strained off. Of the strained fluid, 25 c. c. was introduced into each of two flasks, one of which was boiled and then cooled. To each flask I then added 10 c. c. of a mixture of one part of fresh white of egg in 10 parts of one-twentieth normal hydrochloric acid. These were then put in the thermostat for four hours. They were then neutralized, 10 c.c. saturated sodium-chloride solution was added, the mixture was then boiled, rendered slightly acid with acetic acid, boiled again, then rendered slightly alkaline with sodium hydroxid, boiled again and filtered perfectly clear. The filtrate was then tested by the biuret-test and by precipitation with phosphotungstic acid. The bulk of the precipitate to the latter indicated the amount of digestion-products, and the intensity of the biuret-test indicated the same.

RESULTS.

CASE 1.—Atrophic child of 2 years, had been emaciating for a year after preceding digestive disorder. The filtrate from the two flasks containing intestinal extract gave, after digestion, the following figures for nitrogen:

Unboiled specimen	0.0200
Boiled	0.0191
Increase	0.0009

Witte peptone digestion: Boiled and unboiled indistinguishable in biuret test.

Pepsin Test.—Biuret entirely absent in the boiled specimen; decided in the unboiled. A slight precipitate to phosphotungstic acid in the boiled specimen; much more marked in the unboiled.

CASE 2.—Atrophic infant of six months; weaned at four months; very ill-nourished then and had grown progressively worse since: Erepsin digestion experiment.

Unboiled	0.0117
Boiled	0.0088
Increase	0.0029

Witte peptone digestion: Boiled slightly more marked than unboiled.

Pepsin Test.—A trace of biuret in the boiled specimen; marked reaction in the unboiled. Phosphotungstic precipitate slight in boiled; marked in unboiled specimen.

CASE 3.—Atrophic infant of five months; weaned at three months; emaciating continuously since: Erepsin digestion experiment.

Unboiled	0.0144
Boiled	0.0144
Increase	0.0000

Witte peptone digestion: Boiled and unboiled indistinguishable.

Pepsin Test.—Biuret absent in boiled specimen, distinct, but not very marked in the unboiled. Phosphotungstic precipitate very slight in the boiled; more bulky in the unboiled, but less marked than in the other cases.

CASE 4.—Dementia præcox: Erepsin digestion experiment.

Unboiled	0.0156
Boiled	0.0137
Increase	0.0019

Witte peptone digestion: Boiled and unboiled indistinguishable.

Pepsin Test.—A trace of biuret in both the boiled and the unboiled specimen; very slight in both, and no difference observable. Slight phosphotungstic precipitate in both; no marked difference.

CASE 5.—Hydrocephalus: Erepsin digestion experiment.

Unboiled	0.0182
Boiled	0.0179
Increase	0.0003

Witte peptone digestion: Boiled and unboiled indistinguishable.

Pepsin Test.—Faint trace of biuret in both the unboiled and the boiled specimen, and a very slight phosphotungstic precipitate in each.

CONTROL CASES.

CASE 6.—Infant of nine months, dead of general tuberculosis: Erepsin digestion experiment.

Unboiled	0.0306
Boiled	0.0112
Increase	0.0194

Witte peptone digestion: Boiled pronounced biuret, unboiled very slight.

CASE 7.—Infant of five and a half months, dead of slow starvation. (Extremely insufficient feeding by an ignorant mother; admitted moribund): Erepsin digestion experiment.

Unboiled	0.0215
Boiled	0.0147
Increase	0.0068

Witte peptone digestion: Boiled very distinctly more marked than unboiled.

CASE 8.—Adult, died in convalescence from typhoid fever, after a long illness and extreme emaciation: Erepsin digestion experiment.

Unboiled	0.0229
Boiled	0.0117
Increase	0.0112

Witte peptone digestion: Boiled marked, unboiled slight.

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THE USE OF THE X-RAYS IN UNRESOLVED PNEUMONIA.

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That exposure to the *x*-rays might be useful in the treatment of unresolved pneumonia was suggested by one of us[1] in discussing the effects of the *x*-rays on metabolism in leukemia. It was then stated that the remarkable effect that this agent usually exerts upon metabolism is most readily and most satisfactorily explained by considering it to be due to action upon ferment processes normally resident in the tissues; the action in this instance apparently being to accelerate autolytic processes inherent in the tissues. The reasons then evident for adhering to this view were given at that time, and continued studies of the effect of *x*-rays upon metabolism in various diseases—studies now amounting to twelve—have emphasized our opinion that this is the most satisfactory conclusion to be reached. Further consideration will be given this point in a more extended discussion of the accumulated results in the various conditions studied, and it is, therefore, unnecessary to burden the present communication with it.

Granting the correctness of the view mentioned concerning the action of the *x*-rays, the idea at once presents itself that treatment with this agent may be beneficial in many conditions in which metabolism is not sufficiently active; but there is great difficulty in determining this point, on account of our very limited knowledge of most conditions in which such metabolic inactivity is suspected of being present. As was said, however, in the paper first referred to, our present knowledge of the process of resolution of a pneumonic exudate indicates that unresolved pneumonia is the most evidently suitable condition in which to try the effect of the *x*-rays from this point of view. We know that ferment processes cause the

[1] Musser and Edsall. Trans. Assoc. Amer. Phys., 1905; Univ. Penn. Bull., September, 1905.

digestion and resolution of the exudate in the ordinary pneumonias that pursue a satisfactory course; and lack of resolution, while sometimes really a continued inflammation, appears from Flexner's observations to be often due to insufficiency or absence of digestion of the exudate. In the latter case evidently the rational therapy is, if possible, to excite or accelerate the action of the ferments that should digest the exudate.

The possible suitability of the *x*-rays as a therapeutic measure in this condition led to its being used, in April, 1905, in a case that has already been mentioned.[2] Since that time we have kept under careful observation the cases of delayed resolution of pneumonic exudate that have come to our notice, with a view to choosing from them, for this treatment and for a study of metabolism while under treatment, those cases that seemed fairly certain not to undergo resolution under ordinary treatment, or to resolve so slowly and imperfectly as to lead to permanent crippling of the lung. We limited our choice also to cases in which noteworthy fever and all other evident signs of continued active pneumonitis were absent.

Of the five such cases that became available—all fever and evidences of distinct toxemia having disappeared, and the signs of solidification having been stationary for at least ten days or a fortnight—three patients grew weary of the waiting that we had imposed upon them and insisted upon leaving the hospitals in which they had been kept under observation, so that our further studies of this question have been confined to two cases. The conditions of metabolism observed in these cases while under treatment with *x*-rays were, however, so striking and the clinical effects in them and in the case previously mentioned appeared so uniformly good, that it seems proper to describe the results in them, in order to encourage a more extensive test of the treatment. In such tests, however, a few considerations need to be kept in mind, in order that the conclusions may be just.

In the first place no results can be expected unless the duration of the condition has been reasonably short—a few weeks at most—for, if organization of the exudate has occurred, a satisfactory result of treatment is almost inconceivable.

Secondly, the condition should be chiefly a real lack of resolution and not a continued inflammation of the lung. We are unable to state what effect the *x*-rays may have upon chronic pneumonia, but we are not dealing with this point; and in testing the effect upon delayed resolution as such, active continued inflammation should be excluded as far as possible. To exclude even slight grades of chronic inflammation would be exceedingly difficult, for such slight grades produce no symptoms that are distinguishable

[2] Musser and Edsall, loc. cit.

from those due to the exudate itself; and, indeed, a low-grade inflammation is probably always present, even comparatively early, and certainly when organization begins. Such a condition we could not reasonably desire to exclude, but we should exclude those cases in which decided fever and other evident symptoms of persistent active inflammation and toxemia exist; for, when these are the chief abnormalities present, resolution of the exudate may be impossible, and may also be of little or no value for the time being. In the low-grade inflammation, however, that appears to be due largely, and perhaps entirely, to the persistence of the exudate, resolution of the latter would probably be accompanied by cessation of the inflammation.

Thirdly, it is exceedingly important to determine, as far as possible, that one is actually dealing with unresolved pneumonia and not with tuberculosis. Many cases that are hastily thought to be unresolved pneumonia are, of course, unquestionably tuberculous; and judgment as to the value of a treatment of unresolved pneumonia cannot be based upon them. If cases fail to resolve under the influence of the *x*-rays, it should be determined before using them, in reaching a decision, whether they are or are not instances of tuberculosis.

Finally, we would earnestly recommend that the use of the *x*-rays in the treatment of cases of this or any other kind be undertaken with a proper realization of the fact that there are dangers associated with it; and the treatment should, therefore, be begun tentatively, and with brief exposures and small doses, until it is determined in the individual case that serious results are not likely to ensue. This is an additional reason for excluding those cases in which there is marked fever and in which other evidences of toxemia are present. For reasons that we shall point out in another paper, we are convinced that persons that are already the subjects of a noteworthy degree of toxemia are more likely than others to be dangerously affected by exposures to the *x*-rays; and until our knowledge of the contraindications to the use of the *x*-rays becomes better defined, we believe that with all such persons the use of this agent should be withheld unless there are urgent reasons for administering it.

We would also at this point, and for the reason just given advise that the *x*-rays be not tried, at least until their effects are better understood, in the treatment of pneumonia during the course of this disease. Such treatment has already been used purely empirically, and if we are correct in thinking that resolution may be hastened in unresolved pneumonia by the use of the *x*-rays, a very natural corollary of this idea would be the thought that exposures to the *x*-rays during the course of pneumonia might hasten resolution and shorten or favorably modify the course of the disease. We do not, however, subscribe freely to such a notion, the chief objection to it being that the most important factor in the course of most

pneumonias is not the presence of a mass of exudate in the lung, but the presence of a dangerous toxemia. Resolution of the exudate might, if it could be accomplished, be associated with control and reduction of the toxemia, but it is equally possible that it might not influence the toxemia to an important degree; and the point we would make at present is that whatever might be the result upon the local mass, there is actually serious danger that, if resolution could be accomplished, the sudden digestion of the exudate and absorption of its products might, if occurring during the course of a severe toxemia, be productive of much more harm than good.

The main clinical features of our cases will first be given, including the case that has already been briefly reported in the paper referred to.

Case I.—A man, aged fifty-six years, was admitted to the Episcopal Hospital in the service of Dr. A. A. Stevens, on March 13, 1905. He had been taken acutely and severely ill three days before with high fever, dyspnea, and pain in the right side; and presented the usual signs of a pneumonia involving the whole right upper lobe. His disease ran a moderately severe course, and crisis occurred on March 20. The fever and the signs of toxemia disappeared at this time. but the consolidation persisted, and was still present and but little changed when seen by Dr. Edsall on April 1. There was no noteworthy change, except a very moderate degree of lessening in the intensity of the signs, up to April 21, on which date it was ordered that he be given over the affected area five-minute exposures to the *x*-rays. These were continued for four days.

During Dr. Edsall's temporary absence from town, Dr. George W. Norris kindly watched the course of the case during the next week. There was no special change in the man's general condition, which was already satisfactory, but on April 23 it was noted that there were many rales in the affected area of the lung and that the breathing was somewhat cavernous in type in the upper portion of the lobe, below this bronchovesicular. Three days later he was noted still to have a moderate number of rales in this lobe, while the breathing had become bronchovesicular everywhere. The dulness had greatly decreased. When seen by Dr. Edsall on April 27 the rales had disappeared; there was very slight dulness over the upper half of the lobe, with no dulness elsewhere; the breathing was a little weak over the whole lobe, expiration being slightly prolonged. A week later, when discharged, there was, except for slight weakness of the breath sounds over this lobe, practically no abnormality left. The man's general condition was entirely satisfactory.

Case II.—A Norwegian sailor, aged twenty-eight years, was admitted as a British Consul case to the University Hospital under the care of Dr. Hollingsworth Siter, who kindly gave us the opportunity to study the patient. It was difficult to secure a detailed

history from him; but it appeared that while at sea he had been taken acutely ill with fever, dyspnœa, and pain in the left side. He had been ill for eight days, when he had had an apparent crisis; and the day following, when he arrived in port, he had been sent at once to the University Hospital. When admitted his temperature and pulse were normal and his general condition was entirely good, but he still had the signs of marked solidification in the left lower lobe, involving the whole of the upper part of the lobe and reaching down to the level of the ninth rib.

For three days there was no change in these signs; but throughout the next five days there appeared to be a slight improvement, the dulness becoming less intense and the breath sounds less harshly bronchial. From this time on, however, for two weeks the signs remained stationary; and when he was first exposed to the *x*-rays he had, over the whole upper part of the left lobe down to the level of the ninth rib, a moderate degree of dulness, with moderate bronchial breathing and increased fremitus. Rales were absent. An *x*-ray picture was taken at the first exposure, and this showed a moderately intense shadow in the area corresponding to the signs described.

He was exposed daily for seven days. Two days after the first exposure there was no striking change, although it was noted that the dulness was perhaps less marked and that there were a few fine rales in the affected area. Two days after this it was noticed that the dulness had receded upward for about an inch and a half and that even above this point the dulness was less marked; the breathing was much less harsh, and was bronchovesicular; it could not be determined that the fremitus was increased, and there were many fine rales over the upper part of the lobe. Three days later, at the end of the experiment, no abnormalities could be discovered, except slightly weak breathing over the diseased lobe and a small area of dulness, about an inch in diameter, at the upper extremity of the lobe. An *x*-ray picture taken at this time showed nothing abnormal except a small, indistinct shadow at the area in which a trace of dulness was still found. The man appeared to be entirely well in other ways.

Case III.—A Cuban, aged thirty-four years, was admitted to the Pennsylvania Hospital, in the service of Dr. Arthur V. Meigs, who kindly gave us the opportunity to study him. Dr. Longcope also made frequent notes of his case, of which we shall give an abstract, and was likewise kind enough to watch carefully over the details of the weighing of his food in the metabolism experiment, the securing of the twenty-four hours' urine, etc.

The patient was admitted on the fourth day of an illness that had come on with the usual symptoms of an acute pneumonia of the right side. Examination of the right lung showed dulness over the whole lower lobe, with bronchial breathing and increased fremitus and vocal resonance, and with fine crepitant rales over this

area. The upper portion of this lung was negative, as was the left lung. The examination, otherwise, is of no consequence. On the 5th, his condition was worse, the pneumonia having extended throughout the lung. The signs over the lower lobe, however, had decreased somewhat in intensity. On the 8th, he had the usual signs of crisis, but the lung remained solidified. Three days later the lower lobe appeared to be slowly clearing up, but the uppper lobe remained solidified. On the 21st, thirteen days after the crisis, the lower lobe had cleared up with practical completeness, but the upper lobe remained unchanged and was entirely solidified. Tubercle bacilli were absent from the sputum.

On this date the first *x*-ray exposure was given him, a picture being then taken which showed a shadow corresponding with the signs of solidification in the upper lobe. Two days later it was noted that the breathing was less harsh and the dulness less marked, but the signs were not strikingly changed. On the 26th the signs were decidedly less marked, dulness and bronchial breathing being much less pronounced. On the 28th there was still some dulness, but it was decreased. The breathing was blowing, but not distinctly bronchial. On March 1 the dulness reached only to the third rib, and was slight, the breathing still being somewhat blowing. On the 3d the signs were about as last noted. On the 6th there was still slight dulness to the third rib anteriorly. Posteriorly, the resonance above the spine of the scapula was skodaic. The breath sounds were somewhat harsh over the dull area, but not tubular. Rales were absent. The patient was discharged two days later, at his own request, in apparently normal condition, except for the signs mentioned. The *x*-ray exposures subsequent to the 21st occurred on the 24th, 26th, 27th, and 28th of February; and the 1st, 3d, 4th, 5th, 6th, and 7th of March.

Metabolism experiments were carried out in the two cases last described. As previous studies had shown no noteworthy influence of the *x*-ray exposures upon absorption from the alimentary tract the feces were not studied. The patients were given a diet composed of milk, bread, butter, eggs, rice, potatoes, and sugar. The food was from he sa me source each day and was accurately weighed or measured. The amount of nitrogenous intake was calculated from the weight records of the food, using figures that we had previously obtained from numerous determinations of the same food. The salt also was kept at the same amount each day, in order that variations should not influence the chloride determinations; and it should be noted that the diet was purin-free and hence that variations in the uric acid were due solely to changes in metabolism, and not to changes in the food. Before studies of metabolism were begun, the patients were put for three days on the diet described. For several days control studies were then made, and after this the *x*-ray exposures were commenced.. Each "x" in the second column

indicates an exposure; it is to be noted that the effect is shown in the figures of the following day.

TABLE I. CASE II.—URINE.

Date.	x-ray exposures.	Nitrogen ingested Grams.	Nitrogen.	Chlorides.	Uric acid.	Phosphates.
Jan. 12	...	6.54	8.971	12.600	0.2295	1.900
" 13	...	6.54	5.262	8.262	0.1944	1.296
" 14	...	13.08	14.840	11.125	0.3022	2.710
" 15	...	13.08	9.908	13.360	0.3424	1.996
" 16	x	13.08	8.153	12.350	0.2427	1.716
" 17	x	13.08	17.875	20.900	0.3248	2.257
" 18	x	13.08	Lost			
" 19	x	13.08	10.819	14.630	0.3190	2.296
" 20	x	13.08	11.464	14.490	0.3622	2.250
" 21	x	13.08	9.222	14.170	0.2754	1.861
" 22	x	13.08	8.119	16.250	0.3917	2.168
" 23	x	13.08	9.863	17.250	0.3346	1.905
" 24	...	13.08	11.752	16.880	0.3720	2.080
" 25	...	13.08	7.207	14.560	0.2388	1.565

TABLE II. CASE III.—URINE.

Date.	x-ray exposures	Nitrogen ingested. Grams.	Nitrogen.	Chlorides.	Uric acid.	Phosphates.
Feb. 19	...	9.25	4.872	2.400	0.1260	0.720
" 20	...	"	9.016	3.920	0.2835	1.169
" 21	x	"	8.288	4.300	0.3000	1.170
" 22	...	"	17.096	8.400	0.4662	2.380
" 23	...	"	12.776	7.475	0.4215	1.794
" 24	x	"	5.264	3.200	0.1380	0.795
" 25	...	"	8.895	5.330	0.2007	1.404
" 26	x	"	6.428	2.780	0.2120	0.888
" 27	x	"	9.872	5.800	0.3757	1.430
" 28	x	"	7.915	5.060	0.2268	1.408
Mar. 1	x	"	19.958	8.937	0.7137	2.614
" 2	...	"	10.668	6.300	0.2962	1.800
" 3	x	"	4.368	2.240	0.1440	0.552
" 4	x	"	11.230	4.042	0.2756	1.764
" 5	x	"	4.211	2.880	0.0740	0.920

Clinically then in these three cases the result was in each instance a rather rapid clearing up of most—in two cases practically all—of the signs of solidification that had previously persisted in the three cases, respectively, for one month, two weeks, and thirteen days, without improvement. The relation of the improvement to the *x*-ray treatment may have been merely a coincidence, for these exudates often, without any evident reason, clear up after more or less delay. Three cases do not suffice to decide this point, but that the *x*-rays played a lively part in causing the improvement appears to be at least probable, when one considers the influence that the *x*-ray exposures had upon metabolism.

In Case II, as a result of the first exposure (which was *only eight seconds long*, but was actually a fairly intense exposure, since it was one intended to produce a negative), the nitrogen increased to more than double what it had been before, and the chlorides showed an almost equally striking increase; the phosphates were

somewhat less decidedly increased, while the uric acid showed relatively little change. The increase persisted in less-marked degree, gradually decreasing coincidently with the decrease of the solidification, and when the latter had disappeared, excretion had reached about its former level.

In Case III, the relation of the excretion to the *x*-ray exposures is even more striking. The first exposure was followed by a decided increase. Owing to a misunderstanding, the next exposure was not given for three days, and in the interval the excretion dropped decidedly; after the second exposure there was a moderate rise and then there was again an interval of two days between the exposures, and the second increase of excretion was also followed by a decided drop. The subsequent daily exposures were accompanied by an increase that was somewhat irregular, but became extremely remarkable on March 1. Again following the omission of an exposure on March 2, the urine of the 3d shows a striking drop, and finally, in this case also, as the solidification largely disappeared, the excretion appeared to be dropping pretty well to the original point, in spite of continued exposures, though, as the patient was soon to leave the hospital we could not carry the observations far enough to determine the latter point positively. At the end of the experiments in the two cases the first patient was retaining a great deal of nitrogen and the second patient was showing a strong tendency to retention; while in the periods during which they showed a marked increase in the excretion as the result of the *x*-ray exposures both were showing a very decided loss of nitrogen.

The figures that we have given show that the effect upon metabolism was indeed a most remarkable one. We have seen similarly profound effects only in one of the cases of leukemia that we have previously described—in which there was an extremely rapid improvement in general condition, splenic tumor, and leukocytosis—and in the two cases of general toxic reaction that we shall describe in another paper, though it should be noted that in the two latter cases the effect, while profound, differed strikingly from that in the case of successfully treated leukemia and in these cases of unresolved pneumonia.

Since such a remarkable effect was exerted upon metabolism, and since this was coincident with rapid improvement in the pulmonary signs, it would appear highly probable that the *x*-rays caused the improvement. The conditions observed are, in fact, extremely similar to those that occur at the time of an ordinary crisis in a favorably progressing pneumonia; that is, the exudate grows moist and clears up within a short time and, coincidently with this, there is a large increase in the metabolic output through the urine.

Whether the *x*-rays will prove to be of great importance in the treatment of unresolved pneumonia is, therefore, a question that

is worth settling, but it is one for the future to decide. While, however, this decision is of importance, it seems to us that there is a broader interest in the question whether the theory that was the basis of these observations—the theory that the *x*-rays act upon metabolism chiefly as a ferment accelerator—is correct or not. When, for example, one administers hydrochloric acid with pepsin or alkalies with pancreatin, one consciously or unconsciously uses, to be sure, the same principle; that is, one attempts to provide conditions that are known to be especially favorable to the rapid action of these ferments; but in the manner in which these measures can now be used artificially, the results of such treatment do not at best distantly approach those accomplished in natural circumstances. Except in a few such simple and comparatively ineffectual instances, this principle of using measures that provide conditions that directly accelerate special ferment processes has not, to our knowledge, been deliberately used previously in the treatment of pathological states. In case our view is correct this study furnishes the first example of the deliberate use of this principle in the treatment of disease that lies beyond the digestive tract, and more especially the first instance of the conscious use of this principle with results that are so striking in their effect as to approximate those that the human organism itself accomplishes when successfully reacting to disease.

If, therefore, we are correct this is of considerable interest when one reflects upon the importance that ferment processes have assumed in the last few years in our conceptions of physiology and pathology. There is at present a widespread and somewhat excited tendency to give ferment processes a much more overwhelmingly important place than has been demonstrated to be their due; but the fact that they play an important part in the body economy is perfectly evident, and that methods that would clinically influence them in definite and controllable ways would be of great value scarcely needs to be stated.

Numerous attempts have been made to isolate and administer ferments themselves, of various kinds, in the treatment of diseases in which they are supposed to be absent; but such attempts have certainly been, in almost all instances, largely or entirely failures. This is scarcely to be wondered at, for in the first place knowledge of these ferments and of their relation to disease is in most instances at best very hazy, and, furthermore, attempts at isolating them are built upon most incomplete and insecure methods; and it is likely to remain most questionable whether tissue ferments can ever be obtained in active form, and then guided to the proper spot still in active form. It is equally questionable whether, should they arrive there, the disordered medium in which they would often find themselves would be such as to permit them to act. Indeed, it is exceedingly doubtful whether the whole idea of administering ferments is not as a rule wholly unphilosophical, both for the reasons given and

because in many of those instances in which they appear to be absent they are probably not entirely absent, perhaps not even reduced in amount, but are merely unable to act properly owing to unfavorable chemical or physical conditions. It is possible that we may ultimately learn to stimulate the production of ferments in different organs with some accuracy, and this may prove to be occasionally a successful measure; but it is at present in the distance, and for the reason mentioned in the last sentence, it would frequently have only ineffectual results, for it is wholly rational to conceive of most varied chemical and physical conditions that would more or less completely interfere with the action of ferments in the tissues, and many such conditions, both simple and complex, are already known. If such conditions were present, increasing the amount of ferment would, of itself, be of no avail; and the essential matter would be to substitute for existing substances or conditions others that would inaugurate or accelerate the action of the ferment that is present. This is probably done already in using various therapeutic measures that have been evolved empirically; many drugs, for instance, are known to have a very marked effect upon a number of catalytic processes, and observations yet unpublished, that Dr. Casper Miller and Dr. Edsall have made, indicate that the striking lesions produced by toxic doses of mercury, and probably the remarkable effect that mercury exerts on syphilitic tissues, are, partly at least, the result of increased autolytic activities. The conditions under which a ferment acts are probably more frequently important in producing pathological states than is the amount of ferment present, for ferments are exceedingly sensitive to the conditions under which they act, in both a positive and a negative way, and the conditions influencing them are exceedingly numerous and varied. The almost inconceivably energetic effect of conditions that have a very marked accelerator action is shown, for example, by the fact that the intestinal wall appears to be able in the brief period that is necessary for their passage through it, to rebuild into the native protein of the individual the fragments of protein broken down in digestion, while the best conditions that experimenters can now provide furnish, even after long periods of action, at most, only doubtful evidence of slight artificial imitation of such a process; and, on the other hand, as is well known, mere traces of certain substances, such as hydrocyanic acid, will greatly retard or wholly interfere with the action of relatively enormous quantities of some catalyzers.

This casual mention of some of the most evident conditions that are known to influence the action of ferments suffices to make it reasonably clear that if a study of ferments is to become of value clinically it is likely to be chiefly through determining the conditions that influence the activity of individual ferments under normal and pathological conditions and through making use of measures, clinically applicable, that can be shown to provide, of themselves

and directly, favorable conditions for the action of these ferments, or that overcome unfavorable conditions.

Whether our view regarding the action of the *x*-rays and their effect in unresolved pneumonia is correct or not the future will probably see the principle upon which we were working used many times, as knowledge of ferments and of their accelerator and anti-accelerator conditions increases. That which has just been said must not, however, be misinterpreted. It is intended largely as a protest against the blind but common belief in a mysterious value of ferments as therapeutic agents, a faith that gives opportunity to manufacturers to foist upon many of the profession preparations that are even supposed to contain, isolated and in active form, ferments that are by no means definitely known to exist; and still more would we protest against the excited enthusiasm of those investigators whose work has been such as to lend them the respectful attention of the profession, and who now seem occasionally to be heralding the approach of a therapeutic millenium that is to be distinguished chiefly by the administration of ferments. We would not be thought to believe, however, that there is, instead of this, a nearer-by millenium, in which knowledge of the conditions in which ferments act will lead to inevitable success in the treatment of disease. We would merely point out that in contrast with the dubious plan of treating disease by administering ferments, those who think conservatively in regard to this matter can scarcely believe that much will ever be accomplished in a large proportion of cases in which ferment action is at fault except by modifying the conditions under which ferments act. Through happy chance it will not improbably occur that occasionally the knowledge that accumulates will be made of service in successful therapeutic practises, if this manner of viewing the relation between ferments and therapeutics is held in mind; but any such success will almost certainly, for a long time to come, be largely the result of happy chances that are pointed out by a modicum of suggestive investigation. It will surely be a wearily long period before slow, painstaking, and complex investigations make it possible to apply any such principles in a considerable number of cases with a just expectation of success. The exciting work on ferments that has occurred in recent years has greatly transformed the point of view assumed in attacking problems in pathology, but has not in other ways profoundly simplified these problems. The difficulties and complexities have not been essentially lessened; their nature has rather been made more evident.

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THE NATURE OF THE GENERAL TOXIC REACTION FOLLOWING EXPOSURE TO THE X-RAYS.

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In the course of the last few years evidence has been accumulating that *x*-ray exposures may have seriously undesirable effects upon the tissues in the interior of the body, as well as upon the skin and other superficial structures; and of these evil effects that which arouses most marked attention, because it is most dangerous, is the more or less profound and sometimes fatal reaction that has occasionally been observed soon after exposure, and that is characterized chiefly by signs indicating an acute intoxication. It would be superfluous to review the evidence demonstrating the occurrence of such reactions and their definite relation to *x*-ray exposures. Both these points have been shown with sufficient clearness, and both are generally accepted. We have ourselves seen three cases in which a most severe reaction occurred after one exposure to the *x*-rays; two of these cases ended fatally a short time afterward, while the third patient became profoundly ill, but ultimately recovered. In two of these cases the exposure to the *x*-rays was ordered by colleagues; in the other, we were ourselves responsbile for its use.

Since the *x*-rays are of great importance in the diagnosis of many conditions, and apparently also of considerable therapeutic value, it is most earnestly to be desired that the character of the disturbance producing these occasional toxic reactions be determined, in order that we may thereby attempt to devise a well-founded method of preventing the reactions, while still continuing to use the *x*-rays, when they are in place. We have had the rather remarkable fortune of having studied the conditions of metabolism in two such cases, just before, during, and after violent reactions; the cases having

been subjected to study for other reasons, and without, of course, any expectation that reactions would occur. We have by this chance been enabled to determine the alterations in metabolism at the time of the reaction, and have obtained results that seem to demonstrate the general nature of the reaction and to sound a warning against the use of the *x*-rays in certain kinds of cases. With us, indeed, these results will constitute a prohibition against the use of *x*-rays in such cases until, at any rate, our knowledge becomes more exact, unless most urgent and exceptional reasons seem to justify us in running some risk in occasional instances.

The cases do not require extended clinical description, and, because both may be reported for other reasons by those who had clinical charge of them, we shall give only the details essential to our purpose.

Case I.—A man, aged forty-three years, with pernicious anemia, was seen in Dr. Stengel's service at the University Hospital. During several weeks of treatment with the usual measures he grew gradually but persistently worse. Owing to the successful results previously observed by Dr. Elliston Morris and one of us in a case of pernicious enemia that was resistant to ordinary treatment, but that improved to a remarkable degree under exposures to the *x*-rays, it was suggested that this agent be tried in this case. At the same time, however, it was urged that the exposure be brief and mild, because in another case of pernicious anemia in which a single exposure had been ordered by Dr. D. J. Milton Miller, which case, as well as that last mentioned, has previously been briefly reported,[1] a violent reaction occurred. It should be especially noted, for reasons that will soon be apparent, that when the exposure occurred, and for some time before, the man presented slight fever, nausea, prostration, and other evidences of a noteworthy degree of intoxication. His exposure was partly over the thighs and partly over the splenic region, its duration was, all told, only five minutes, and its intensity was very mild. Dr. Pancoast, who gave it, informed us that it was as mild an exposure as he had ever administered.

In spite of this caution, about four hours afterward the man became evidently very ill and had a chill. His temperature rose to 103.4°, his pulse became rapid and weak, and he was much prostrated. The fever and prostration continued the next day, and for a week afterward he refused to eat on account of anorexia and more or less nausea. His temperature gradually declined to the previous level and he improved a little, but the gain was, at most, very slight, and while he was still desperately ill his family insisted, about three weeks after the occurrence of the reaction, upon removing

[1] Musser and Edsall. Trans. Assoc. Amer. Phys., 1905; Univ. Penna. Med. Bull., September, 1905.

him to his home, which was several hours' journey distant, and he died on the train.

The figures for his metabolism follow: It is to be noted that, beginning with the day after the exposure to the *x*-rays, the intake dropped to a very low point. Two days later he refused all food, and the only method of nourishment was through nutritive enemas. We did not determine the amount absorbed, and therefore give no figures for the intake; but from our previous observations on this point and from the fact that he retained his enemas poorly, there is little doubt that the amount of nitrogen absorbed was not above 2.5 grams. The figures given at the end of the table are also not absolutely accurate, as the food at this time could not be so carefully controlled, but they are reasonably accurate and certainly sufficiently generous. The drop in the intake is a point of importance, as will be noted later. The "x" in the second column in the table indicates the date of exposure to the *x*-rays.

TABLE I.—URINE.

Date.	*x*-ray exposures.	Nitrogen ingested. Grams.	Nitrogen.	Uric acid.	Phosphates.
Oct. 9	...	10.18	13.892	0.9192	1.170
" 10	...	11.20	14.346	0.9200	1.210
" 11	x	11.83	14.496	0.9594	1.680
" 12	...	9.76	8.400	0.4500	1.164
" 13	...	3.40	10.668	0.4908	2.745
" 14	...	2.50	12.096	0.7630	1.680
" 15	...	...	12.623	0.8376	1.200
" 17	...	...	16.128	0.9292	1.476
" 18	...	...	11.028	0.8769	1.440
" 21	...	...	12.096	0.7406	1.575
" 24	...	2.20	13.608	0.6255	2.131
" 26	...	3.60	11.092	0.8495	1.480
" 31	...	3.00	13.440	0.6836	1.456
Nov. 2	...	2.00	8.400	0.498	1.728

CASE II.—This man, aged fifty-two years, who presented the typical lesions of rheumatoid arthritis, was under the care of Dr. Charles W. Burr, at the Philadelphia Hospital. *x*-ray exposures were ordered by Dr. Burr for the purpose of treating his joint condition; only one such exposure was given, however, owing to the violent illness that followed it. His direct exposure was confined to one arm, from above the elbow down to and including the hand, and was only five minutes in duration; the arm was lying well out from the body, but as the trunk was not screened he got a diffuse and more or less distant exposure of the whole person. It is to be noted in this case, also, that the man was somewhat toxic, having for some time had slight fever, moderate prostration, and occasionally a little delirium at night. These symptoms were apparently the result of a rather severe chronic cystitis. He had no evidence of disease of the kidneys.

After the exposure the temperature rose slightly and he became

evidently worse than he had been before. On the second day he was decidedly more prostrated, his temperature was more elevated, and his condition was serious. On the third day he was so much worse that it was thought that he was moribund, and on this day it was impossible to collect his urine accurately, so that the figures for this day are absent. After this he began to mend distinctly, and in a few days had returned to about the condition that he was in before the exposure. The figures for his metabolism follow:

TABLE II.—URINE.

Date.	x-ray exposures.	Nitrogen ingested. Grams.	Nitrogen.	Chlorides.	Uric acid.	Phosphates.
Mar. 21	...	12.55	10.1848	6.267	0.1445	1.620
" 22	...	14.10	11.667	6.555	0.3363	1.440
" 23	...	14.45	11.177	4.000	0.3730	1.624
" 24	...	12.74	8.969	3.175	0.4078	1.576
" 25	...	13.34	11.088	6.800	0.4912	1.370
" 26	x	13.22	10.164	6.000	0.4762	1.450
" 27	...	11.85	8.920	4.545	0.4117	1.170
" 28	...	11.96	11.180	8.300	0.6198	1.650
" 29	...	13.24	5.376	4.100	0.2310	0.760
" 30	...	12.26	16.296	7.250	0.7835	2.080
" 31	...	...	Lost	appeared	moribund	
April 1	...	12.15	10.2816	4.330	0.5568	
" 2	...	12.96	7.774	...	0.3318	

The chief point to be noted in regard to the metabolism in these two cases is the remarkable drop in the excretion that followed the exposure, this drop being followed subsequently by an equally striking rise in the excretion to a point much beyond that at which it had previously been. In the first case, the drop occurred directly after the exposure; in the second, it was postponed for two days, but occurred, as in the first case, at the time when the man had become seriously ill. The figures for the intake demonstrate that in neither instance was this drop due to a reduction of the food, for the reduction in the first case occurred after the drop took place, and in the second case there was no marked change in the intake. Likewise, the subsequent rise was not due to the intake, for in the first case the intake was, on the contrary, at this period, very greatly reduced, and in the second case it was not increased. The importance of the great reduction in intake in the first case becomes evident in this connection—the man's excretion from the time of the reaction on must be compared with this reduced intake, and not with the previous intake, in order to appreciate the conditions of metabolism that were actually present at that time.

The only apparent explanation of these changes in metabolism is the following: Previous work has shown that in cases that respond favorably to the action of the *x*-rays an increase in tissue-destruction, that may be of remarkable extent, occurs directly after exposure to the rays. It appears to us that in these cases this occurred: that the organism was overwhelmed by the sudden necessity for

carrying on the complete disintegration of a mass of early products of tissue destruction, and that after a little time, as the organism reacted somewhat, complete disintegration could be accomplished and the products were excreted. At first, therefore, owing to sudden severe overtaxing of the organism, metabolism was apparently halted; but the reduction in excretion seems to have been due to mere retention of incompletely decomposed tissue products, and the usual reaction, which is characterized by marked tissue destruction, appears actually to have occurred, though slow in making itself evident, for the later figures show conditions that are quite[2] comparable to those seen in two unresolved pneumonia cases, and in a successful case of leukemia[3] previously reported.

In the first case, in which the reaction was much more severe and certainly hastened death, failure of metabolism occurred at once. In the second case there appears to have been at first some difficulty in getting rid of the tissue products and then an attempt to respond to the action of the *x*-rays, for the excretion rose decidedly on the second day after exposure. But after this a metabolic collapse seems to have occurred, and there was a marked drop in excretion, coincidently with the man's grave symptoms, and this was followed by a very striking output as the condition improved. This latter case is of especial interest in that it perhaps offers an explanation of late toxic reactions; that is, the organism bears up at first under the extra strain, but, sooner or later, collapses as a result of its increased burdens.

We have insisted somewhat upon the fact that both the patients now under discussion appeared to be already the subjects of a noteworthy degree of toxemia. This fact seems to us to help in the explanation of the nature of the reaction and also to offer a probable explanation of the fact that a toxic reaction occurs only occasionally. We believe, from these and other experiences, that a toxic reaction i particularly likely to occur in persons that are already the subjects of a toxemia. Their organisms are already taxed to a considerable degree, and sometimes severely, in attempting to control the intoxication that is already present, and, if to this strain is added the metabolic labor of carrying out the complete decomposition of a large amount of tissue products, it seems quite natural that metabolism should occasionally, in the cases most severely taxed by this, suffer more or less complete collapse; and that, in consequence, the signs of severe intoxication should appear.

This is particularly likely to be true, because the tissue destruction accomplished by the *x*-rays undoubtedly involves chiefly tissues that are especially rich in nucleoprotein. The decomposition products of this form of protein are especially rich in substances that are, of themselves, more or less toxic and also difficult to metabolize and excrete. The figures for the first case, particularly, show that

[2] Amer. Jour. Med. Sci., 1907, cxxxiii, 286. [3] Musser and Edsall, loc. cit.

the man soon regained his ability to excrete the main portion of the urinary nitrogen, which comes chiefly from the simpler proteins; and also his ability to excrete phosphates. The uric acid, however, which is the direct indicator of the conditions in regard to the nuclein substances (the products of which are more toxic and more difficult to metabolize and excrete), only slowly regained its previous level. In appreciating the latter point, it should be remembered that the diet was purin-free; and hence that, while changes in the intake influenced the excretion of nitrogen and phosphates, they did not influence the uric-acid excretion.

The nature of the toxic reaction to the *x*-rays would then appear to us to be a sudden demand upon the organism for the complete disintegration and excretion of a large amount of the products of tissue breakdown, with inability on the part of the organism to accomplish this, and a consequent halting of metabolism, resulting in an intoxication produced by incompletely disintegrated tissue remnants. That the intoxication in these cases was not dependent directly upon alterations in the excreting power of the kidneys, but upon alterations in metabolism, appears to be at least highly probable, because examination of the urine of these two patients, at the time of the reaction, and for several days afterward, showed no evidence of irritation of the kidneys. It is, however, undoubtedly very probable that in many instances, after a little time, the kidneys do become overtaxed by the added labor thrown upon them, and their excretory power fails to a greater or less degree, and this may increase the toxic symptoms. It is possible, indeed, that moderate but increasing failure of metabolism, together with increasing failure of kidney function, may cause a late accumulation of toxic symptoms and give rise to the late toxic reactions that have been seen both in human cases and in experiments on animals. It seems evident, at any rate, that such symptoms are more likely to occur not only in those that have severe metabolic or infectious intoxications, but likewise in those that have pre-existing kidney disease; and it has, indeed, been already shown in a number of instances that actual nephritis may be set up by exposure to the *x*-rays. Hence, unquestionably, a pre-existing nephritis may readily be made worse by *x*-ray exposures.

If we are correct in all the statements that we have just made, it would appear highly inadvisable, unless urgent reasons to the contrary exist, to use *x*-rays in cases that are already the subjects of a noteworthy degree of general intoxication that is produced by either infectious disease or metabolic disorder. Whether all our observations are correct or not, it would appear that there is at any rate some danger in adding to such an intoxication the sudden necessity for metabolizing and excreting a large amount of the products of tissue breakdown. It has already become evident that cases of nephritis should be exposed to the *x*-rays only with great caution, and our observations emphasize this point still farther.

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PECULIAR TYPES OF GANGLION CELL DEGENERATION.

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With the study of the finer anatomy of the ganglion cell, following the application of the methylene-blue stains to nervous tissues many contributions of value have been made to the anatomy of degeneration of ganglion cells. The Nissl method and other modifications of the use of methylene blue as used by Nissl served a purpose in calling attention to the presence of areas in the cell protoplasm outside of the nucleus, taking the basic stain intensely, and to which was given the name of chromophilic elements. Much has been written as to whether these areas are artefacts produced by the fixing process, or, as some maintain, by the section of acid agents on the cell substance. If sections of nervous tissues be made, much after the same manner as blood smears, and this material is fixed by heat, the same result is obtained, as far as the staining properties are concerned, as if formalin or alcohol is used.

Independently, however, of the question as to whether this material is the result of fixation or other processes, the fact remains that normal cells present an appearance which is constant, and that degenerating cells present a picture deviating from this. It is not the idea of the writer of this

paper to consider the usual forms of degeneration of ganglion cells, but to call attention to certain irregular types of degeneration not commonly met with.

If the nervous material is taken from the body within twelve hours and hardened in 96 per cent. alcohol, and then stained by the Nissl method, a picture is presented of a circular nucleus, vesicular, in a central position in the cell, and surrounding this arranged in regular order are seen the

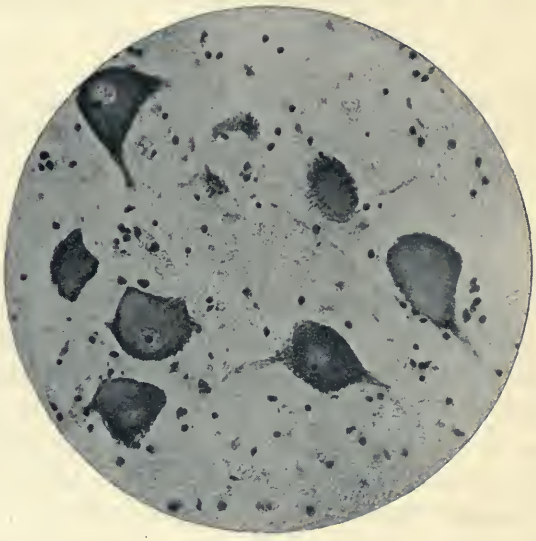

FIG. 1.—Diffuse chromatolysis. In cell in upper section of the picture, the nucleolus is seen outside the nucleus.

chromophilic bodies. When the cell undergoes degeneration, the cell protoplasm may take a deeper stain, the so-called pyknosis, with an arrangement of the chromatin in clumps, and clumping especially around the nuclear wall. The nucleus or more frequently the chromophilic elements either entirely or partially disappear, and the cell body stains with a light diffuse stain, giving the so-called diffuse chromatolysis (see Fig. 1). This is best seen in the effects of intoxication of different kinds on the nerve cells. The cells in this

form may present a perinuclear diffusion of the chromatin, with the chromophilic elements intact at the periphery of the cells, or the process may be complete throughout the cell. The cells in Fig. 1 present this form and are from a case of Landry's paralysis complicating pulmonary tuberculosis, at the Henry Phipps Institute. The nucleus in a degenerating cell becomes irregular in outline, loses its chromatin reticulum and finally disappears. During this process it

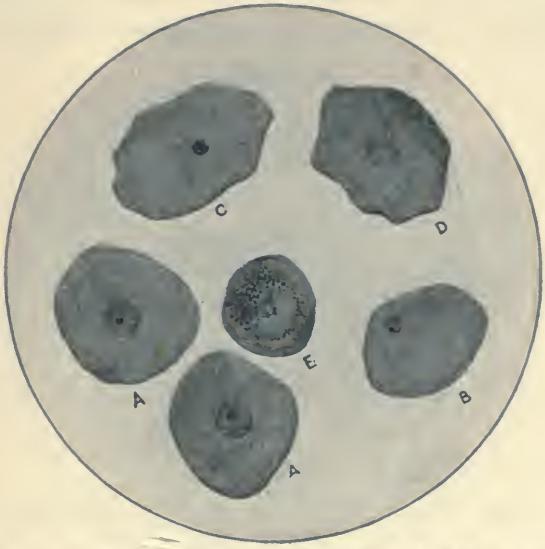

FIG. 2.—Cell changes in the spinal ganglia in a case of rheumatoid arthritis, with advanced arteriosclerosis. A, normal cell; B and C, diminution in size of nucleus; D, shadow nucleus; E, arrangement of pigment in Marchi stain. All stains except E stained by carbol hemalaun.

"wanders" from its central position and takes a peripheral position at the edge of the cell body.

DEGENERATION OF GANGLION CELLS IN ADVANCED ARTERIOSCLEROSIS ESPECIALLY WITH REGARD TO CHANGES IN THE NUCLEUS.

In a cervical and lumbar enlargement of a cord of a case of rheumatoid arthritis with extensive cerebrospinal arterio-

sclerosis, 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 number of dendrites. The nuclei of most of the cells were of much smaller size and stained very deeply with the nuclear stain. The nucleus with the hemalaun eosin took a pale-violet stain, in which the filaments of chromatin could be seen under a high power. In the cells under consideration (see Fig. 2) the nucleus was reduced to one-half or even one-third of the

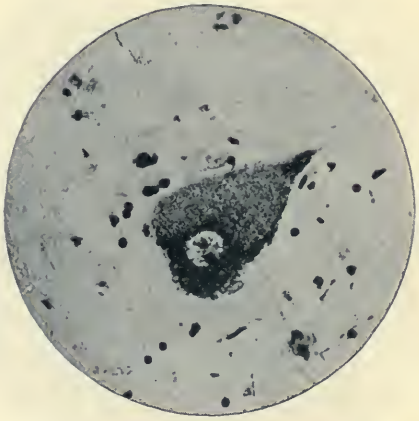

FIG. 3.—Ganglion cell showing ballooning and reticulum.

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 normal ganglion cells should be spherical with a large vesicular nucleus, staining a very pale violet with hemalaun, with the cell substance 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 the exception 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.

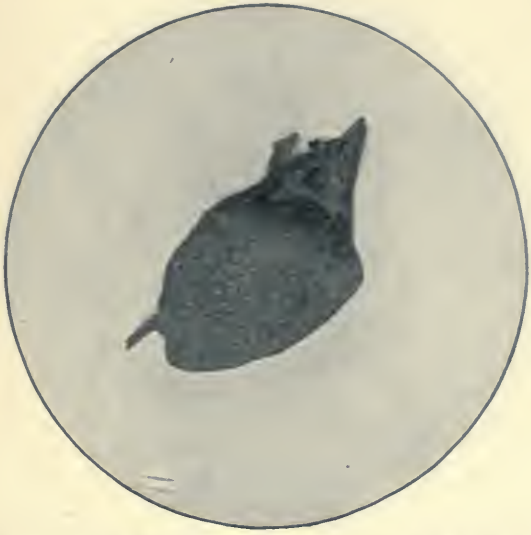

FIG. 4.—Ganglion cell from case of idiocy reported with Dr. Spiller.

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

FIG. 5.—Photograph of ganglion cells, showing early stage of iron infiltration. Iron-hematoxylin stain.

these cells, especially toward 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 time 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.

ABIOTROPHY.

Gowers has used the term abiotrophy to designate an inherent defective vitality of tissues manifested by loss of tone

FIG. 6.—Ganglion cells, showing advanced stage of iron infiltration, with degeneration of ganglion cells. Iron-hematoxylin stain.

and vitality and degeneration after a certain period. This is manifested most distinctly in the muscular dystrophies in which the condition is dependent upon lack of vital tone of the muscles.

The same term can be used in another sense to apply to certain changes in the nerve cells. The problem that often confronts us in dealing with both conditions of nerve cells is to determine whether the changes are inherent in the develop-

ment of the cell or acquired after the cell has reached its full development.

The study of the nerve cells in defective development of the nervous system gives us a picture distinctly different from that seen in the usual degenerative changes. Different grades of these changes may be seen.

In the case of a man of full cerebral development, but with a defectively grown spinal cord, occurring in the service of Dr. C. W. Burr, and reported by him, these changes were present. In this case a man of forty-three had a fully devel-

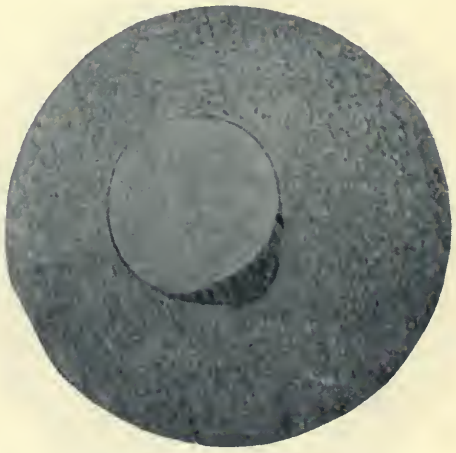

FIG. 7.—Vacuole formation in ganglion cell of anterior horn of spinal cord in a case of tuberculous meningitis.

oped and normal-shaped head, with fairly normal intelligence, but with the body of a child of four or five years of age. The gross examination of the brain and spinal cord showed a fully developed brain, but with a spinal cord smaller than normal. The spinal ganglia is of normal size and appeared to be larger than normal on account of the small size of the cord. The anterior-horn cells in this case were normal in number and arrangement. The microscopic examination by the Nissl method gives the following changes: Cells appear tumefied and of an irregular balloon shape (see

Fig. 3); the nucleus and chromophilic elements were heaped at one end of the cell corresponding to the apex of the balloon; the rest of the cell area was filled with a light-yellow material throughout which a dark reticulum could be easily discerned.

In a case of idiocy, in a girl of six, reported by Dr. Wm. G. Spiller and the author, the same type of cell degeneration or defective development, but to an extreme degree, was present (see Fig. 4). The changes in the nerve cells in these cases gave

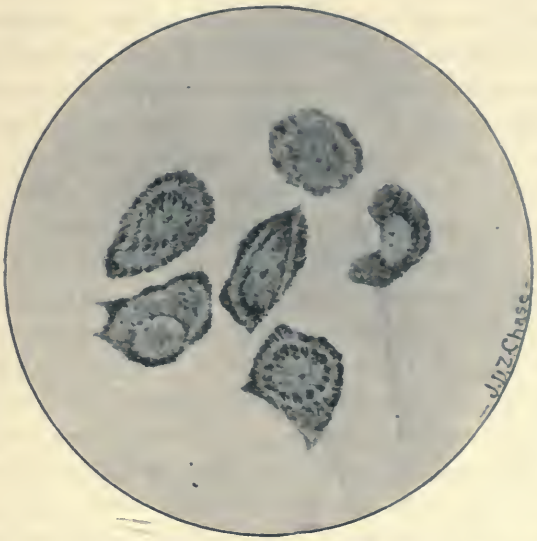

Fig. 8.—Ganglion cells from the suprarenal gland of a chicken. Stained by Nissl method. (Zeiss, oc. 2, ob. 3 mm.)

the same extremely tumefied, balloon-shaped appearance with the chromatin at one end of the cell. That this condition of the nerve cell was not due to hemorrhagic pachymeningitis was shown by the presence of the same changes in the basal ganglia, pons, medulla, and spinal cord. In another case of idiocy, which presented in its formation the symptoms of cerebrospinal meningitis, but in which there were no meningeal changes at autopsy, the same changes were found by Spiller. Hirsch and Sachs found the same changes in

amaurotic family idiocy. While Hirsch considered these changes in amaurotic idiocy to be of toxic origin, Sachs holds that a disease so widespread as this, beginning always at the same period of life and attacking several members of the same family, with the exemption of others, could not be due to a toxic influence.

The presence of these cell changes, which have been found only in cases of idiocy or defective development, leads me to agree with Sachs that they are not of toxic origin, but are examples of defective development of the ganglion cells. This is confirmed by the presence of these cells only in the spinal cord in the case here reported, with normal-cell structure throughout the brain, which presented, neither during life nor autopsy, evidence of defective development.

A study of the ganglion cells of the adrenal gland in fowls presents a type of retrogressive abiotrophy. Embryologically the adrenal gland is developed in part from the Wolfian duct and in part from a branching off of the spinal ganglia. Distinct ganglion cells are observed as such as an essential element of the adrenal structure, no higher in the animal kingdom than fowls. A study of these cells gives the following characteristics: When a basic nuclear stain is used the nucleus presents marked changes. In some of the cells it is very pale; in some it is much darker than normal. The shape of the nucleus is very variable. In practically none of the cells examined was there a perfectly spherical nucleus. From a slight irregularity to a very marked lance-shaped nucleus, all varieties were observed. The nucleus is often peripheral in position. No normal nucleoli can be observed. Many of the cells have multiple nucleoli. In the majority of the cells what appears to be a distinct nucleolus is so irregular in shape as to constitute merely a massing of chromatin in the nuclear reticulum. The arrangement of this material is as irregular as the nuclear arrangement of polymorphous polynuclear leukocytes, and very often the nucleus has the appearance of such a stained leukocyte. In the body of the cell the

chromatin is arranged in two distinct layers; one immediately surrounding the nucleus and the other at the periphery of the cell with a comparatively chromatin-free area between. The cells are of more irregular shape than that of normal ganglion cells (see Fig. 8).

METABOLIC DEGENERATION OF THE NERVE CELLS WITH IRON INFILTRATION.

In early life, even antenatal life, the function of the ganglion cell is not definitely determined, and while irritability and other nerve functions are predominant characteristics of such cells, they may take on the other functions of cells in general. This is manifested when free blood is extravasated in the neighborhood of developing ganglion cells. This to a certain extent is true of fully developed ganglion cells, but not to the same degree. The ganglion cells, under these circumstances, take on an absorptive and metabolic function, as manifested by the presence of hemosiderin and other blood products within the nerve cells. When this condition takes place in the full-grown cell it is associated with degenerative and atrophic changes (see Fig. 6). In the developing cell, however, it gives rise to certain microchemical reactions, but with little chromophilic change in the cell outline (see Fig. 5). This condition may be seen both in the lower animals and in the human beings. In the case of a newborn puppy with deformities in the posterior extremities, sclerotic and hemorrhage foci were found in the lumbar enlargement, antenatal in their development. The microchemical and microscopic changes in these cells were as follows: When sections are stained by the Weigert or iron-hematoxylin stains, both of which stain the red blood corpuscles a deep black, the following changes in the neighborhood of the hemorrhage are seen: In the cells, at a distance from the hemorrhage, the nucleoli alone takes a black stain. This is true of nucleoli in general. As we

approach the area of hemorrhage the cells become smaller and the nucleus becomes irregular and takes a jet-black stain. The rest of the cell body takes a very pale brown in which the chromophilic elements may be seen by careful inspection. In the next stage of iron infiltration the protoplasm of the cell body becomes darker; this is followed by granules of jet-black pigment, and in the area usually occupied by chromophilic elements. As this condition advances these areas are connected by fine filaments of jet-black pigment giving a reticular appearance to the cell protoplasm. In more advanced cases the clear areas in the cell are encroached upon by the pigment masses until the whole cell area, including the processes, present a jet-black appearance and the nucleus is no longer distinguishable. The nucleus is usually found in a central position, although it may occupy a very eccentric position. The neuroglia cells in the neighborhood of the above cells do not present the same change. They are somewhat darker and may contain a few jet-black granules, but are not completely infiltrated.

Van Giesen. The normal ganglion cell by the Van Giesen method presents the following picture: The cell body takes a deep-red stain in which can be seen the chromophilic elements. The nucleus has a vesicular appearance and is also red in color. It has a nucleolus of slightly darker tint. In the cells affected by the iron infiltration the cell body and the nucleus take a deep-yellow stain. The nucleoli cannot be seen in the deeply yellow-staining nucleus.

Hematoxylin Eosin. In the normal ganglion cells the slight pink tint of the cell body is in striking contrast to the nucleus, which has a vesicular appearance and takes a violet stain, as does also the nucleolus. The cell showing hemoglobin infiltration takes a deep-red stain and the depth of the stain increasing with the degree of pigmentation. The nucleus takes a deeper stain of red than does the cell body. The nucleolus cannot be seen. The position of the nucleus of some of the cells is eccentric.

As will be seen from these staining reactions, the cells take on the reactions for hemoglobin, and while, on account of the material in this case having been used for serial sections, the hemosiderin reaction could not be used, it has been found in other cases giving identical changes by Weber and myself. In a case of iron infiltration in the neighborhood of a hemorrhagic foci in the cortex of an adult, not only were the above changes found but also the hemosiderin reaction by the ferrocyanide-hydrochloric acid test. Weber, in his case, found identical changes.

It is not probable that a cell, whose function has been so disturbed during its developmental period, will develop to the same degree as the cell whose function has not been interrupted. Results, therefore, of traumatism and slight meningeal hemorrhage in the developmental period must be considered in other relations than that of simple traumatic pressure on nervous tissues.

These changes, to a lesser degree, are seen in cases of acute destruction such as rattlesnake poisoning, etc.

In Fig. 7 an extreme grade of vacuolization of the nerve cell is pictured. The chromophilic elements are massed at one end of the cell, with a few elements around the wall of the vacuole. There was no evidence of postmortem change in this case.

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SOME ANOMALOUS AND PATHOLOGICAL CONDITIONS OF THE CEREBRAL VASCULAR SYSTEM,

WITH A DISCUSSION OF THE PATHOGENESIS OF CEREBRAL THROMBOSIS.

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AND
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(From the William Pepper Clinical Laboratory and the Laboratory of the Henry Phipps Institute.)

The middle cerebral artery may be considered as the direct continuation of the internal carotid. After giving off the anterior cerebral, it enters the Sylvian fissure, and in its normal state occupies a position at the bottom of the fissure, in close contact with the convolutions forming its floor. Under pathological conditions, the position of the vessel is decidedly altered. In conditions of prolonged hypertension, and especially when there is an extensive arteriosclerosis, instead of occupying a position at the bottom of the fissure, the vessel is either curved markedly outward toward the surface or assumes a tortuous, serpentine course, depending upon the grade of hypertension and the change in the vessel walls.

This change in the position and in the course of the vessel is the most important factor in the production of thrombotic lesions in the important vessels given off from the main trunk.

In the normal state, the subsidiary arteries supplying the posterior portion of the frontal lobe, the motor area, the parietal lobes, and the upper portion of the temperosphenoidal lobes are given off in a posterior direction at an obtuse angle of more than 120 degrees, measured in the direction of the course of the vessel.

Inasmuch as the course of the smaller vessels is more or less definitely fixed by the position of the fissures in which they run, the altered position of the main trunk changes the direction of the incidence in such a way as to materially alter the angle. Even in the comparatively simple change of a long outward curve toward the surface, a distinct sharp curve in the secondary vessels is not infrequently noted.

In the more marked cases of tortuosity of the Sylvian artery, a distinct sharp curve, or series of curves, is produced in the secondary vessel, and its angle of incidence altered in one or more directions. When the elasticity of the vessels is interfered with by such a process as arteriosclerosis in the vessel wall, the gradual curve in the vessel is lost, and a decided kinking is produced. We have, therefore, presented two factors which favor the formation of a thrombus, the pathological change in the vessel wall itself and the acute angle produced by the torsion of the main trunk, both of which lead to a slowing of the blood current, and when the angular condition becomes sufficiently marked, to complete obstruction.

From an analysis of a large number of cases, we are convinced that the secondary change in position to the main trunk is the most important factor in the production of cerebral thrombosis. While these observations are concerned mainly with the middle cerebral artery, they apply with equal force to the other main trunks.

The anterior cerebral, from its point of origin from the internal carotid, takes a direction toward the median line, to be united with its fellow of the opposite side by means of the short anterior communicating artery. It continues its course along the superior surface of the corpus callosum, supplying the mesial and the external portion of the frontal lobe not supplied by the middle cerebral. On account of its straight course, and its protected position, and the few large trunks given off, it is relatively rarely affected by the accident of hypertension and arteriosclerosis above noted.

The two vertebral arteries, after their entrance into the cranial cavity through the foramen magnum, give off the posterior inferior cerebellar arteries, and then unite to form the basilar artery at the junction of the pons and medulla. The basilar artery gives off several small transverse branches, which supply the pons and adjacent parts of the brain. It also gives off four larger vessels, as follows: the two anterior inferior cerebellar arteries, which pass along the crus cerebri to supply the anterior border of the under surface of the cerebellum, and the two superior cerebellar arteries, which, arising from the main trunk at the upper portion of the pons, wind around the crura cerebri near the fourth nerve, and divide on the upper surface of the cerebellum into branches, which supply this area. The basilar, while it occupies a superficial position on the surface of the pons and medulla, is subject to high tension and marked tortuosity. Next to the Sylvian, the vessels supplied from this trunk are most frequently affected by thrombotic lesions. This gives rise to areas of softening in the pons, the cerebellum, and the medulla. The basilar artery at the anterior surface of the pons divides into two posterior cerebrals, which, after winding around the crura cerebri, course along the under surface of the cerebrum, anastomosing with the middle and anterior cerebral arteries. Apart from the posterior choroid, which supplies the velum interpositum and the choroid plexus, only one large branch is given off. Thrombosis in the dis-

tribution of the posterior cerebrals is of relatively rare occurrence.

The posterior cerebral is united to the external carotid on either side by a vessel of smaller caliber, the posterior communicating, thus completing the circulation at the base of the brain and forming the circle of Willis.

A pathological lesion closely related in its etiology to the vascular conditions above described is that of cerebral aneurysm. Miliary aneurysms have been frequently described, and from the literature one would gather that they are of frequent occurrence. The careful study of a large number of cases leads me to the conclusion that nodular areas of sclerosis have been frequently mistaken for miliary aneurysms. This is more particularly true of the smaller vessels. Certain it is that the type of large isolated aneurysm is of relatively infrequent occurrence. I have in my collection but two examples. The smaller of these is an aneurysm the size of a hazelnut, in the position of the anterior communicating artery. It produced no symptoms during life, and was discovered in the routine examination of the brain at autopsy. The other specimen was much larger, about the size of an English walnut. It affected the posterior cerebral artery at the junction of the middle and posterior lobes of the brain on the inferior surface. A rupture of the aneurysm produced sudden unconsciousness, marked contraction of the pupils, a first slowing of the respiration, which later became of the Cheyne-Stokes variety, and finally death. At the hospital to which the patient was removed a diagnosis of opium poisoning was made, and the patient treated accordingly. At the autopsy, the posterior and middle fossæ of the skull were filled with clotted blood.

ANOMALIES OF THE CIRCLE OF WILLIS.

We cannot take into consideration the variations in the size of the bloodvessels constituting this important structure. This subject is worthy, however, of a special study, on

account of the importance of the blood supply in the functional activity of the cerebral tissues. A study of 100 brains will show a marked variation in the size of the constituent vessels. In some cases the caliber of all the vessels will be reduced to one-half the size of what may be considered the normal, and this, independent of any pathological process in the vessels themselves.

This deficiency in the size of the vessels sometimes has an apparent relation to the structure of the brain itself. It is not at all surprising that with small bloodvessels, important structures such as the pons and medulla should also present such a relatively small size as compared with the rest of the brain. This was particularly striking in a case of hysteria presenting irregular periods of mental disturbance extending over many years.

The development of the brain is dependent to a large extent upon its blood supply, and with insufficient building material to any one portion, a lack of structure and of functional activity might be expected.

Irregularity in the size of the individual vessels of the circle of Willis would not, in all probability, have any disturbing value either as to structure or function. It has been shown experimentally that constant pressure is maintained in the vessels of the circle when the blood supply of one of the branches or its supplying artery is cut off.

The simplest anomaly, and one not infrequently met with is the union of the vessels to form the basilar artery before its entrance into the cranial cavity. In the three cases showing this anomaly the extracranial course of the vertebral arteries could not be studied. In the removal of the brain, however, the medulla was severed either at the first or second cervical segment. At this level there was but one vessel which continued as a single structure to its division into the posterior cerebrals (see Fig. 1). In other respects the circle of Willis was normal. There were no other anomalies of the brain in these cases.

In case No. 2 a condition almost opposite to that described in case No. 1 is presented. The basilar artery is very short; the vertebrals do not join to form the basilar until the junction of the pons and the medulla has been reached. The right vertebral at the level of the pyramidal crossing divides into two branches, practically forming three vertebrals, extending

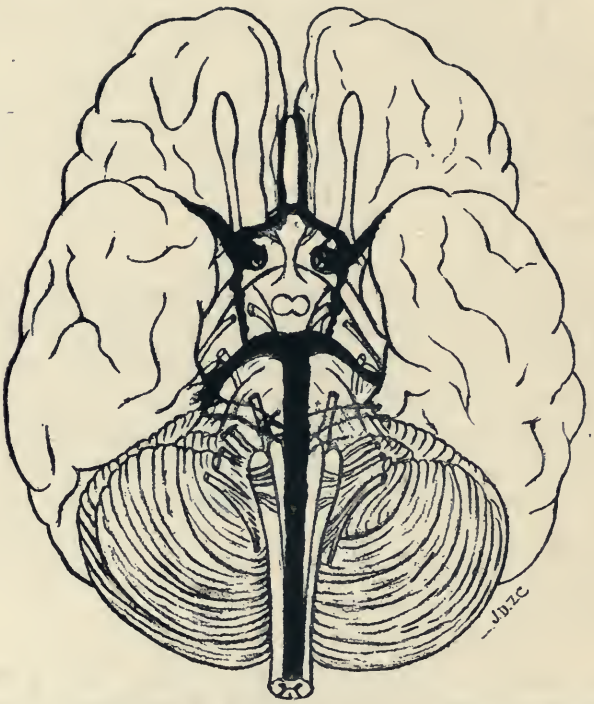

FIG. 1.—Anomaly of the basilar artery, *i. e.*, a single vessel within the skull cavity, the two vertebrals having already united before entrance.

the length of the medulla, and finally uniting a short distance above the junction of the pons and the medulla to form the basilar artery.

The divided branches of the right artery were relatively small in size as compared with the left. An anomaly such as existed in this case would naturally predispose to the forma-

tion of thrombi in the smaller vessels or at their junction when the constituent vessels became the seat of the endarteritis.

Case No. 3 also presents an anomaly of the vertebral branches. In this specimen the basilar is of normal length, but at a distance of 1.5 cm. below the junction of the verte-

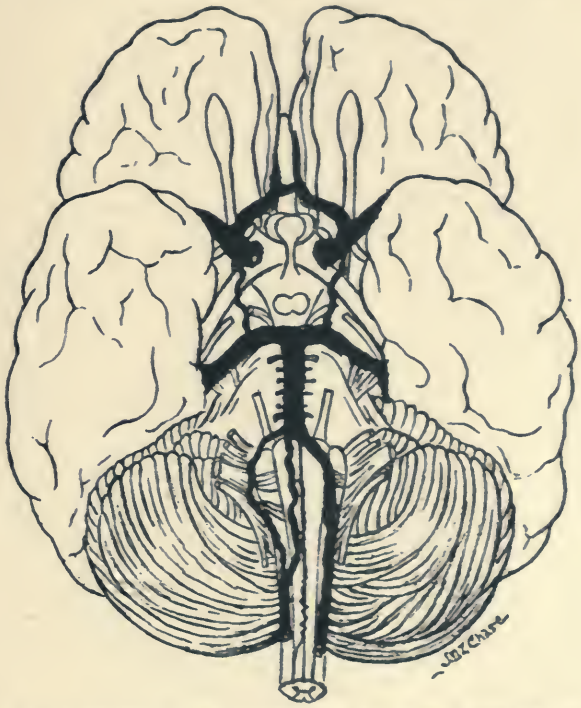

FIG. 2.—Anomaly of the right vertebral, which divides into two smaller branches, these finally uniting with the left vertebral to form the basilar.

brals to form the basilar there is a transverse branch joining the two vertebrals. The transverse branch was of the same caliber as the vertebrals themselves. In this way a double circle at the base of the brain was formed, the inferior being of triangular shape.

In case No. 4 a marked anomaly of the vertebral is pre-

sented. At the junction of the pons and the medulla to the spinal cord a large transverse branch joins the two vertebrals. The right vertebral artery is slightly narrower than the left after this branch has been given off. The right vertebral extends in an anterior direction 0.5 cm. and divides into three branches, one of these extending to the left to join the main trunk of the left vertebral, to form the basilar artery. The

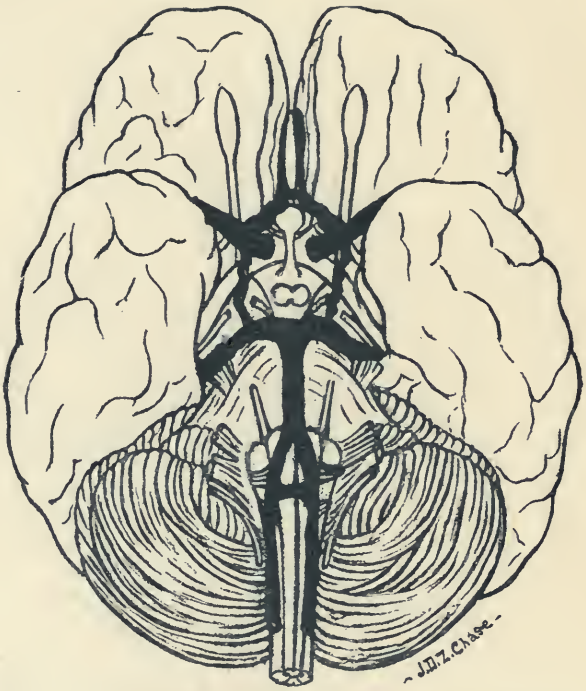

FIG. 3.—Anomalous branch connecting the two vertebrals.

posterior of the remaining branches curves backward at a level corresponding with that of the posterior superior cerebellar artery on the left. The anterior continues in the course of the right vertebral for a short distance and then curves outward at a level corresponding with that of the anterior superior cerebellar artery on the left. At this level it receives a small branch from the basillar.

In case No. 5, as in case No. 3, a double circle was formed at the base of the brain, the inferior circle in this case being irregular and quadrilateral in shape. An anomaly of the anterior portion of the circle of Willis is presented. The posterior half of the circle is normal. The right anterior cerebral, at a short distance from its origin from the internal

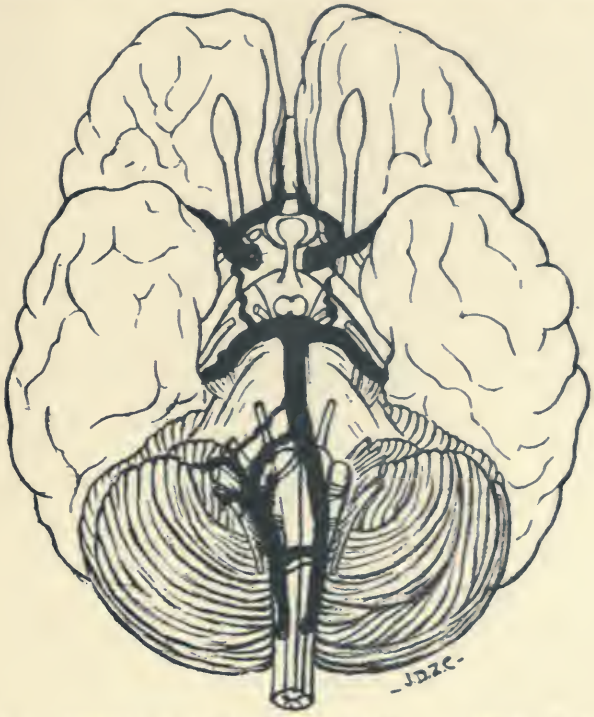

FIG. 4.—Anomaly of the vertebral arteries. A division of the right vertebral into three terminal branches, and an anomalous artery connecting the two vertebrals.

carotid, divides into three branches. The first and most external of these may be considered to represent the continuation of the main trunk. The second branch joins this branch almost at the junction with the anterior communicating. The third branch joins a small branch from the left anterior cerebral and empties into the anterior communicating

at its middle position. This case also presented some anomalies of the gyral distribution of the cortex.

It will be noted in the above collections that six of the seven cases involve the formation of the basilar artery. In the study of an extensive number of brains it will be found that this artery is prone to an anomalous structure. Obersteiner

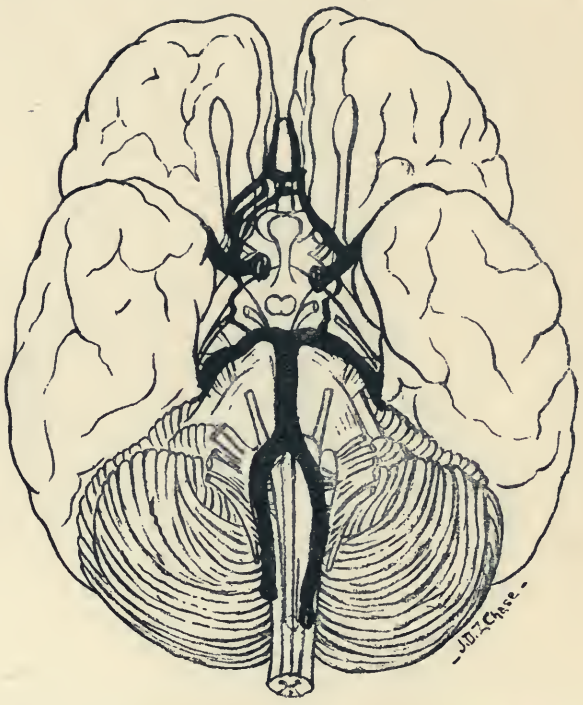

FIG. 5.—Anomaly of the right anterior cerebral and anterior communicating arteries.

called attention to the formation of a persistent septum after a union of the two vertebrals, and also a division of the basilar into two distinct vessels after its formation. It would be surprising to find an anomalous structure in vessels whose functions are so important for vital economy as the vessels at the base of the brain did we not consider the fact that the

anomalous change is more of the nature of an excess than a diminution. This is true of all the cases here presented, with the exception of the first three cases. Anomalies of the anterior portion of the circle of Willis are most frequently confined to the multiplicity of structure of the anterior communicating vessels. It is not infrequent to find double anterior communicating arteries.

An interesting structural change with a secondary variation of the vascular supply was frequently met with on the mesial surface of the brain in the distribution of the pia arachnoid in studies at the Phipps Institute by Dr. Carncross. Not infrequently the arachnoidal membrane, instead of covering the entire mesial surface of the brain, and then being reflected to the opposite side, bridges this space at various levels, not infrequently leaving the anterior half of the mesial surface of the brain free from this membrane. The convolutions most frequently affected are the convolutions of the anterior half of the corpus collosum, and sometimes the mesial surface of the frontal. Under such conditions, it is necessary for the small arterial branches given off from the anterior cerebral to bridge this space in order to reach these convolutions.

Microscopic examination of the areas not covered by the meningeal membrane shows in some areas no trace of covering for the cortex. In other areas a few delicate connective tissue fibrils are present. These are, for the most part, attached to small vessels. These delicate fibrils could, of course, be considered as a trace of the arachnoidal membrane; they certainly do not represent the arachnoidal membrane as we ordinarily understand it. A few connective tissue fibrils could, at most, make up a meshwork of fibrils over the cortex, but this would not, in the ordinary sense of the word, constitute a membrane. The gross examination of the denuded areas shows no evidence of a distinct membranous layer.

JUGULAR. An interesting anomaly of the nervous system of the brain and also of the structures at the base of the skull

was presented in a case at the Philadelphia Hospital. The posterior fossa of the skull on the right side was much smaller than on the left. The posterior lacerated foramen was entirely wanting. The vessel corresponding to the jugular vein was formed from the superior petrossal, inferior petrosal, and lateral sinuses, and made its exit from the skull at a large auricular foramen at the position usually occupied by the mastoid foramen. In this case it was impossible to follow the anomalous course of the vessel outside of the skull without unnecessary mutilation of the corpse.

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CARCINOMATOSIS OF THE MENINGES.

Presentation of a Case of Carcinomatosis of the Meninges, with a Consideration of the Diagnosis of Multiple Carcinomatosis, Tuberculosis of the Nervous System, Disseminated Syphilis, and Multiple Sclerosis.

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

The case which forms the subject matter of this paper is worthy of record not only on account of the rarity of the condition present, but also because the mistake in diagnosis, made after a careful clinical study, may be of some value in the consideration of similar cases.

Multiple secondary carcinomatosis of the nervous system limited to the meninges is a rare condition. Only eleven cases were discovered after a careful search of the literature. In all of the four cases reported by Siefert (1) there was a primary tumor of the brain. In the two cases of Scanzoni (2) tumors of the brain were secondary to carcinoma elsewhere, and the meningeal infiltration took its origin from these. In the case of Lilienfeld and Benda (3) the meninges of the cord were alone affected.

In some respects our case of secondary carcinomatosis localized to the meninges is unique. Scholz (4), it is true, under the title of meningitis carcinomatosa, reports two cases diagnosticated as menin-

gitis, in one of which the clinical diagnosis was substantiated by spinal puncture. Westenhöffer (5) reports a similar case of carcinomatous meningitis (confirmed by autopsy) where colon bacilli were found in the cerebrospinal fluid during life, and after death in the bloodvessels of the pia and dura. In only one of Scholz's cases is there mention of the involvement of the spinal cord or its meninges. In the other case the spinal meninges were involved, but no mention is made of spinal roots or ganglia, and the histological report is meagre. Although Scholz does not mention specifically the presence of collections of leucocytes, the case was reported as meningitis carcinomatosa, which Seifert had previously distinguished from simple meningeal carcinomatosis, in which signs of inflammation were absent. In Scholz's and in Westenhöffer's cases, however, the membranes were tense, the bloodvessels were highly injected, and the pia infiltrated with turbid exudate showing here and there traces of blood or clots. On post mortem examination the conditions could not be distinguished from simple meningitis.

Of Siefert's cases, one was a case of meningitis carcinomatosa. Of the others, one shows the membranes adherent to the brain substance at the site of the tumor. Very careful histological examination showed that the meninges were extensively involved. Hæmorrhages and collections of leucocytes were seen. There was penetration of the brain substance by the columns of cells. In the second case the meningeal changes in the brain were not extensively studied, but those of the spinal cord showed the presence of collections of leucocytes and hæmorrhages in addition to the carcinomatosis. In the case of Lilienfeld and Benda there was œdema of the membranes of the brain, infiltration of the spinal meninges, invasion of the periphery of the cord by carcinoma, and involvement of the roots and of several cranial nerves. In the cases of Scanzoni the meninges of the cord were also principally involved.

The following case reported at the May meeting,

1907, of the Association of American Physicians, by Dr. Peabody, is evidently a case very similar to the one here reported, and the only case we have been able to find at all similar to it. In reporting this case, Dr. Peabody called attention to the case here reported from an abstract of the history and clinical

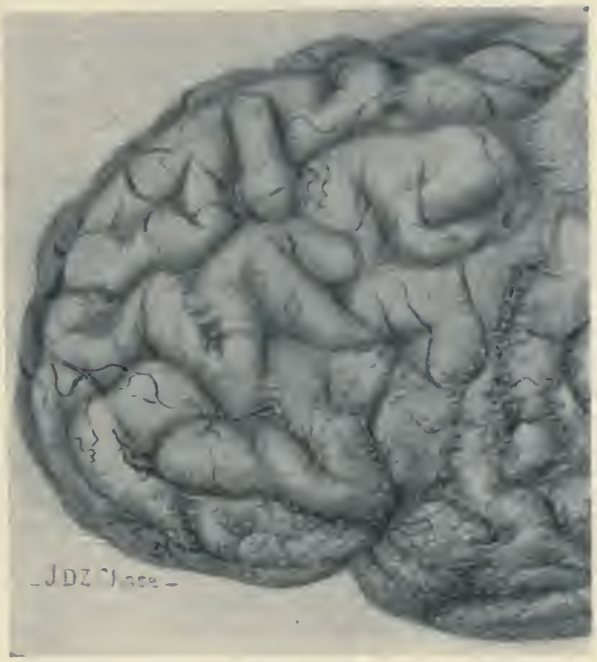

FIG. 1.—Left prefrontal lobe, showing miliary carcinomata and their relation to the cerebral veins.

findings published in the transactions of the Philadelphia Neurological Society, three years ago, at which the brain was shown as a card specimen.

Dr. Peabody's case was a woman forty-three years old. Four years after the removal of the breast for carcinoma she developed pains, especially marked in the lower extremities, back, and shoulders. The

pain was severe and the prostration became intense. Electrical reactions were normal. Treatment did not relieve her pains. She slept but little and gradually became mildly delirious. Lumbar puncture gave normal fluid. About a week before death she was attacked with partial ptosis of the right eye, partial paralysis of the muscles of the right side of the face, weakness of the right palate muscles, and partial deafness of the right ear. Diplopia was present in part of the field of vision. Pain in thighs and legs persisted, and pain was noted in the lumbosacral region on attempting to sit upright and on pressure. There was no other alteration of sensation. The eye grounds were normal. Urination and defæcation became involuntary. The muscles of deglutition gradually became impaired, and water regurgitated through the nose. She died of œdema of the lungs three weeks after coming under observation.

Autopsy showed metastatic carcinoma of the thyreoid, of one suprarenal, of kidneys, of one lung, of wall of an old cyst in cerebellum, numerous small metastatic growths in the pia of pons and medulla, without lesion of the pons or the medulla. There was diffuse infiltration, with carcinoma of the perineural lymph sheaths of one trunk nerve of the cauda equina, and in one place the nerve trunk itself was similarly invaded. The pia covering the cord showed small metastatic growths. This case has since been reported in the literature (6).

In the case about to be presented it will be noticed upon reading the pathological report that the lesions were small pin point, and closely scattered like small grains of sand over the surface of the brain and cord.

CASE.—M. S., colored, age thirty-eight, by occupation cook, was admitted to the woman's nervous wards of the Philadelphia General Hospital, April 9, 1905. She complained of pains in both lower extremities and in the lumbar regions. At times the pains extended into the left chest.

Family history: Mother died at the age of eighty-one and father at the age of ninety-three, of senility. One

brother died of typhoid fever at ten years of age. The cause of death of one sister at eight years was unknown to the patient. One sister died at the age of forty-six, of asthma, and one at fifty, of heart disease. There was no history of tuberculosis in the family.

Previous history: There was a history of the usual diseases of childhood, malaria at thirteen, nettle rash at nineteen, acute articular rheumatism at thirty; she had been subject to sick headaches for a long time, and had complained of cough throughout the winter.

History of present illness: Three months ago the present trouble began with pain in the right elbow and hand, and headaches in the occipital and temporal regions. Two days later the pain extended to the left hand. Several days later she complained of pain in the lumbar region and in both lower extremities. There was a persistent cough associated with pain in the chest and back.

The examination of the patient on April 9, 1905, revealed a well developed, well nourished negress. Motion was retained normally in all four extremities, and sensation was normal over the entire body.

Cranial nerves: Examination of the cranial nerves revealed no abnormal symptoms in their distribution, with the exception that the right pupil reacted sluggishly to light. The right knee jerk was absent; the left knee jerk was present, but diminished. The Achilles jerk was present on both sides and decreased. There was no ankle clonus and no Babinski reflex. There was flexion of all the toes to plantar irritation. The superficial abdominal reflexes were normal. The biceps and triceps jerk of both upper extremities were exaggerated.

Examination of the chest revealed impaired resonance over the left chest posteriorly, below the angle of the scapula. Over this area there was bronchovesicular breathing and moist râles, more marked on expiration. Vocal and tactile fremitus were increased over the same area.

April 15, 1905. There was severe pain in both legs and over the lumbar region.

April 29, 1905. An opthalmoscopic examination was made by Dr. Sweet. The left pupil reacted promptly, the right sluggishly. The eye grounds were normal, the nerves were of good color. The ocular movements were unimpaired. The visual fields, roughly tested, were normal.

May 10, 1905. The pain in the legs still persisted. There was a sixth nerve palsy on the left side, and some hyperæsthesia of the chest posteriorly. There was no Kernig's sign on either side. The muscles of the left leg were more flabby than those of the right. While there was still flexion of the toes to plantar irritation on the right side, on the left side there was a well defined Babinski reflex.

May 15, 1905. The patient was only semiconscious. There

was partial ptosis of both eyes, and she was unable to completely close the right eye. Attempts to swallow milk resulted in choking spells. In addition to the physical signs, there were some moist râles at the base of the right lung.

May 17, 1905. There was almost complete facial palsy on the right side, in both the upper and lower distribution of the nerve. The right eye was held in a third nerve paralytic position with marked dilatation of the pupil. There was marked ptosis of both sides. The exit points of both nerves were sensitive to pressure on both sides, with a well defined paralysis in the distribution of the fifth nerve on the left side. There was a slight Kernig's sign on the right side, but none on the left.

The last examination of the urine, made on May 17, 1905, showed specific gravity of 1.024, an acid reaction, and a slight trace of albumin. On microscopical examination, a few red blood corpuscles, a few leucocytes, a number of hyaline casts, and cylindroids were found.

Pathological Report (Dr. Funke): Chronic pleurisy, hæmorrhagic infarct of the lung, carcinoma of the lung (primary), chronic diffuse nephritis, secondary carcinoma of the liver, primary carcinoma of the pancreas.

The heart, spleen, kidneys, suprarenal bodies, and other organs not mentioned in detail, showed nothing abnormal.

The left lung weighed 530 grammes. Its upper lobe crepitated throughout and was pinkish red in color with black mottlings on its anterior surface. Only a slight œdema was present. At the apex of the upper lobe crepitation was still perceptible, while in the remainder of the lobe crepitation was absent, and a dull note of percussion was elicited.

On section, a cavity measuring 1.5x2 cm. in diameter was found in the centre of this lobe. Its wall was grayish white, showing a granular substance. Around the cavity was a consolidated area made up of quite firm, confluent nodules, grayish white in color.

The left lobe of the liver contained a nodule 3 cm. in diameter. This reached the external surface and projects. The centre of the nodule was yellowish gray and granular. The periphery was granular and pinkish gray in color. To the right of this was a similar nodule.

On the upper surface of the pancreas were two nodules each measuring one and a half cm. in diameter. They were firm and were cut with resistance. The cut surfaces were grayish pink in color. They were apparently associated with the pancreas, possibly having taken origin from that structure. These nodules rested directly below the nodules described in the liver. Similar growths were found along the course of the portal vein.

The uterus showed a large, subserous fibroid arising from

the right lateral surface a few cm. from the superior border of the fundus. The left ovary showed cysts.

The brain, gross examination: The entire brain was covered with minute white areas varying in size from a pin point to a pin head. These areas were most frequent along the course of the bloodvessels, and occurred in scattered points over the entire meninges. They were most marked and occurred in the greatest numbers over the base of the brain, and especially in the interpeduncular spaces.

Spinal cord: The same condition was present over the spinal meninges, and most marked over the cervical enlargement. There was a tumor mass the size of a split pea on the tenth dorsal root. The second and third spinal ganglia were increased to the size of a small bean (5x7 mm.), were of hard consistence, and protruded as tumor masses on the inner side of the dura. The same miliary tumor formation was present on the inner surface of the dura as far down as the middorsal area.

Microscopical examination: Cerebral cortex: The tubercles of the cerebral meninges were composed of a reticulum of connective tissue containing large masses of a columnar type of epithelial cells arranged in cell nests, and having the appearance of a carcinoma. The nests of cells were extended in an irregular way into the brain tissues, without, however, producing any degeneration of the underlying white matter as seen by the Weigert and iron hæmatoxylin stains. The cells were of a columnar type with an irregular deeply staining nuclei, and had the appearance of epithelial origin. Sections of the cortex stained by Mallory's connective tissue stain showed the fibres of connective tissue beginning about the bloodvessels and extending between, but not into, the alveoli.

There was no degeneration of the spinal cord by the sheath stains.

Hæmatoxylin eosin method: The main changes noted by this method were seen in the meninges; the tubercles scattered here and there over the spinal cord in an irregular fashion, noted in the gross examination, did not follow any regular distribution. They were widely distributed, not only over the meninges, but were also seen on the spinal roots. The sixth cervical segment of the spinal cord, for instance, showed a tumor mass in the meninges just within the left posterior spinal root and infiltrating it and extending to the posterior median fissure. There was also a miliary tumor infiltration of the anterior root of the opposite side. The axis cylinders of the roots presented a swollen appearance, caused by infiltration of the roots by irregular shaped cells about the size of polynuclear leucocytes. These cells had deeply staining nuclei. The nucleus varied greatly in size, but in the main made up a relatively small portion of the cell area. Many of the

cells had a circular, clear, unstained area in the protoplasm presenting a vacuolar appearance. These cells were held in alveolar spaces between the nerve fibres, but presented nothing regular in their arrangement. In the tumor infiltration of the meninges, the same microscopic appearance was seen in the centre, but towards the periphery there was a distinct cell nest arrangement. The cells here took a distinctly columnar type, having much the appearance of cells in adenocarcinoma, composed of columnar cells.

In the sections stained by Mallory's connective tissue stain there was no infiltration of the connective tissue fibrils between the cells. The tumor tissue was surprisingly free from connective tissue. A small tumor mass the size of a split pea noted before, on the eleventh dorsal root, completely surrounded the root, but had a well defined capsule, over which bands of connective tissue extended into the interior, somewhat after the manner of a lymph gland.

In the alveolar space formed by the connective tissue, groups of columnar cells were seen here and there, following the same arrangement as described before. The degenerated and infiltrated root occupied the centre of the tumor mass. As one approached the centre of the tumor, the columnar shape and acinus arrangement of the cells was lost. The cells were grouped in an irregular way within the connective tissue. The connective tissue fibrils did not penetrate between the cells. In the lumbar enlargement the tumor infiltration completely surrounded the spinal cord and had the same microscopic picture as that seen in the cervical enlargement. The cord was indented by the pressure of the tumor mass, but there was no true infiltration of the white substance of the cord.

Sections stained by the Van Geisen method added nothing to that described by the other methods.

Marchi method: There was a recent marked secondary degeneration in the posterior columns of root origin. There was also some degeneration of the direct pyramidal tract of the left side, and a few scattered dots here and there in the right crossed pyramidal tract. There was a degeneration in both crossed pyramidal tracts and also in the posterior column. There was a degeneration of the posterior roots and a slight degeneration in the direct pyramidal tracts. The same was true of the dorsal cord.

Nissl method: In sections from the dorsal cord and lumbar spinal cord the majority of the ganglion cells of the anterior horn were in an advanced state of chromatolysis. Only a few of the cells even approached a normal appearance. In the cervical enlargement, many of the cells were degenerated. There was a much larger proportion of normal cells than in the cervical or dorsal cord.

Spinal Ganglia.—The nerves in the ganglion cells had

entirely disappeared. There was also marked degeneration of the nerve fibres. The entire ganglia had been transferred into a mass composed of a reticulum of connective tissue, between which were arranged long rows of a columnar type of cell. In many of the alveolar spaces the cells had taken a more irregular arrangement, as already noted in the meninges.

Pathological Discussion.

The gross appearance of the brain when removed at autopsy, studded closely as it was with small tubercles, gave the impression at the first glance of a

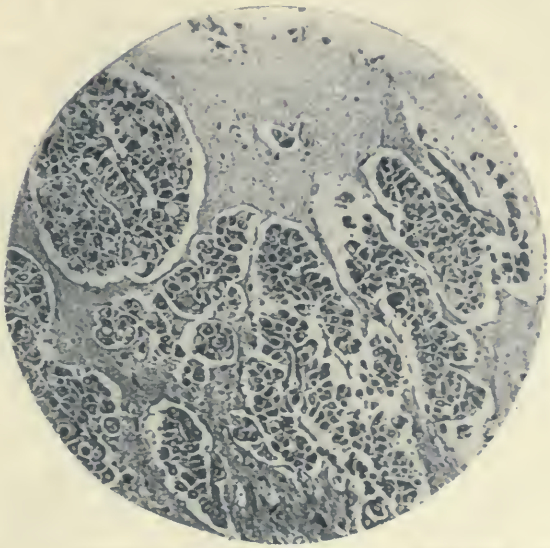

FIG. 2.—Photomicrograph of miliary tumor of meninges of brain, with extension into the cortex.

syphilitic meningitis. The more careful examination and the finding of the tumor masses in the other viscera led to a correct diagnosis. The microscopical examination presented a typical picture of carcinoma (see Fig. 2). The involvement of the cortex was unquestionably an extension from the meninges, and was more a displacement of the cortex,

and could, in no sense, be considered a true infiltration.

Involvement of the spinal roots is not an uncommon condition, but involvement of the spinal ganglia is relatively rare. We have not been able to find a case in which this condition has been definitely stated. The pain in the extremities was probably the result of the tumor infiltration of the spinal ganglia and involvement of the roots.

The peripheral nerves and muscles were not examined.

The involvement of the cranial nerves is explained by the presence of miliary carcinomata in the piaarachnoid, surrounding their points of exit. There are no tumor masses on the nerves themselves.

Clinical Remarks.

A diagnosis of cerebrospinal syphilis was made in this case, in spite of the fact that the patient presented no history of syphilis. This negative symptom, if it can be so called, was not given its proper value. This is not a matter of surprise when there is taken into consideration the difficulty in securing a positive history of syphilis, even when the patient is aware of it, and, what is more frequently the case in the class of patients under discussion, who either never knew or had forgotten such a "trivial matter." It should be remembered, however, when the diagnosis is under discussion that too much importance cannot be given to the elements of a carefully taken history. Ten years of constant effort has not sufficed to eliminate the Blockley mental attitude as to the presumption of syphilis in the diagnosis of a doubtful case, quite irrespective of the history. As an undergraduate student, resident physician, and assistant physician in the wards of the Philadelphia General Hospital, an atmosphere of syphilis of the nervous system in the diagnosis of obscure cases with multiple manifestations always led unconsciously to a presumption in its favor.

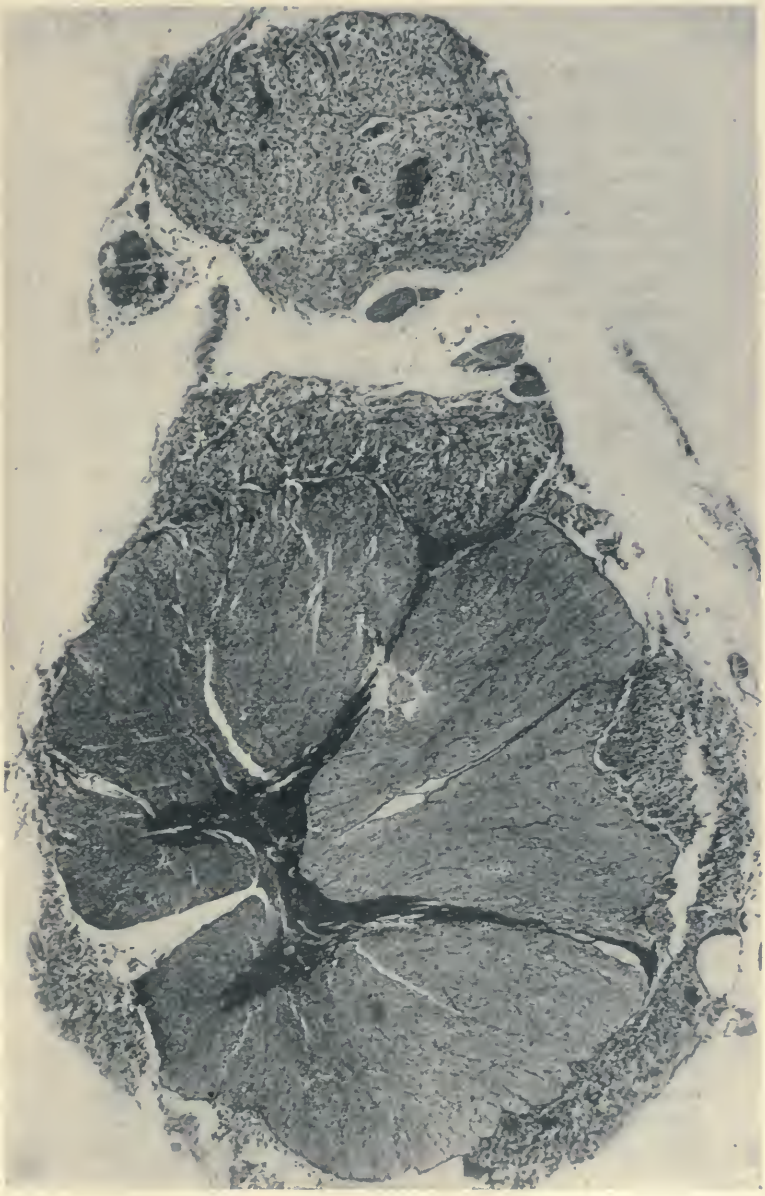

FIG. 3.—Carcinomatous infiltration of meninges, with secondary carcinoma of spinal, posterior root.

Multiple syphilis of the nervous system is not now, nor was it then, a very frequent condition. By this is meant lesions of the nervous system presenting the histological characteristics of syphilis. Scleroses, low grade inflammatory processes, and tract degenerations are present in large numbers, but it remains to be proved how frequently these are due to syphilis. Tabes dorsalis, conceded to be a parasyphilitic disease, does not present the histological lesions of syphilis, and is rarely associated with syphilitic lesions elsewhere in the body. Tabes, however, is diagnosticated as such, and not as cerebrospinal syphilis.

In an extensive collection of brains and spinal cords, obtained for the most part from the Philadelphia General Hospital, multiple cerebrospinal syphilis is present in only a very small percentage.

It should be remembered in this connection that tuberculosis presents the multiple lesions of the nervous system similar in their character and distribution to those seen in syphilis. Lesions of multiple sclerosis, being widely distributed, not only present the multiple symptom group seen in syphilis, but the reverse may also be true—i. e., disseminated syphilis may present the classic clinical picture of multiple sclerosis. Oppenheim (7), and more recently Spiller and Camp (8), have written on this subject. In a paper recently published by Dr. C. W. Burr (9), a case of disseminated syphilis presenting the clinical picture of multiple sclerosis was reported, together with a discussion of the diagnosis of the two conditions.

It is conceded that a distinctive diagnosis between some types of multiple sclerosis and disseminated syphilis is impossible. The importance, therefore, of paying attention to a history of syphilis in order to prevent a mistake in diagnosis is evident. It will be seen from the clinical history, as given, and the clinical diagnosis that tuberculosis of the lungs was diagnosticated. At autopsy, a cavity surrounded by epithelial type of tumor formation was

discovered. In the absence of a history of syphilis, a natural presumption should have been in favor of multiple tuberculosis of the nervous system. Had this patient presented herself at my service, at the Phipps Institute, such a diagnosis would have been undoubtedly made, but the Blockley atmosphere interfered with such a simple logical conclusion. An important question in this discussion, however, is why a diagnosis of secondary carcinomatosis of the nervous system was not made. The patient was thirty-four years old and in good condition. There was no cachexia. A careful examination of the different viscera showed no other lesions than impaired resonance over the left chest posteriorly, below the angle of the scapula; expiratory râles in the right axillary regions and at the base of both lungs; in the left axillary regions, an area about three inches in diameter, over which bronchovesicular breathing could be heard; increase in the vocal and tactile fremitus over the left lung posteriorly. Urinary examination showed some albumin and hyaline casts, but no other evidence of kidney insufficiency. The primary growth in the liver and the secondary growth were too small to give physical evidence of their existence. There was therefore no evidence of the presence of carcinoma, and it is questionable whether such a diagnosis of either the hepatic or pancreatic lesions was possible.

The predominating symptom on admission was pain in the lower extremities. The knee jerks were absent. On the following day, the left knee jerk was present. The right pupil reacted sluggishly to light. On admission, there was pain in the lower extremities, with headaches from three months previous. One month after admission, and nine days previous to death of patient, she first began to show cerebral symptoms. These began with affection of the sixth nerve on the left side, and after a few days were followed by an affection of both third nerves. On the following day the seventh nerve on the right side became affected, with an almost similar af-

fection of the fifth nerve on the left side. On the day before her death, the difficulty of swallowing indicated an involvement of the ninth or tenth nerves. One week previous to her death there was a progessively developing stupor. Such a group of symptoms, with their progress, irregular distribution and development, indicated multiple lesions affecting first the spinal cord and later the brain. For this reason and for no other was the diagnosis of syphilis of the nervous system made.

In a patient presenting symptoms with an evident carcinoma elsewhere in the body, or with a history or evidence of its removal, the diagnosis of multiple secondary carcinomatosis of the nervous system could be made. A frank, active tuberculosis elsewhere in the body would lead to the diagnosis of tuberculosis of the nervous system. The history of syphilis, or distinct evidence of syphilis elsewhere in the body, would lead to a diagnosis of cerebrospinal syphilis. The history of the case with the rapid development of cerebral symptoms such a short time before death would practically exclude multiple sclerosis.

Optic Nerve Involvement.—Optic neuritis is found in 80 to 90 per cent. (Oppenheim, 10) of cases of brain tumor and in 15.5 per cent. of cases of meningitis (Uhthoff, 11). The absence of any optic nerve involvement, at least within a reasonable time before death, may be considered as an indication of a lack of extensive intracranial pressure.

The presence of Kernig's symptom in this case is a matter of some interest. The general impression among clinicians, and especially among pædiatrists, is that Kernig's symptom is diagnostic of meningitis. Kernig (12) in his original contribution reports thirteen cases of cerebrospinal (infectious) meningitis, one case of tuberculous meningitis, and one case of purulent cerebral meningitis, with chronic parenchymatous nephritis, all of which showed Kernig's symptom. He regrets that he had

not been able to study it in the transitory meningitis that may usher in typhoid fever, typhus fever, and recurring fever. He also reports it present in six other cases, on all of which autopsy was performed. These were œdema of the pia of obscure origin; hæmorrhagic pachymeningitis with intermeningeal bleeding; circumscribed pachymeningitis and leptomeningitis, and thrombosis of the pertosal sinus, secondary to caries of the petrous bone; growth of the dura to the skull and chronic leptomeningitis accompanying carcinoma of the brain; slight hæmorrhagic meningitis with hæmorrhage into the ventricle; slight general hyperæmia of the pia (questionably tuberculous). On the first day that the last patient was observed there was no contracture of the knees; on the second, however, the sign was present, although modified. Kernig especially notes this case as affording an instance where his sign was present, even in the absence of genuine inflammation.

On the other hand, Kernig's sign may be absent in meningitis (Netter, 13, Morse, 14). Morse found it in three of twenty cases of tuberculous meningitis, but in more than three of twenty cerebrospinal cases.

It will be noticed that this symptom was not present in the first and subsequent examinations up to a short time before death, and then it occurred only on the left side and to a limited extent. Microscopical sections did not show a meningitis in a strict sense of the term. There was only a tumor formation. This could, of course, have constituted the meningeal irritation in the broader sense of the term.

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SYPHILIS OF THE NERVOUS SYSTEM

REWRITTEN FROM LECTURES DELIVERED TO THE STUDENTS OF THE UNIVERSITY OF PENNSYLVANIA

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Syphilis of the nervous system is so broad a subject that it would be impossible to do justice to it in a short paper, and therefore I prefer to limit myself to a discussion of certain manifestations of the disease, and to describe some abortive forms that are rather common even in a general medical practice, and that may cause difficulty in diagnosis.

The physician often sees nervous syphilis in an early stage, and hesitates in deciding whether such a case is really one of syphilis or not.

There is much doubt as regards the time of appearance of nervous symptoms after the primary infection, as regards the possibility of preventing the implication of the nervous system, and as regards the best methods of treatment.

I do not believe that a period can be set for the implication of the nervous system after syphilis has been acquired, and in my opinion no one can be regarded as free from the danger of nervous symptoms if he has once contracted syphilis. I have seen very early and very late appearance of syphilis of the nervous system. I do not believe that the danger can be warded off by active treatment following the infection, although it is possible that it may be lessened.

Little can be done in treatment of the disease if the symptoms have existed a long time, because nervous tissue has been destroyed and neuroglia has proliferated and taken the place of tissue that has been destroyed. The prospect for improvement is not bad, however, if the patient is properly treated so soon as the first signs of involvement of the nervous system are detected. Some physicians prefer to give the mercury by hypodermatic injections, but I have obtained

in some cases such excellent results by inunctions of mercurial ointment, ½ to 1 dram (2 to 4 grams) daily, rubbed in at a different part of the body each day, and rubbed in during 20 to 30 minutes, with the simultaneous administration of iodid of sodium or of potassium, that I prefer this method of treatment to all others. If the case is not severe I usually begin with 10 grains (0.6 gram) of iodid of sodium three times daily, and increase by about 5 grains (0.3 gram) daily until 60 grains (4 grams)—seldom 100 grains (6 grams)—are taken three times a day. I fail to see any advantage in going beyond this amount, and I believe that, at least in some cases, larger doses may do harm; especially is this true if a mistake has been made in the diagnosis. Even with great care salivation may develop rapidly, as in a recent case under my observation, in which severe cerebral symptoms entirely disappeared as a result of not very large doses of mercury and iodid, but the man became rapidly and seriously salivated. He recovered from the salivation entirely within a week or ten days.

It has seemed to me preferable to give the iodid at the same time as the mercury, rather than to follow the mercury by the iodid, as some have recommended.

Syphilis of the nervous system is commonly not seen soon after the primary infection, and usually one year or several years elapse before nervous symptoms appear; but I have in two cases seen distinct manifestation of nervous symptoms while the syphilitic rash was still on the body. One patient, a man, was under the care of Dr. F. X. Dercum, at the Philadelphia General Hospital, and while still presenting a syphilitic rash had the Brown-Séquard form of paralysis. The other patient, a woman, was in the venereal ward of the same hospital, and was under the care of Dr. A. C. Wood. I saw her at his request. In this case the diagnosis was confirmed by microscopic examination. The notes of this case are as follows:

C. C. was admitted to the Philadelphia General Hospital September 9, 1902, and died September 17, 1902. She contracted syphilis from her husband, and on admission was in the late stages of secondary syphilis. The body was covered with copper-colored macules. The woman seemed dazed and could not reply to questions, although she seemed to understand them. She could say only "Yes" and "No." At times she became maniacal. The left pupil was larger than the right. She vomited and did not eat much and

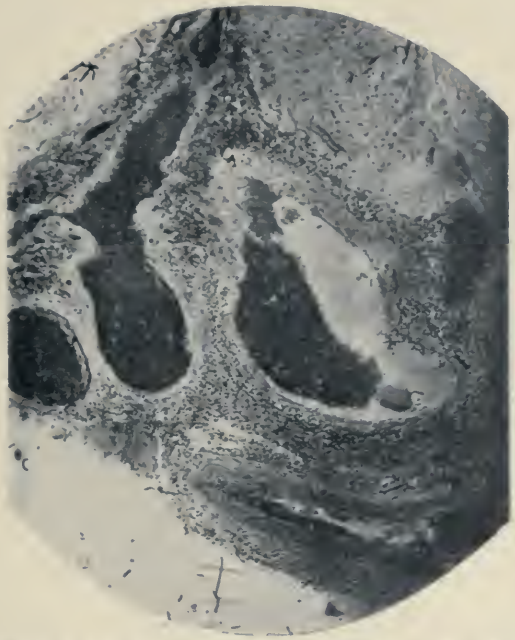

FIG. 1.—Photograph of a section from the spinal cord in a recent case of syphilis of the nervous system, showing intense round-cell infiltration of the pia and congestion of the blood-vessels. These lesions are more common than the gumma.

slept badly. She had much headache and had also ulceration of the genitalia. She was weak and could not walk. She was married in November (presumably 1901). Notes made a little later state that the pupils were equal. The woman lay with her eyes closed and showed little recognition of what was going on about her. The irides reacted to light. Right hemiplegia was present, the face was drawn to the left side, and the right side was paralyzed. She seemed to be aphasic. The post-cervical glands were enlarged.

I am indebted to Dr. A. C. Wood for the clinical notes and the pathologic material.

Sections through the medulla oblongata show no recent nor old degeneration by the Marchi method in the anterior pyramids. (The hemiplegia evidently had been of short duration.) Sections through the spinal cord show intense round-cell infiltration of the pia and about the blood-vessels within the cord (Fig. 1). The condition is like that commonly found in syphilis of the nervous system.

In another case, I have seen early manifestations of nervous syphilis within three or four months after the primary infection. In contrast to these cases it may be well to relate the following case as an example of syphilis of the nervous system appearing long after the primary infection. The patient was referred to me by Dr. W. M. Robertson, of Warren, Pa. A man, 40 years of age, contracted syphilis eighteen or twenty years ago. The disease at that time was pronounced syphilis by a physician. The man had a chancre, and this was followed by a rash and an ulcer on the lower third of the leg. He was well until about two years ago, when stiffness of the lower limbs began. Now he is constipated constantly, is dizzy in the morning or when the first rises from a chair after he has been sitting some time, and he is obliged to steady himself before he begins to walk. He sleeps well, except that he is awakened by the desire to urinate and often is unable to urinate. He has lost all sexual desire. The difficulty in passing his urine has increased during the past year. He stubs his toes on inequalities in the sidewalk and has fallen. His gait is slightly spastic and he cannot hurry. He has been obliged to have plates put on the soles of his shoes at the toes to prevent this part of the shoes from wearing away. The patellar reflex is much exaggerated on each side, and patellar clonus and the Babinski reflex are present on each side. Romberg's sign is not present, and the gait is not ataxic. The upper limbs are not implicated.

This man has not had any of the pains so common in syphilis of the nervous system. Dr. W. C. Posey has found a commencing simple atrophy of each optic nerve, which has caused no disturbance of vision.

I think there is little doubt that the spastic condition of the lower limbs in this patient, taken in connection with the disturbance of micturition and of the sexual functions, the optic atrophy, and positive history of syphilitic infection, is to be attributed to syphilis contracted sixteen to eighteen years before symptoms indicative of involvement of the nervous system developed.

Some patients with syphilis of the nervous system present symptoms so mild that they may cause difficulty in diagnosis to one not familiar with nervous diseases, and indeed in some cases even the neurologist finds a diagnosis by no means easy. Such, for example, is the following case referred to me by Dr. Wm. T. Shoemaker. The patient, a man aged 35 years, has paralysis of the left oculomotor nerve, with paralysis of accommodation and of the iris in each eye. The optic nerves are not affected. He had a chancre when he was 22 years old. Two years ago he began to have difficulty in seeing. About six weeks ago he began to have vertigo and diplopia developed. Six months ago he had much difficulty in passing his urine during two weeks. His memory is impaired and now his lower limbs soon become "tired." He has had cramps in the calves. The patellar reflexes possibly are a little exaggerated. The Achilles jerk is absent on each side. Sensation of pain is diminished on the sole of the left foot and in a band about the trunk in the area of the nipples. He has lost all sexual desire, and has difficulty in passing his urine.

It is exceedingly difficult, if not impossible, to decide whether this is a case of tabes incipiens or of early nervous syphilis, but the somewhat doubtful exaggeration of the patellar reflexes is in favor of syphilis.

For the sake of contrast I give briefly the notes of a much more pronounced case of syphilis in which no doubt could exist as to the diagnosis.

W. S., 32 years old, a patient under Dr. A. Stengel's care at the University Hospital, was admitted to the hospital June 12, 1903. He had been infected with syphilis six years previously. On May 12, 1903, he took a long trolley ride, without having on an overcoat,

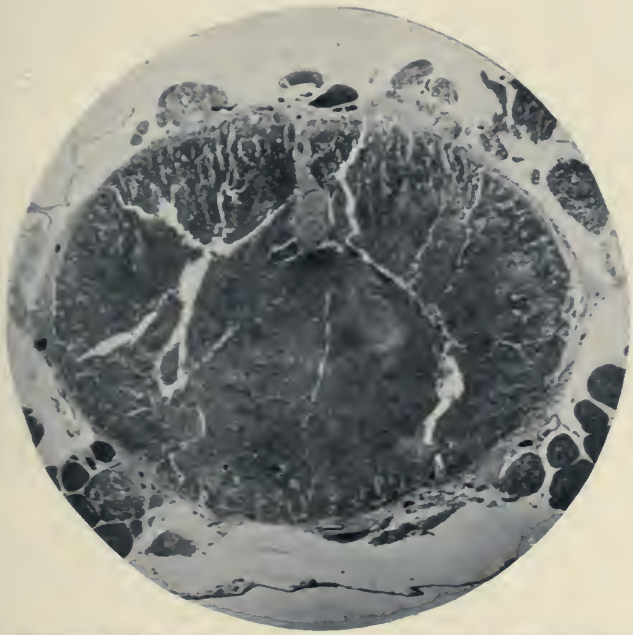

FIG. 2.—Photograph of a section from the lumbar region in a case of intense syphilitic softening and disintegration of the spinal cord. The gray matter cannot be distinguished from the white, and cracks have occurred during the process of hardening the diseased tissues. (Hematoxylin stain of Weigert.)

which was the more necessary as he had changed from winter to summer underwear. He caught a severe cold and had chills and a sore throat. Ten days later his lower limbs became very weak, although he had felt some weakness in these members before May 22. Synchronously with the weakness in the lower limbs he suffered from retention of urine, which soon gave place to incontinence. He lost control of the bowels about the same time. Pains in the legs and girdle-sensation were felt about June 4. His condition remained unaltered until June 12, 1903, when he was brought to the hospital.

On admission the temperature, pulse, and respiration were about normal. I saw him soon after he came to the hospital and found no impairment of function in any part above a line passing around the abdomen one or two inches below the umbilicus, *i.e.*, above the area supplied by about the eleventh thoracic segment of the cord. The lower limbs were completely paralyzed, and were flaccid and flexed, but could be easily straightened. The patellar reflex was entirely absent on each side, even on reinforcement. He had no ankle clonus, no Achilles jerk, no Babinski reflex, and no plantar reflex. The lower limbs were atrophied. Sensation was entirely lost as high as a line one or two inches below the umbilicus. It was impossible to determine the exact limit of the anesthetic area because of the inattention of the patient. He had a bedsore over the external malleolus of the left leg, and an enormous sore over the sacrum, suppurating and surrounded by an extensive area of inflammation.

The man died suddenly June 13, 1903.

The lumbar portion of the spinal cord, 4 cm. from the termination of the cord, was swollen, grayish yellow, and softened for about 4 cm. in extent. On section the cord in this portion was found transformed into a grayish-yellow, pulpy mass, slightly stained by disorganized blood.

Microscopic sections through the lumbar region show intense disintegration and softening of the spinal cord. Round-cell infiltration of the pia and about the blood-vessels in the cord is intense. Sections from the mid-thoracic region show the same condition in the cord, but the cellular infiltration of the pia has almost disappeared (Fig. 2). In this case, contrary to the usual condition, the syphilitic lesions seem to be almost confined to the portion of the cord below the mid-thoracic region.

I am under the impression that it is not generally known—per-

haps, however, I am mistaken in this—that the paralysis in syphilis of the nervous system may develop within a very short time, even within an hour or two. Dejerine especially has insisted on this rapid appearance of palsy, and I have seen it in some of my cases.

Perhaps the most rapid development of intense and general paralysis in syphilis that I have ever observed was in a case reported by Dr. C. K. Mills and myself.[1] A man, aged 45 years, fell from his wagon and struck his left shoulder. Two weeks later he was obliged to quit work on account of pain in his left upper limb. The pain diminished, and the man returned to his work. About three months after his fall pain in the left upper limb and between the shoulders became severe, and after another month he suddenly lost the use of his left upper limb. This paralysis was followed in a short time by paralysis of the left lower limb, then of the right side of the face, of the right upper and finally of the right lower limb. Five or six hours elapsed between the time when he first noticed paralysis of the left upper limb and the time when the right lower limb became paralyzed. He complained of swelling and of dull pain in the parts after they were paralyzed, but 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. While he was in the hospital his voice was a whisper, bilateral ptosis was present, the muscles in the distribution of the right facial nerve were paralyzed, he could shrug his shoulders well, but with the exception of this movement paralysis of both upper extremities was complete; the limbs were flaccid, and the tendon reflexes were diminished or lost. Sensation for temperature and pain was more affected than that for touch. The man died, and meningo-myelo-encephalitis was found, with intense softening of the fourth, fifth, and sixth cervical segments of the spinal cord. Numerous small hemorrhages were present in the inflamed and disintegrated cord.

Another interesting example of rapidly developing paralysis in syphilis is the following: A man, 45 years of age, consulted me September 28, 1901. Five years previously he contracted syphilis, and about a year later he suddenly lost control of his right lower limb. He was a commercial traveller, and while showing the book contain-

[1] Mills and Spiller. Journal of Nervous and Mental Disease, Jan., 1903, p. 30.

ing photographs of his wares he dropped it. This seems to have been the first sign of weakness. He was in Pittsburg at the time, and took a train for Altoona. He had no symptoms of disease until he attempted to leave the train, when he found that his right lower limb gave way beneath him, although he did not fall. He was assisted from the car. The right lower limb remained weak about a week, after which it became as strong as it had been. He had no further symptoms until January, 1899, when numbness was felt in two of the small toes of the left foot, and then the big toe of the right foot became sore. The numbness gradually extended up the left leg as far as the hip. His sexual powers had diminished. When I saw him his right lower limb was somewhat rigid, the patellar reflex on each side was much exaggerated, and the right pupil was a little smaller than the left.

This was probably a case of spinal syphilis, and is especially interesting because of the sudden onset of paralysis in one lower limb and the rapid recovery. I can recall, however, another case in which the onset of paralysis was equally rapid. A man ascended to the top of an omnibus in Paris without difficulty, but when he had finished his ride and wished to descend he found he was scarcely able to do so because of weakness in his lower limbs.

Rapid paralysis may occur in myelitis of other nature, but is, in my opinion, more common in spinal syphilis, because the blood-vessels of the cord are much diseased and complete occlusion of one or more vessels with rapid softening is not infrequent.

The question may arise as to whether operation is ever justifiable in a case of syphilis of the nervous system. In the case of gumma of the dura reported by Dr. C. K. Mills,[2] in which operation was done and the gumma removed with great benefit to the patient, much delay occurred before the patient submitted to the knife. He was under my care during two terms of service at the Philadelphia General Hospital before he came under the observation of Dr. Mills, and while I carefully considered the question of operation I postponed surgical intervention because the symptoms then were not of localizing value, and I decided to wait until we could feel that the opening of the skull would permit the removal of a syphilitic tumor. Finally such a time came, and under Dr. Mills's direction the opera-

[2] C. K. Mills. The Philadelphia Medical Journal, 1902.

tion was performed. A very similar case to this was also under my care about the same time. I had the skull opened and a gumma of the dura was removed.

Of course, neither of these patients was cured by the operation, and each still has cerebral syphilis, but they both were much benefited, and in one of the cases, the following, death was probably prevented until the present time at least. The case history is as follows:

M. McI. probably acquired syphilis some years ago. He began to have constant and severe frontal headache in July, 1901. He occasionally vomited after eating and nausea was worse in the evening. He had his first convulsive attack February 3, 1902. The attack began with pain in the tips of the fingers of the left hand, and then his fingers began to " twist," a creeping sensation extended up the left upper limb and consciousness was lost. This attack was followed by other similar attacks. In April, 1902, he had astereognosis in the left hand. In some of his convulsive attacks the left side of the face as well as the left upper limb was affected. In June, 1902, astereognosis was complete in his left hand, and he had marked loss of pain sensation in this hand, and tactile sensation was lost in the left upper limb, at least in the distal end of the limb. Sensations of touch and pain were much diminished in the left lower limb. He had great difficulty in placing the first finger of the left hand on the end of the nose, and could not find his nose with this hand except by feeling his way over his face. The sense of position was also much impaired in the left lower limb. The left side of the face was weak. By June 14, 1902, the grasp of the left hand had become much impaired and the man was in mild stupor.

An operation was performed on this date by Dr. John B. Roberts. The right parietal bone was carious in an area about the size of a half dollar. The dura at this part was much thickened and was adherent to the brain. The thickened part was removed, and was found by microscopic examination to be the seat of a gumma.

After the operation paralysis was present in the left side of the face and left upper limb, and the left lower limb was paretic. By July 2, 1902, the left-sided weakness had almost disappeared. Antisyphilitic treatment was vigorously pushed, both before and after the operation.

Syphilis not infrequently affects the base of the brain more than other parts. I have recently had the opportunity to study another case of this kind. The patient was under the care of Dr. Alfred Stengel, and the pathologic material and clinical notes are from him.

The patient, F. B., a woman, 42 years of age, was admitted to the Pennsylvania Hospital November 18, 1902. She had had three children, all were dead, one having been still-born. It was said that the other two died of diphtheria. The patient had always been healthy until within the past year. She was taken sick last January with pain in the back of her neck and head. She had severe pain throughout her body, and had had three or four attacks of vertigo. She had been able to do light housework until a week ago. Last winter her body was covered with an eruption which lasted about six weeks and did not itch, and was pronounced syphilitic by a physician.

On November 10 the patient suddenly fell against a door, but thinks she did not strike her head. She was able to walk to her bed without assistance. Shortly after this some friends noticed that her face was drawn to one side. Since the accident she has had diplopia.

On examination she was found to be a fairly well-nourished woman. The left pupil was slightly smaller than the right and both were contracted. The left side of the face was smoother than the right and the mouth was drawn to the right. There was slight contraction of the muscles on the left side of the face. She had internal strabismus, the external rectus of the left eye being paralyzed. Wrinkling of the forehead was more distinct on the right side, but the eyelids could be closed on each side. There was no impairment of sensation, no impairment of motion in the extremities, no paralysis of the vocal cords or throat muscles. The patellar reflex was exaggerated on each side, but ankle clonus was not present. She had pulmonary symptoms and died November 25, 1902.

The interesting features of this case are: Syphilitic infection followed within a few months by pains in the neck, head, and body, and within a year by paralysis of one side of the face and of the left external rectus, unequal pupils, and exaggerated patellar reflex on each side. The symptoms were indicative chiefly of lesion of the medulla oblongata, viz., paralysis of one sixth and of one seventh nerve, and the microscopic examination explains the symptoms.

Sections through the medulla oblongata show numerous small hemorrhages within the nervous tissues, especially in the dorsal part of the medulla oblongata. Swollen axis cylinders are found in one of the anterior pyramids. The round-cell infiltration of the pia is intense and the blood-vessels are much thickened. The round-cell infiltration of the pia is found also at other parts of the base of the brain.

Numerous hemorrhages within the central nervous system, such as are seen in this case, without softening of the tissues, are uncommon in syphilis, in my experience.

In view of the interesting paper by E. S. Reynolds[3] on the early manifestations of tabes dorsalis, a disease acknowledged by most neurologists to be usually a parasyphilitic affection, it may be well to add the abridged notes of two cases of my own of this type.

E. M., 45 years old, male, contracted syphilis about fifteen years ago. He has had pain in the front of each thigh and back of the left thigh occasionally during the past two years, but has not had pain elsewhere. The pain is sharp and causes him to cry out. He has never had any disturbance of micturition or defecation, except that lately he has been a little constipated. In walking in a dark room he wanders considerably from a straight line. Sexual functions have been impaired for two or three years. The patellar reflex is absent on each side. With eyes open he stands fairly well, but sways distinctly though not excessively with eyes closed. His gait is normal with eyes open, but he sways slightly in turning quickly when his eyes are closed. The Achilles jerk is absent on each side in the Babinski position. Sensation for touch is normal in the feet, but sensation for pain is impaired in the soles of the feet. He has a band of slight hypalgesia about each side of the thorax in the nipple line, and slight ataxia in touching the end of the nose with one finger. His sight has been failing about one year.

Dr. W. C. Posey examined this man's eyes and found that the right pupil was 2½ mm. in diameter, while the left was 3½ mm. The irides were quite sluggish to light, but reacted well to accommodation stimuli. The right optic nerve was healthy, but the left optic nerve was somewhat infiltrated.

A man, 42 years old, had a chancre when about 22 years of age.

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[3] E. S. Reynolds. Review of Neurology and Psychiatry, March, 1904.

His papillæ have been pale for many years, and at present Dr. W. C. Posey finds simple optic atrophy in each eye. The right pupil does not react to light or in accommodation, whereas the left is active. He has a relative scotoma in each eye. The right pupil is larger than the left. After a thorough examination I was able to find that during the past year he had difficulty in expelling the urine, and sometimes was unable to do so, that he had a distinct band of hypalgesia and hypesthesia, about two to three inches in width just below the right nipple, but that this band did not involve the left side of his trunk. The patellar reflex seemed possibly a little exaggerated on each side, but this was uncertain.

The zone of disturbed sensation about the right thorax was very valuable in this case, as being one of the few symptoms pointing probably to early tabes. The thoracic band of disturbed sensation should always be carefully sought for in suspected and doubtful cases of tabes or syphilis. Hypalgesia of the soles of the feet, likewise, may be one of the earliest signs of tabes.

Another sign that is often present in early tabes and is too often overlooked is absence of the Achilles jerk, especially when this reflex is tested in the Babinski position. I know of no other means of testing this reflex so successfully. The patient should kneel on a chair with his legs resting comfortably on the seat; in this way the best relaxation of muscles can be obtained.

The case just described is interesting because of the slow progression of optic atrophy with the development of few signs of tabes, and is a good example of the optic form of tabes. Byrom Bramwell [4] has expressed the opinion that early optic atrophy does not always have the effect of arresting the development of tabes, and he reports a case in support of his statements, in which certainly the disease progressed although the optic atrophy occurred early. Most rules have exceptions, and my case to which I have just referred shows that the optic atrophy does seem to arrest in some way the disease. I could refer to other examples. I have frequently lectured on a colored man at the Philadelphia General Hospital who has tabes with optic atrophy, and has had it for years, but the other symptoms of the disease are comparatively slight.

The opinion has been expressed by French neurologists [5] within

[4] Byrom Bramwell. Clinical Studies, Jan. 1, 1904.

[5] Revue Neurologique, Jan. 15, 1902, No. 1, p. 56.

the last few years that tabes as it now appears is not so severe as formerly, and is of slower development, and that cases of arrested tabes are more numerous than they were ten or twenty years ago. This opinion, I think, must be correct, and I am quite certain that I see many cases in a very early period of the disease. The early cases of tabes and syphilis are those that have been, and still are, most frequently overlooked, and it is possible that a more general recognition of these types may lead to a modification of our ideas regarding the symptomatology of the affections. It is in the early stages that much may be expected from treatment.

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A CASE OF ANEURYSM OF THE ARCH OF THE AORTA PRODUCING A BRONCHO-ŒSOPHAGEAL FISTULA.

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AND

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(From the Department of Clinical Medicine, service of Professor Musser, and the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst foundation.)

The case that we report herewith is interesting in view of its remarkable clinical manifestations and the unusual pathological findings which serve to explain the sequence of the clinical events. It occurred in the University Hospital in the service of Dr. Musser, to whom we are indebted for the use of the clinical data.

The clinical history of the case is as follows: The patient, a woman, aged thirty-seven years, and a native of Ireland, was admitted to the hospital, November 13, 1905. She came to this country twenty-two years ago. Her family history presents no features bearing any relation to her condition. She was married at twenty-three, has had no children, and claims to have had no miscarriages. No history of specific infection is obtainable in herself or her husband.

Previous Medical History. The patient had measles, whooping-cough, scarlet fever, and chicken pox in childhood. There is also a doubtful history of diphtheria. Menstruation began at twelve years, was regular, painless, and lasted from three days to a week, until after she was married. After having been married several years she began to have dysmenorrhœa and the flow became prolonged at each period until finally she had a continuous flow and pain for nearly two years. She was operated on about four years ago at the Pennsylvania Hospital, the uterus being removed, she says, because of a tumor. She was perfectly well otherwise until January, 1905, when she had some cardiac trouble, manifesting itself by œdema, dyspnœa, palpitation of the heart, and precordial pain, increased upon exertion. At this time she had also a severe cough occurring in paroxysms that lasted at times an hour. These symptoms passed away and she felt perfectly well and was able to perform her own housework until the present illness began.

History of the Present Illness. About two and one-half months ago, without any known cause, the patient began to have pain in the right side of the chest. This pain was worse on exertion and was especially aggravated by using the right arm. It was at times relieved by lying down, but grew progressively worse. About six weeks ago her sister looked at her chest and noticed a lump, which, as she expresses it, "jumped up and down." From that time on the patient herself has been aware of the "beating" of this lump. For the past month the patient has suffered excruciating pain and has at times been unable to sleep during an entire night. This prominence has been growing progressively more tender and she is troubled with some dyspnœa, palpitation, and a little cough, and she says her voice is becoming husky.

Physical Examination by Dr. Kelly. The patient is a fairly well-developed female subject with good bony development, fair musculature, and slight panniculus adiposus. There is no œdema, no cyanosis, no jaundice, no pallor

of the visible mucous membranes and no noteworthy enlargement of the superficial lymphatics. The chest is of good length, good anteroposterior diameter, and symmetrical, except for the bulging presently to be noted. The inspiratory expansion of the chest is slight, less on the left side than on the right.

Normal pulmonary resonance extends to the sixth rib anteriorly in the midclavicular line; at the left edge of the sternum to the third interspace, and posteriorly to the eleventh dorsal spine on both sides; all move downward slightly on deep inspiration. The note in the interscapular spaces on both sides from the third to the seventh spines is somewhat impaired. The respiratory murmur throughout both lungs is vesicular in character, but throughout the whole left lung it is very faint, especially at the apex anteriorly.

The apex beat is visible and palpable in the fifth interspace, almost in the anterior axillary line; it is strong and somewhat heaving in character. To the right of the sternum from the first to the third interspace there is a globular bulging of the chest reaching forward about 1.5 cm. It exhibits a pulsation distinctly expansible in character; and over it a systolic thrill, a diastolic thrill, and a distinct diastolic shock are palpable. The superficial cardiac dulness extends upward to the upper border of the third rib, where it joins the sternum; to the left as far as apex-beat; and to the right, a half inch to the right of the sternum. The right border of dulness continues upward along the right sternal border to the third rib, then curves outward and reaches two inches from the sternum at the second rib; it then curves upward to the top of the sternum, and finally descends along the left edge of the sternum to the third rib. The deep dulness reaches upward to the second rib; to the left as far as the apex beat; to the right one and one-quarter inches to the right of the sternum. Over the bulging a rough blowing systolic murmur and a less loud diastolic murmur are quite audible. The systolic murmur is more circumscribed to the middle and lower portions of the bulging.

The second aortic sound is markedly accentuated, and the diastolic murmur sometimes seems to follow it, but apparently is not transmitted down the sternum or toward the apex. At the apex there is a soft, long, blowing, systolic murmur. The pulse in the right carotid and right radial arteries is much less marked than in the left. The liver dulness reaches to the margin of the ribs in the nipple line; the organ is indistinctly palpable.

The left pupil is slightly larger than the right; rough measurement puts the left pupil at 5 mm., the right at 3 mm.; both react well to light and accommodation. There is no change in the color of the two sides of the face, and no unilateral sweating.

Urine Analysis: November 14th: Pale, almost colorless; clear; heavy, white precipitate; faintly alkaline; specific gravity, 1018; no albumin; no sugar. Microscope shows many ammonio-magnesium-phosphate crystals.

Examination of the Blood Revealed: Hæmoglobin, 80 per cent.; red blood corpuscles, 4,340,000; white blood corpuscles, 8800.

The following notes indicate the progress of the patient's condition:

November 14th. The patient is suffering severe pain at the seat of the aneurysm and is comfortable only when kept propped up and leaning forward.

19*th.* Pain is complained of at the site of the bulging and along the vertebral border of the right scapula.

23*d.* The patient to-day experiences some difficulty in swallowing, and complains of a lump rising in her throat when she tries to swallow.

24*th.* The difficulty in deglutition is much more marked and the patient cannot swallow solid food. She has more cough to-day and some difficulty in breathing. She is unable to lie down. Pain persists in the back, in the precordium, and over the bulging.

25*th.* The prominence to the right of the sternum previously noted has markedly subsided, being now elevated

scarcely above the general level of the chest. The palpatory signs remain unchanged. Posteriorly the right side seems considerably more prominent than the left. The point of maximum bulging is in the interscapular space near the spine. Over the interscapular space on the right side there is marked dulness from the third to the eighth rib. Below, there is a narrow area of resonance. Over this dull area, breath sounds and fremitus are absent; there is no palpable pulsation.

30*th*. There has been no material change in the patient's condition. Examination of the eye-grounds by Dr. de Schweinitz shows the retinal arteries presenting a marked expansile pulsation, similar to that in aneurysm of the aortic arch.

December 6*th*. Condition is little changed. The patient eats almost nothing, due to the increasing difficulty in swallowing. She is rapidly losing weight and strength.

9*th*. The bulging in the right of the sternum has not only greatly subsided, but the expansile pulsation is no longer visible and the palpatory signs have largely diminished, the systolic thrill alone being distinctly felt. The auscultatory signs remain unchanged, but the murmurs are not so loud as they were. The difficulty in deglutition becomes progressively greater, and the patient has a much more persistent hard cough with considerable expectoration of thick gray clumps of mucus.

11*th*. The difficulty in deglutition has become more marked during the past twenty-four hours. She can swallow practically nothing without having a severe paroxysm of coughing, so that it is necessary to resort to rectal feeding, and to the giving of water by the bowel to relieve thirst. To-day the patient coughs a great deal and at times the breathing is harsh and noisy, as though the bronchi were compressed.

14*th*. Dyspnœa and cough are more marked; otherwise the condition is unchanged.

15*th*. This morning the patient's condition is much

worse than at any time since she has been in the hospital. She is markedly cyanosed, her lips and finger-nails being a distinct blue; she is very dyspnœic and loud bronchial rales can be heard some feet away from the bed. She can no longer swallow and complains of pain over the entire chest and back. Her mind is not perfectly clear.

15*th*, 11 A.M. The patient suddenly became extremely cyanosed, her face grew purple, and she fell over dead.

From the time of admission the temperature, pulse, and respiration presented no markedly abnormal features, except an occasional rise in the respiratory rate, until November 29th, when the respirations rose to between 24 and 28 in the minute, and remained so until December 5th, when they increased to between 32 and 40, ascending at one time to 42. At about the same time variations in the temperature were noted, and the fluctuations varied between 98° and 102° from then until death. The pulse-rate remained between 80 and 100 throughout the patient's stay in the hospital.

With these clinical data at hand little hesitancy would be entertained in making a diagnosis of aneurysm of the arch of the aorta. The particularly interesting features to determine were the cause of the disappearance of the pulsating tumor in the upper thorax anteriorly, the coincident onset of dyspnœa and dysphagia, and the cause of the patient's sudden death with symptoms of asphyxia. It is in regard to these questions that interesting findings were contributed by the postmortem examination, from the notes of which we have extracted the following:

The only features of any pathological interest in the organs of the abdominal cavity were a moderate degree of chronic passive congestion of the liver, spleen, and kidneys.

The organs of the thoracic cavity presented in brief the following findings: As the sternum was removed there was found to be adherent to it, at the junction of the second costal cartilage with the sternum, an aneurysm arising from the junction of approximately the ascending and the transverse portions of

the arch of the aorta (Fig. 1). Its main axis was anteriorly in the direction of its attachment to the sternum. It contained a grayish-red laminated clot which projected into

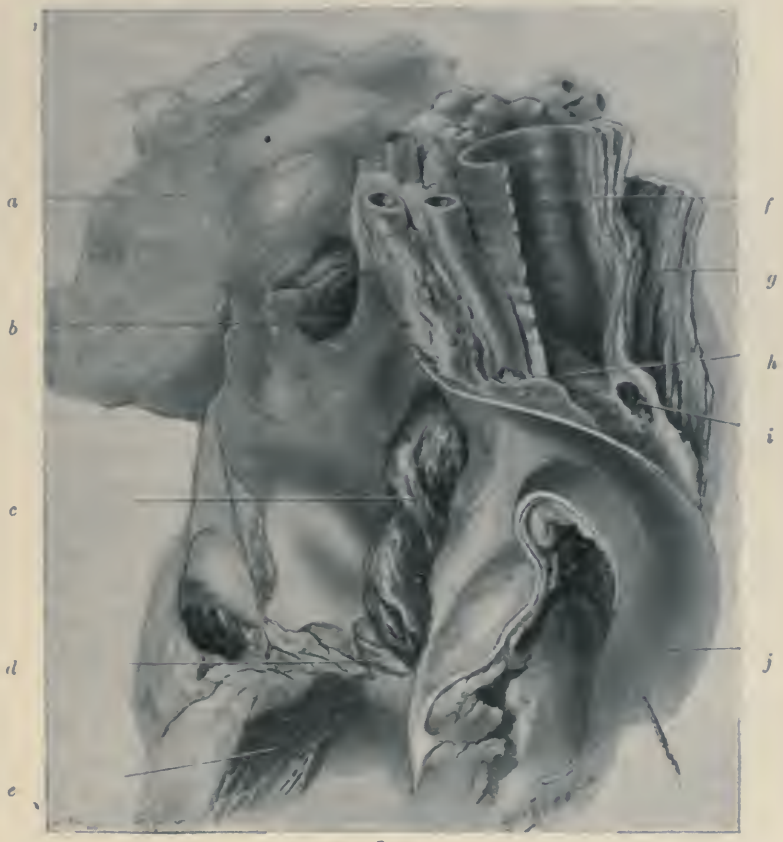

Fig. 1.—Gross appearance of the aneurysm and adjacent organs, to show the broncho-œsophageal fistula: *a*, sternum; *b*, anterior aneurysm; *c*, posterior aneurysm; *d*, aortic valve; *e*, left ventricular wall; *f*, trachea; *g*, œsophagus; *h*, bulging due to aneurysm; *i*, fistula between left bronchus and œsophagus; *j*, aorta.

the left ventricle, where it was attached to the musculi pectinati.

On the posterior wall of the ascending arch and considerably nearer to the aortic leaflets than the preceding aneurysm,

was a second aneurysm, which, extending posteriorly, compressed the trachea at the level of the bifurcation. The aneurysm had broken down the arch of the tracheal rings and had exerted such pressure on the posterior wall as to produce necrosis with a resulting fistula between the left bronchus just below the bifurcation and the œsophagus. This perforation was approximately 0.5 cm. in diameter, its edges necrotic and foul smelling. As the trachea was incised considerably above the level of the fistula, it was found filled with a milky substance presenting throughout the characteristics of ingested liquid food. The mucous membrane of the trachea was intensely congested. The bronchi were partially filled with a liquid having the characteristics of that described in the trachea. With the slightest pressure exerted on the lungs this fluid welled up in the bronchi. The lungs presented throughout all five lobes a partial consolidation. On section numerous grayish-white prominences were noted, giving the tissues an extremely granular appearance. These areas were especially numerous in the lower right lobe, where, by their confluence, the lung assumed a practically solid appearance.

Histological Examination. Sections were prepared and studied from all the organs, but only that of the lung has any bearing upon the interesting features of the case. This section shows areas in which the tissue is practically free from pathological lesions and adjoining them and scattered through them, areas in which the alveoli are filled with an exudate composed primarily of polynuclear and mononuclear cells and a few epithelial elements. There is a moderate amount of œdema and many alveoli contain a granular material apparently of extraneous origin. The peribronchial vessels are intensely congested and in the submucous layers a moderate round-cell infiltration is seen.

Our interpretation of the pathological findings as bearing on the clinical features of the case are as follows: When the patient entered the hospital there existed the aneurysm

which presented anteriorly and became adherent to the sternum, and in all probability the one of smaller dimensions arising from the posterior wall of the ascending arch. Later the wall of this aneurysm weakening permitted its increase in size, thus compressing the trachea and œsophagus and producing the consequent dyspnœa and dysphagia. Furthermore as this aneurysm was situated nearer to the left ventricle than the one located anteriorly, it received the force of each systole and thus permitted the subsidence of the signs associated with the aneurysm presenting anteriorly. This was apparently the existing state until about December 5th, when the rise in respiratory rate occurred, and was followed within a few days by the beginning of rather marked temperature fluctuations and the clinical observation that the patient had a much more persistent cough than previously, and associated with it considerable expectoration. It was at this time that a slight perforation in all probability occurred between the œsophagus and trachea, sufficient to produce an aspiration pneumonia. These conditions existed until just prior to death, when the fistula suddenly becoming enlarged, permitted the flooding of the respiratory tract by the ingested fluids, which had been prevented from passing into the stomach by the obstruction of the œsophagus from the aneurysm.

Œsophageal fistulæ may be divided primarily into two general classes, congenital and acquired.

Congenital œsophageal fistulæ, according to the exhaustive analysis of congenital anomalies of the œsophagus by Kraus,[1] are of one of two types: (1) Simple tracheo-œsophageal fistulæ. In this type there is a simple communication between the œsophagus and the trachea at the point of bifurcation of the latter. The position of the fistula at this point is determined by the fact that here the closure between the respiratory passages and the gut tract, from which the former develops, occurs latest. (2) The more common type of congenital œsophageal fistulæ is associated with imperforate œsophagus. The upper portion of the œsophagus is usually more or less

dilated, ending abruptly at the level of bifurcation of the trachea, just above which occurs a communication between the œsophagus and the trachea.

Acquired œsophageal fistulæ may be primary or secondary. Primary fistulæ are those resulting from diseases of the œsophagus itself. Secondary fistulæ are those consequent upon diseases of neighboring parts which involve the œsophagus by extension or cause sufficient pressure to induce necrosis and consequent perforation. In general, primary and secondary perforations have occurred with almost equal frequency, the slight inequality being in favor of the primary. Of twenty-four cases observed by Zenker[2] twelve were primary, nine secondary, and three doubtful. However, when we consider perforations from the œsophagus into the air passages alone we find primary perforations greatly preponderating, the secondary almost a rarity. As to sex, œsophageal fistulæ are much more frequent in males than in females. Of Zenker's twenty-four cases, nineteen occurred in males, and in an analysis of one hundred and fourteen cases by Zenker and Ziemssen, seventy-seven were in male subjects, twenty-five in female, while in twelve the sex was unknown. Of Vigla's[3] eighteen cases, fourteen were in males. In regard to age, the greatest number appear to occur between the ages of forty and fifty. As to the frequency of the various causes of primary perforation,* leading to fistula between the œsophagus and the neighboring parts, carcinoma of the œsophagus is usually looked upon as the most common, an opinion seemingly warranted by the fact that of sixty-four reported cases of primary perforations, thirty-eight were the result of œsophageal carcinoma. Zenker and Ziemssen, in a very careful analysis, look upon the apparent frequency of carcinoma as a cause of perforation as false, claiming that on account of the more striking clinical picture and the greater severity of symptoms

* Cases of sudden perforation in a previously healthy œsophagus, classed as ruptures, an exhaustive analysis of which will be found by McWeeney (Lancet, July 21, 1900), are not considered in this paper.

in carcinoma of the œsophagus, as compared with the other causes of perforation, these cases are more commonly reported in the literature. They hold that the true proportions are more accurately expressed by the twelve cases of their own observation, in which eight were due to traction diverticulæ, two to carcinoma, and two to ulcerations of a non-carcinomatous nature.

As regards secondary perforations, amongst the various causes are abscesses and softening of either tuberculous or anthracotic tracheal or bronchial lymph glands; abscess of the mediastinum or the retropharyngeal tissue, resulting from tuberculosis of the cervical or upper dorsal vertebræ; ulcerations of various origin of the trachea, amongst which those of syphilitic and carcinomatous origin are the most prominent; gangrene of the lung; finally, pressure on the œsophagus from without, amongst the causes of which may be mentioned aneurysm, goitre, and the various tumors of the neck.

To consider the various organs and parts with which œsophageal fistulæ may communicate, Zenker and Ziemssen in an analysis of one hundred and seventeen cases, found the communication to have occurred in the following frequency with the organs mentioned:

Right bronchus	14	
Left bronchus	12	= 26
Trachea	21	
Right lung	17	
Left lung	6	
Right pleural cavity	10	
Left pleural cavity	1	
Pericardium	7	
Left auricle	1	
Aorta	18	
Pulmonary artery	1	
Carotid artery	1	
Subclavian artery	2	
Inferior thyroid artery	1	
Intercostal artery	1	
Vena cava	1	
Azygos vein	1	
Cyst of thyroid	2	

In the above tabulated cases, practically 60 per cent. of the perforations were between the œsophagus and some portion of the air passages, and 22 per cent. occurred between the œsophagus and one of the bronchi.

A brief reference to the more prominent features of our case shows it to belong to the type of secondary fistulæ. Though perforation between the œsophagus and bronchus is one of the relatively frequent forms the case is unique by reason of its cause. In the literature on the subject we are able to find but one similar case, that reported by Habershon:[4] The patient, a man of twenty-three years, gave a history of a traumatic aneurysm of the ascending arch of the aorta which produced death by perforating into the pericardium. For a week preceding death he had experienced considerable difficulty in deglutition, and at the autopsy, pressure necrosis and a resulting fistula were found between the œsophagus and the left bronchus just below the point of bifurcation. The rupture of the aneurysm was not at this point. It is an interesting fact that the position of the fistula in this case corresponds exactly with that in ours.

Amongst the numerous cases of fistula between the œsophagus and the air passages of various origin reported are some with most bizarre features. Aufrecht[5] reports a case in which there was a fistula in the suprasternal notch from the larynx to the external surface, and 2 cm. below the level of the suprasternal notch was another between the bronchus and the œsophagus, so that a great portion of the liquids swallowed reappeared at the suprasternal notch. Cartier and Masson[6] report a case of tracheo-œsophageal fistula resulting from a cannula left in the trachea for six years after a tracheotomy.

In the diagnosis of broncho-œsophageal or tracheo-œsophageal fistula, naturally the pathological condition producing the fistula must receive due consideration. An almost constant feature is, moreover, laryngitis and cough consequent upon it and upon irritations of the laryngeal mucous membrane by food particles. Later, almost in-

variably, aspiration pneumonia develops and is usually a forerunner of death, though abscess or gangrene of the lung may develop before death relieves the patient of a miserable existence.

There are many phenomena that may be observed to lend evidence to the diagnosis of fistula between the œsophagus and the air passages. Kohlenberger,[7] in an article on tracheo-œsophageal fistula, states that if after a smooth act of swallowing, in which the larynx is not irritated, food is coughed up the diagnosis is certain. Martius[8] administers fuchsin-colored bouillon and watches for its reappearance. In a patient of his own, on whom he used this test, there was perfect quiet for two minutes after the swallowing, during which time the patient rinsed his mouth well, and then coughing commenced, lasting for six minutes, during which time most of the ingested colored liquid was expelled.

Attempts have been made to apply to the diagnosis of communications between the œsophagus and the air passages the variations in pressure in the œsophagus during respiration. The first observations bearing upon this subject were made by Gerhardt.[9] While an assistant in Griesinger's Clinic in Tübingen, using the Green method of injection of astringents into the air passages for the cure of bronchitis, he attempted to evolve a definite test to determine when the tube was in the bronchus. Introducing a tube into the bronchus and holding a lighted candle before the free end, the flame was drawn toward the tube in inspiration and blown away from it in expiration. The tube was then introduced into the œsophagus, and much to Gerhardt's surprise the same phenomena were observed. The undoubtedly correct explanation for these occurrences was offered by Gerhardt: that all of the hollow organs contained within the thorax are subjected to a negative pressure during inspiration, but on account of the soft flexible walls of an organ such as the œsophagus, its upper portion acting as a valve, no air flows in from the exterior. This explanation harmonizes well with the fact that when the inner end of the

tube passes beyond the boundary of the thoracic cavity, *i. e.*, into the pharynx or stomach, the movements of the flame cease.

Sixteen years later Gerhardt's assistant, Emminghaus,[10] working along the same line, attached the external end of the tube to a water manometer to determine accurately the normal inspiratory and expiratory pressure in the œsophagus. He found that during quiet respiration the inspiratory pressure was equal to 4 cm., the expiratory pressure the same. In forced respirations the inspiratory pressure increases to 22 cm., the expiratory to 16 cm.

In 1886, Martius[11] attempted to carry the subject still farther by obtaining graphic representation of the variations in pressure in the œsophagus by means of a revolving drum. He succeeded in doing this in a very graphic way, as is shown in the accompanying diagram (Fig. 2).

The small curves superimposed on the larger ones are apparently due to the heart's action. The larger ones represent the respiratory movements. This apparatus was then used on a case of broncho-œsophageal fistula, and there was found to be almost complete obliteration of the curves due to the respiratory act. The cause of this may seem somewhat obscure, but it will readily be understood with the assistance of the accompanying rough diagrams (Figs. 3, 4, and 5).

Letter *A*, Fig. 3, represents the pulmonary apparatus and *B* the œsophagus; on inspiration there is negative pressure in the direction of the arrow *C*, equivalent, let us say, to ten units. If now there be a communication between the pulmonary apparatus and the œsophagus, as shown in Fig. 4, air will flow from the respiratory passages into the œsophagus in the direction of the arrow *D*, equivalent to compensate for the ten units of pressure, and perfect equilibrium will result. This, however, is subject to variations. For if the opening between the air passages and the œsophagus be small and the inspiration be powerful and quick, not sufficient air will pass through the communication to com-

pensate for the negative pressure and there will be a balance left in favor of the latter. To express this diagrammatically, suppose that the inspiratory effort created a negative pressure in the direction of the arrow *C*, Fig. 5, equivalent to twenty units, and air was able to enter through the fistula equivalent to only ten units, there would then be ten units still in favor of the direction *C*. This series of phenomena actually occurred in Martius' patient when he was commanded to take deep inspirations, the curves reinstating themselves

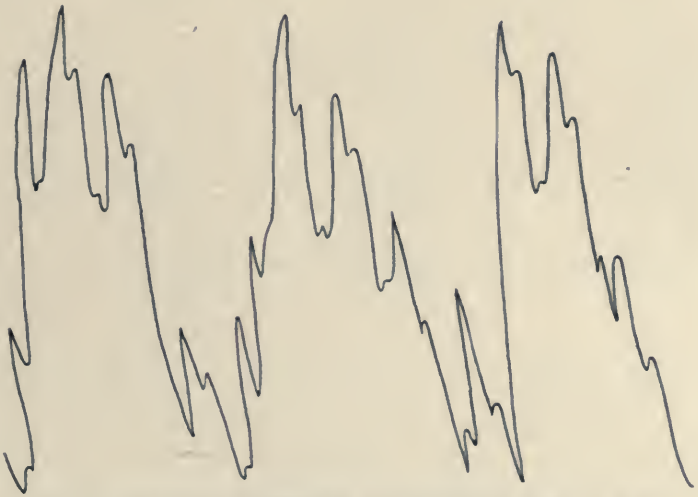

Fig. 2.—Graphic representation of variations in pressure in the œsophagus. (After Martius.)

practically the same as in the normal cases in ordinary respirations.

Another possibility must be taken into consideration in the temporary occlusion of the fistulous opening by food or secretions and the consequent occurrence of a valve-like fistula, as in Quincke's case, in which air could enter from the bronchus into the œsophagus but could not return, in consequence of which entering the gastrointestinal tract it produced enormous meteorism.

It is thus seen that deductions in regard to intraœsophagea

fistulæ must be drawn with the greatest care, at least, until further observations have put the subject on a more trustworthy basis.

As to the treatment of broncho-œsophageal and tracheo-œsophageal fistula, we must look to the daring advances of surgery to furnish the only possibility of a cure. The physician's attention, however, can be directed to guarding against or alleviating the complications resulting from the fistula, chief amongst which are laryngitis, bronchitis, and aspiration pneumonia.

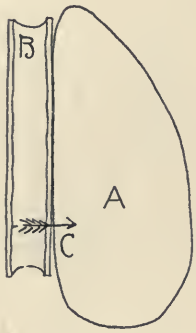

Fig. 3

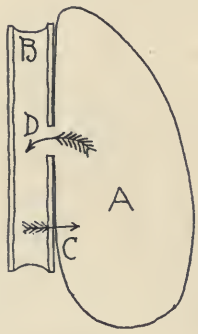

Fig. 4

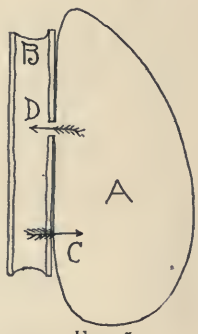

Fig. 5

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2. Zenker and Ziemssen. Krankheiten des Oesophagus, Ziemssen's Handbuch, Band vii, Th. 1, pp. 108–124.
3. Vigla. Arch. gén. de méd., 1846, 4 sér., t. xii, pp 129–314
4. Habershon. Guy's Hospital Reports, 1856, ii, 230–232.
5. Aufrecht. Berliner klinische Wochenschrift, 1869, vi, 317–319.
6. Cartier and Masson. Ann. d. mal. de l'oreille et du larynx, 1876, ii, 344–350.
7. Kohlenberger. Deutsche med. Wochenschrift, 1898, xxiv, 360.
8. Martius. Charité Ann., 1887, xxii, 248, 266.
9. Gerhardt. Deutsche Klinik, 1858, 285.
10. Emminghaus. Deutsch. Archiv. f. klinische Medizin, 1874, xxiii, 446.
11. Martius. Loc. cit.

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ADAMS-STOKES DISEASE (HEART-BLOCK) DUE TO A GUMMA IN THE INTERVENTRICULAR SEPTUM.

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The condition at present recognized as the Adams-Stokes syndrome was first described by Adams[1] in 1827, and more fully studied by Stokes[2] in 1846. Since that time many cases have been reported and studied, but until very recently no really convincing demonstration of the etiology and pathological basis of the condition had appeared. Thus, Charcot held that the lesion was to be found in the medulla; Stokes himself suggested the heart muscle; Huchard[3] held that the circulatory mechanism of the heart, together with disease of the cerebral vessels, should be held accountable; Gibson[4] and Jacquet[5] called attention to a certain similarity with intermittent claudication; and others have ascribed the condition to fatty degeneration of the heart, to tumors of the vagus, or to pressure upon the pneumogastric nerve. Gaskell[6] was the first to demonstrate the fact that, in tortoises, constriction of the circular layer of muscle at the auriculoventricular junction inhibits the normal rhythm of the heart, so that the auricles and ventricles beat independently

[1] Dublin Hosp. Reports, 1827, vol. iv, 396.
[2] Dublin Quart. Jour. Med. Sci., 1846, ii, 73.
[3] Traité du Maladie du Coeur.
[4] The Nervous Affections of the Heart, 1904, p. 65.
[5] Deut. Arch. f. klin. Med., lxxii, No. 2.
[6] Jour. Physiol., 1883, iv, 43.

of each other. Chauveau,[7] Vaquez and Bureau,[8] and Moritz[9] have contributed interesting articles dealing with the dissociation of the auricles and the ventricles.

To Erlanger[10] belongs the credit of first suggesting that the lesion of Adams-Stokes disease lay in the bundle of His, and of offering incontestable experimental evidence supporting his belief. In 1905 Stengel[11] made a preliminary report of a case of Adams-Stokes disease in which the autopsy disclosed macroscopically an atheromatous lesion on "the anterior mitral leaflet toward its base and aortic edge," being, therefore, in the region "exactly over the bundle of His where this band passes from the ventricle to the auricle." Thus far there has been no report of the microscopic findings, so that it is still uncertain whether there was actual involvement of the bundle, although there is strong presumptive evidence that such was the case.

For many years an active discussion has been carried on by physiologists as to the cause of the rhythmic activity of the heart. One school—the followers of the myogenic theory—has held that the heart muscle itself possesses an inherent automaticity, which is influenced by, but not dependent upon, the nervous mechanism. The other school took the opposite view, namely, that the nerves and ganglia are of primary importance. Long ago the fact was pointed out that contractions occur in the fœtal heart before its nervous structures are developed, and this has tended to support the myogenic theory.[12]

It has been demonstrated by the experiments of Gaskell, His, Tigerstedt, and Erlanger that the symptoms of Adams-Stokes disease and those of heart-block, brought about by injury to the bundle of His, are very similar. Erlanger, by an ingenious clamp screw applied to the muscular bundle, was able to bring about a gradual failure of conductivity from auricle to ventricle. When slight pressure was made the ventricle would miss every fourth auricular stmulus; when the pressure was further increased, the ratio would fall from 1 to 3 to 1 to 2, and finally complete dissociation of the rhythm would occur. In other words, a condition of complete heart-block had occurred, and the ventricle setting up a rhythm of its own contracted entirely independently of the auricle. "With each change in rhythm the blood pressure was much affected, falling with the fall of the ventricular rate and rising with its increase. But even in complete block a fair pressure might be maintained. With partial block both auricle and ventricle might be inhibited by

[7] Rev. de Med., 1885, v, p. 161.

[8] Compt. rend. du Soc. Biol., Paris, 1893, p. 170.

[9] St. Petersburg med. Woch., 1897, p. 301.

[10] Jour. Exper. Med., November 25, 1905; Ibid., January 25, 1906, p. 8; Bull. Johns Hopkins Hosp., June, 1905.

[11] Amer. Jour. Med. Sci., 1905, cxxx, 1083.

[12] Erlanger, Jour. Amer. Med. Assoc., 1906, June 2, 1895.

stimulation of the vagus as easily as under normal conditions. But when the block was complete no diminution, or only a slight diminution, of the rate of the ventricle resulted from stimulation of the vagus. The auricles reacted normally to vagus stimulation. Section of both vagi had little or no influence on the rate of the ventricular beat when the block was complete. But stimulation of the accelerator nerve usually increased the rate of the ventricle. The reaction of the auricles to stimulation of the accelerator nerve was not influenced by the block."

In mammalia the muscular structure of the auricle is separated from that of the ventricle by a layer of connective tissue. In order to substantiate the contention of the upholders of the myogenic theory of cardiac rhythmicity it was essential that some bridge of connecting muscular tissue be demonstrated. This was accomplished by Wm. His, Jr.,[13] and by Stanley[14] independently of each other. But His was the first to succeed in sectioning this muscular bundle, and bring about a dissociation of the auricular and ventricular rhythm.

Owing to the meager character of His' preliminary publications which appeared in 1893, the subject attracted little attention until 1904, when the existence of the bundle, its physiological properties, and its exact anatomy were confirmed through the researches of Retzer,[15] Breunig,[16] Humblet,[17] and Hering.[18]

The structure which is now known as the bundle of His consists of a narrow band of fibers 18 mm. in length, 2.5 mm. in width, and 1.5 mm. in thickness, extending from the right auricle and its valves to the interventricular septum.

More recently the structure has been carefully studied by Keith[19] and Tawara.[20] The latter has given a developmental as well as an anatomical description of it. According to him the "bundle of fibers passes forward from the coronary sinus through the interauricular septum to the central fibrous body of the heart, on which it forms a plexus. One of the bundles from this plexus breaks through the fibrous body into the interventricular septum and is distributed subendocardially on the right and the left sides of the latter. The auricular part of the bundle is made up of very fine, richly nucleated fibers, and the fibers of the ventricular part belong to the Purkinje type."[21]

Still further corroboration of the auriculoventricular dissociation

[13] Arbeit. a. d. Klin. zu Leipzig, 1893, p. 23; Zentrbl. f. Phys., 1895, ix, 469; Deut. Arch. f. klin. Med., 1899, lxiv, 316.

[14] Jour. of Physiol., vol. xiv.

[15] Arch. f. Anat., 1904, p. 1.

[16] Arch. f. Physiol., 1904, suppl. 1.

[17] Arch. internat. d. Physiol., 1904, i, p. 278.

[18] Pflüger's Archiv., cviii, p. 267.

[19] Lancet, 1906, i, 623.

[20] Vide Aschoff, Münch. med. Woch., September 26, 1905; Centrbl. f. Physiology, 1905, xix, 70, 298.

[21] Ewart, Progressive Medicine, September, 1906.

which occurs in Adams-Stokes disease has been furnished by Gibson,[22] who has studied the electromotive changes in a case of heart-block by means of Waller's apparatus. By this method the electric variations are indicated by means of a Lippmann capillary electrometer. "Leading off from the basal region of the precordium to the acid, and from the apical region to the mercury, the usual diphasic movements of he capillary column were clearly seen preceding the apex-beat, and evidently resulting from the ventricular systole. But in the interval between these waves other smaller waves were distinctly seen, and can be attributed only to the systole of the auricle."

The electromotive changes have also been most carefully studied by Einthoven,[23] on a still more elaborate scale. Curiously enough the recording instrument was placed in the physiological laboratory while the patient remained in the hospital. The pulsations were transmitted by means of wires. "He employed a specially arranged galvanometer, the movements of which were recorded on a travelling photographic plate, on which two ordinates and abscissæ, representing electric potential and fractions of a second respectively, were simultaneously recorded." In making tracings for a case of heart-block he was able to demonstrate complete dissociation of the auricular and ventricular oscillations. This method, while obviously impractical in a clinical study of cases, owing to the fact that in addition to a complicated apparatus trained observers with a special knowledge of physics, are necessitated, nevertheless presents very accurate and interesting corroboration of other recent investigation.

Symptoms. The cardinal symptoms of Adams-Stokes disease consist of (1) bradycardia, (2) cerebral attacks, and (3) pulsation of the cervical veins, exceeding in rate the arterial pulsation.

The Pulse. In most cases the pulse is habitually slow, sometimes reaching 30 or 20 beats per minute. Often the rate bears a definite relation to that which was normal for the individual in question. Thus, it may be one-half or one-quarter as fast. This is due to the fact that only every other or every second stimulus is able to cross the bundle of His. The arterial pulse is generally regular in rhythm, although arrhythmia is not uncommon. During the acute attacks the ventricular contractions may fall as low as 10, 8, or even 3 beats per minute. Kidd[24] and Laslett[25] found a condition of asystole lasting sixty and ninety seconds respectively. In Stengel's case an interval of two minutes and ten seconds was noted. If the heart is auscultated during these periods one may hear feeble and muffled contractions. These have given rise on

[22] Brit. Med. Jour., 1906, ii, 22.
[23] Arch. neerl. d. sc. exactes, Harlem, 1906, ser. 2, tome xi.
[24] Lancet, February 13, 1904.
[25] Lancet, June 4, 1904.

the part of some authors to the belief that the sounds are due to abortive systoles, too weak to make themselves felt at the wrist. The most generally accepted opinion, however, is that they are due to contraction of the auricles, a condition which, as Gibson and Mallet[26] have long since shown, does produce a definite sound. When simultaneous tracings of the arterial and the venous pulses have been made it has nearly always been possible to prove definitely the etiological agency of the auricle. At times it is also possible to *see* that the jugular pulsation in the neck is synchronous with the doubtful sounds. Maynard's[27] contention, based upon two cases with radial tracings only, that the accessory heart sounds were due to hemisystole, and not to the contraction of the auricles, is not convincing.

The slow pulse in Adams-Stokes disease is due to depression of conductivity in the auriculoventricular bundle. The auricles contract more or less normally, but the ventricle only responds to every other, every second, or every third stimulus. Just upon what the exacerbations of bradycardia depend still is uncertain.

Norfleet[28] has reported a case of Adams-Stokes disease occurring in a man of sixty-nine years, who for over a year had a pulse-rate of 45 or less per minute. With exacerbations of the bradycardia there were convulsive movements. During these attacks the pulse-rate sometimes remained as low as 8 or 9 per minute for periods of twenty-four hours.

The cerebral symptoms consist of attacks of weakness, vertigo, unconsciousness, occasionally convulsive seizures, and at times Cheyne-Stokes respiration. The patient may have an uneasy feeling about the heart, becomes pale and promptly falls unconscious, being practically pulseless at the wrist, and soon breaks out in a clammy sweat, consciousness returning gradually. The attacks may last from a few seconds to several minutes, they may be repeated at varying intervals and anyone of them may end fatally. Upon returning to consciousness the patient often states that he had a nightmare—thought he was dying.

Occasionally attacks like those just described alternate with simple vertigo, but some cases present certain features which closely resemble apoplexy, the patient falling rapidly into a deep coma, with flushed face and stertorous breathing. In one of Osler's[29] cases there was transient motor aphasia. Actual convulsions, as happened in our case, may also occur. When present they are mainly limited to the face and hands, although general epileptiform attacks are not unknown.

In some cases the initial pallor of the face may be replaced by

[26] Jour. Anat. and Physiol., 1879, xiv, 4.
[27] Brit. Med. Jour., 1905, ii, 847.
[28] Medical Record, November 21, 1903.
[29] Lancet, 1903, ii, 516.

congestion. In our case this was a very noticeable feature. A sensation of blood rushing to the head was a marked symptom in Leuchtweis' case. The convulsive attacks occurring in Adams-Stokes disease are probably the result of cerebral anemia. They are apparently similar to those produced experimentally in animals by severe hemorrhage. The apoplectiform symptoms may reasonably be assumed to be due to venous congestion of the brain, a condition which has long been known clinically to be associated with bradypnœa, paresis of the glottis, and spasmodic conditions.

The belief held by Tripier[30] that the convulsive attacks preceded and were the cause of the bradycardia has been definitely disproved by Webster's[31] tracings.

Some cases exhibited features common to other cardiac disorders, such as nocturnal asthma, precordial oppression, pallor, sudation, and dyspnœa.

The case that we report herewith is of very considerable interest: It presented all the cardinal symptoms of Adams-Stokes disease; sphygmographic tracings taken coincidently from the jugular vein, the radial pulse, and the apex beat showed the incoordination of the auricles and ventricles, the former contracting more often than the latter; and at autopsy a growth was found involving the auriculoventricular bundle, which on microscopic examination proved to be a gumma.

According to His, Jr.,[32] dissociation of the auricles and ventricles might be brought about by any one of three conditions: (1) Degeneration of the myocardium of sufficient extent to interfere with conductivity; (2) dromotropic nerve influences—inhibitory impulses—conveyed principally through the agency of the pneumogastric; and (3) localized disease of the auriculoventricular bundle. As the microscopic examination shows, our case belonged to the last named category.

E. B., a white, male, aged thirty years, a native of Ireland, was admitted to the Philadelphia General Hospital May 20, 1906, complaining of vertigo and syncopal attacks.

Family History. Father died from accident; mother from senility, aged ninety years. Mother had seven children; with the exception of one who died of pertussis at four years, all are living and well.

Personal History. Previous illnesses: Pertussis, mumps, scarlatina, and diphtheria in childhood. Typhoid fever in 1895, lasting two months (including a relapse). Ever since then he has had a trifling but persistent cough. The patient was brought up in the country until he was fourteen years of age, at which time he secured employment in a hardware store. At eighteen years he enlisted for three years in the British Army. Afterward he spent eleven years

[30] Rev. d. Med., 1883, p. 1001.
[31] Glasgow Hosp. Reps., 1901, p. 413.
[32] Deut. Arch. f. klin. Med., lxiv, p. 316.

frequently changing his occupation, having for a time been a barkeeper. He then again enlisted, serving in Cairo, India, and seeing actual service in the Boer war. During the last two years he has been a waiter. He has indulged in occasional alcoholic intoxication, but this was exceptional; he has used tobacco to excess. In 1893, he contracted a "chancroid" of the penis, which appeared eight days after intercourse, and lasted eleven days. He received only local treatment. The sores were multiple, he never developed any rash or constitutional symptoms. He has been married two years. His wife has borne two healthy children, and has never had any miscarriages. He has never had any gastrointestinal, or renal symptoms.

Present illness began on May 16, four days before admission, when while riding in an electric car asleep, he had an attack of syncope. He woke to consciousness to find the other passengers looking over him. During the attack he had fallen from his seat. He describes the onset of the attack as beginning with the sensation that blood was rushing to his head, associated with some vertigo which increased. This phase of the attack was very brief, and he was unable to state whether objects seemed to whirl about him, or he about them. He had two similar attacks subsequently on the same day, and on the following day two or three more. He had three attacks on the 18th, and on the 19th had an attack about 1 A.M., while in bed, after a hard day's work. On the day of admission he had attacks every ten or twenty minutes throughout the day.

Physical Examination. The patient is well-developed and nourished. The pupils are equal, and react promptly to light and distance. The ocular movements are normal; the tongue is fairly clean. The chest is well-formed; the expansion equal and of normal extent. The lungs are resonant and clear throughout. The extremities are negative except for decided downward curvation of the finger-nails, and a scar on the right knee, resulting from a former bullet wound.

In the *recumbent posture* the cardiac dulness extends from the right sternal border, and the upper border of the third rib, to the midclavicular line. The apex-beat is fairly diffuse, and is visible and palpable in the fifth interspace. The radial pulses are equal and synchronous. The blood pressure is low—systolic 117 mm. Hg. (Stanton), diastolic 85 mm. There is marked pulsation of the veins of the neck, the rate being about three times as rapid as that of the radial pulse. This pulsation is direct (not transmitted from the carotid) and is slightly arrhythmic. The first sound at the apex is feeble, and it is followed after a fraction of a second by a second sound, apparently muscular in character, which can be clearly differentiated from the normal second sound of the heart, which follows it, and may be heard over the entire precordium. There is a systolic murmur at the apex, which is transmitted toward

the axilla, but not to the angle of the scapula. The ventricular beats are all felt at the wrist. The pulse rate is 48.

In the *sitting posture* the heart sounds become louder, the systolic murmur is more intense, and the irregularity more marked. The radial pulse-rate is unaffected by the change in posture, still remaining 48. The liver can be palpated at the level of the umbilicus.

May 24. The patient has had three attacks since admission, until today, when they have become more frequent, occurring about once every half to three-quarters of an hour. The attacks begin with a sense of fulness of the head, vertigo, and end in syncope; and last altogether about five seconds. In one attack he had twitching of the facial muscles.

May 23. *Ocular examination*, by Dr. Hansell. There is a most unusual condition of the vessels of the right disk. The artery superficial to the vein is distended in an angular shape, and communicates with the large underlying vein by a broad channel—arteriovenous aneurysm. The arteries beyond the disk contain venous blood. The left fundus is healthy, but darker than normal, owing to the number and tortuosity of the veins.

May 28. *Nasal examination* by Dr. Roberts discloses a deviation of the septum toward the left, both bony and cartilaginous. Except for pallor of the mucous membrane there is no other abnormality. The pharyngeal mucous membrane is somewhat glazed and slightly congested.

The larynx and vocal cords are normal.

Urine. 1020, alkaline, no albumin, no glucose; triple phosphates and amorphous urates.

Blood. Hemoglobin, 80 per cent.; erythrocytes, 3,136,000; leukocytes, 7800; polymorphonuclear cells, 77 per cent.; lymphocytes, 23 per cent.

May 25. *Nurse's Report.* During the attacks the patient becomes weak; objects seem to move around; failure of eyesight for two or three minutes; the face becomes red, and the breathing increases in rapidity for a few seconds. He has had two such attacks within an hour. They usually come on after some unusual occurrence in the ward.

3.30 P.M. Another attack; feels flash of heat over body; head is light; eyes heavy; the radial pulse drops several beats. 4.30 P.M. Slight convulsive spell; twitching of hands—head thrown back—duration one minute.

June 3. Patient is out of bed and about the ward. Complains of weakness. No attack for five days.

June 7. Two attacks yesterday. During attacks pulse feeble and irregular. On auscultation heart sounds are fainter. The respiratory sounds increase in depth, rate and intensity. Face flushed—twitching of hands. Some attacks are preceded by rolling of the eyes, which is followed by a tremor of the body and hands,

the latter quite forcibly at the onset. Attacks sometimes last only from seven to ten seconds.

June 8. Has had a series of attacks. Extremities cold, complains of it; cyanosis; pulse-rate generally about eighteen per minute, increasing at frequent intervals to thirty. After one such acceleration the heart stopped for fifteen seconds. Twitching hands and staring eyes. Patient considered the last a slight attack. Has had frequent attacks during the last twenty-four hours. Vomits a good deal, is very weak.

June 9. Has vomited everything put in his stomach since yesterday. Attacks numerous; asthenia marked. Toward evening he became able to retain peptonized milk, and finally had a restful night without seizures.

June 10. Continued improvement; no more attacks; stomach retentive; appears stronger. At night an attack seemingly like the rest proved fatal. The patient a few minutes before death had been resting quietly.

During his stay in the hospital the patient received in addition to certain drugs administered for their effect upon the gastrointestinal tract, strychnine, nitroglycerin, and sodium iodide. None of these had any effect upon the cardiac condition. The pulse-rate remained unchanged; the attacks were neither retarded nor abated. It is hardly likely that the iodide would have been beneficial even if the patient had lived longer, for as the subsequent microscopic examination of His' bundle showed, there was very great destruction of tissue.

The accompanying tracings (Figs. 1, 2, and 3), taken a few days after the patient's admission, show very distinctly that the bradycardia was due to a disturbance of conductivity. The tracing from the jugular vein proves not only a diminution in the function of conductivity as evidenced by the lengthening of the A–C interval—the length of time required for the stimulus to pass from the right auricle to the left ventricle, but also the fact that many of the auricular contractions evoked no response whatever on the part of the ventricle. In other words, we have to deal with a condition of complete "heart-block," or what is a better term, auriculoventricular dissociation. It is also to be noted that the frequency of the auricular contractions was markedly increased by the forced inspiration which occurred during the later part of the tracing, whereas the ventricular wave underwent no corresponding change. This is, of course, further evidence of disturbed conductivity. In the cases reported by Stengel, Dock,[33] and Finkelburg,[34] the administration of atropine had no effect whatever upon the rate of the ventricular contractions. This is due to the fact that atropine in man, as in animals, exerts its influence upon the heart through depression

[33] Med. News, Aug. 19, 1905.

[34] Deut. Arch. f. klin. Med., April 6, 1905.

of the pneumogastric, which affects the auricles directly, whereas the ventricles, if the contraction stimulus cannot pass through the bundle of His, are uninfluenced by it. In Schmoll's[35] case the administration of atropine reduced the auricular cycle from twelve-tenths to eight and one-half tenths of a second, while the ventricular time underwent no change.

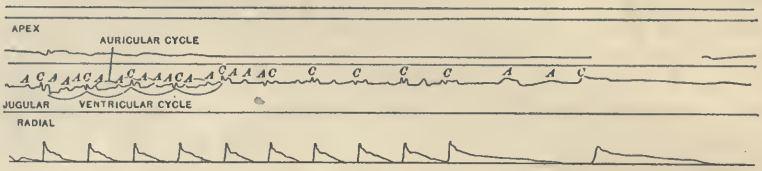


FIG. 1

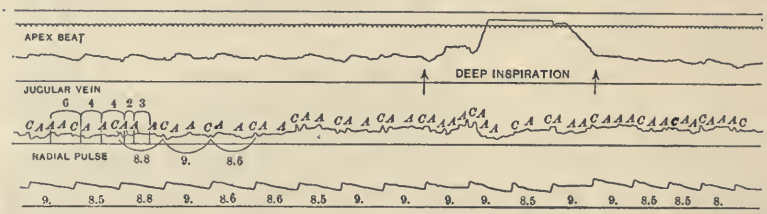


FIG. 2

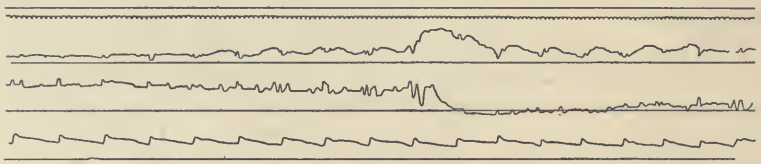


FIG. 3

Cardiosphygmographic tracings. In Fig. 1, during the last two ventricular contractions the speed of the cardiosphygmograph was increased about fourfold. The duration of the auricular cycle varied from four-tenths to twelve-tenths of a second, that of the ventricular cycle from seventeen-tenths to eighteen-tenths of a second. *A*, auricular systole; *C*, ventricular systole. The time marked records one-fifth second.

The fact that the ventricles were not affected by vagus influence was shown by the fact that change of posture on the part of the patient—from the recumbent to the sitting, and from the latter to the standing position—had no influence whatever upon the frequency of the radial pulse. A further study of the tracing shows that the failure of the ventricle to respond to the auricular contraction was not due to any loss of power on the part of the ventricle. The elevations in the systolic phase of the radial tracings are large, powerful, regular in strength, and the blood-pressure is normally

[35] Jour. Amer. Med. Assoc., 1906, xlvi. 361.

sustained. This has also been substantiated by the microscopic examination of the ventricular muscle. The sphygmogram also demonstrates the fact that the accessory heart sounds heard over the precordium between the radial pulses must have been auricular in origin, and were not due to abortive ventricular systoles, since the radial pulse follows regularly each ventricular contraction, as is shown by the apical tracing.

It will be noted that the ventricular cycle required about nine-fifths of a second; the auricular cycle only from three-fifths to six-fifths. The tracing also shows that there is no definite relation between the auricular and the ventricular contractions. If we were simply dealing with a condition of depressed conductivity we should find the A–C interval either constant in time or increasing in length. This is not the case; the A–C interval at the beginning of the tracing steadily decreases in time until the auricle overtakes the ventricle—indicating complete block. In the latter half of the sphygmogram the deep forced inspiration—between the pointers—produced a marked acceleration of the auricular contractions, while the ventricular rate underwent practically no change.

Additional evidence as to the accuracy of the interpretations of the various phases of the jugular pulse in cases of Adams-Stokes disease has been furnished by a number of observers. Ritchie,[36] Gibson, Finny,[37] Villaret, and Brouardel[38] examined their cases by means of the fluoroscope and were able to demonstrate auriculo-ventricular inco-ordination.

Autopsy. The body is that of a moderately well-nourished adult male; weight, approximately 154 pounds. Rigor mortis is marked; cadaveric lividity slight. Panniculus adiposus is moderate. The muscles are of good volume, bright red in color.

The peritoneum contains a small amount of translucent straw-colored fluid. The abdominal organs are normal in position and relations. The spleen weighs 320 grams, and measures 15 x 10 x 6 cm. The consistency is fairly firm; the cut surface dark red in color, and bulges slightly; the follicles are prominent and well-defined; the trabeculæ are moderately prominent. The *liver* weighs 2050 grams; and measures 28 x 23 cm. The surface is smooth, dark reddish-brown in color with lighter mottlings. It cuts with slightly increased resistance; the cut surface shows normal liver markings. In the posterior portion of the right lobe is a spherical nodule 1 cm. in diameter, dark bluish-gray in color, of a spongy consistency. The *pancreas* presents no pathological features. The *stomach and intestines* aside from vascular injection present no unusual features. The *suprarenals* are somewhat smaller than normal; the cortex brownish-yellow. The *left kidney* weighs 190 grams,

[36] Proc. Royal Soc. Edin., 1905, xxv, 1085.
[37] Brit. Med. Jour., 1906, ii, 967.
[38] Arch. d. Méd. Exper., 1906, xviii, 230.

is firmer than normal, cuts with ordinary resistance, its surface does not bulge, and the capsule strips readily. The cortex and medulla preserve their normal relation in width and are well differentiated. Pyramids are dark reddish-purple and streaked, the cortex considerably lighter, showing normal markings. The *right kidney* weighs 250 grams and presents the same characteristics as the left. The *ureters* show no abnormalities. The *bladder* contains a small amount of turbid, yellowish urine. The walls are of normal thickness; mucous membrane deeply injected. The *left pleural cavity* contains 300 c.c. of translucent straw-colored fluid. At the base are a few firm, fibrous adhesions. The *right pleural cavity* contains 100 c.c. of fluid of the same character as the left. The opposed surfaces of both pleural cavities, not involved in adhesions, are smooth and glistening. The *left lung* weighs 690 grams, and crepitates throughout. On section the lung is light pinkish-gray in color. On pressure a considerable amount of slightly blood-tinged, frothy fluid is exuded. The *right lung* weighs 490 grams and presents the same features as the left. The *pericardium* contains about 20 c.c. of translucent straw-colored fluid. The opposed surfaces are smooth and glistening.

The *heart* weighs 510 grams. Both ventricles and the right auricle contain a small amount of cruor and chicken-fat clot lightly adherent to the wall. The wall is somewhat thinner than normal. The right auriculoventricular orifice admits four fingers with ease. The tricuspid leaflets present no pathological features. A small amount of cruor clot is adherent to the wall of the right ventricle. The right ventricular wall measures 4 mm. in thickness. The papillary muscles are of fair size. The cavity of the left auricle is apparently not enlarged. The wall is of normal thickness. The left auriculoventricular orifice admits two fingers with comparative ease. The mitral leaflets show some fibrous nodular thickening along the line of closure. The leaflets are not distorted. The endocardium and myocardium of the left ventricle present, instead of their normal appearance, the following characteristics: excepting in the posterior portion, from the insertion of the mitral leaflets to the apex, there is a mass protruding approximately 4 mm. above the surface of the normal endocardium, considerably firmer in consistency than the cardiac muscle. The involvement of the left ventricle in this mass can be seen in Fig. 4, the area through which the incision (A–B) runs being the portion of the interventricular septum especially affected, and C, D, and E the papillary muscles through which the process has extended. The endocardium in this region is opaque, grayish-yellow, the surface somewhat nodular. As the middle portion (A, Fig. 4) of the interventricular septum is incised, is seen a firm mass, extending from the endocardium 1.5 cm. toward the right ventricle, and containing a number of homogeneous, yellowish, structureless areas, varying in diameter from

0.5 to 2 cm., and surrounding them areas of a grayish translucent appearance. As the upper portion (B, Fig. 4) of the interventricular septum is incised, this mass is seen to involve practically the entire thickness of the septum, presenting on the right ventricular surface of the septum in three nodules, the one (A, Fig. 5) measuring 1.5 cm. by 1 cm., at the base of the papillary muscle of the middle tricuspid leaflet; the second (B, Fig. 5), somewhat larger, a little above this; and the third (C, Fig. 5) at the base of the posterior tricuspid leaflet.

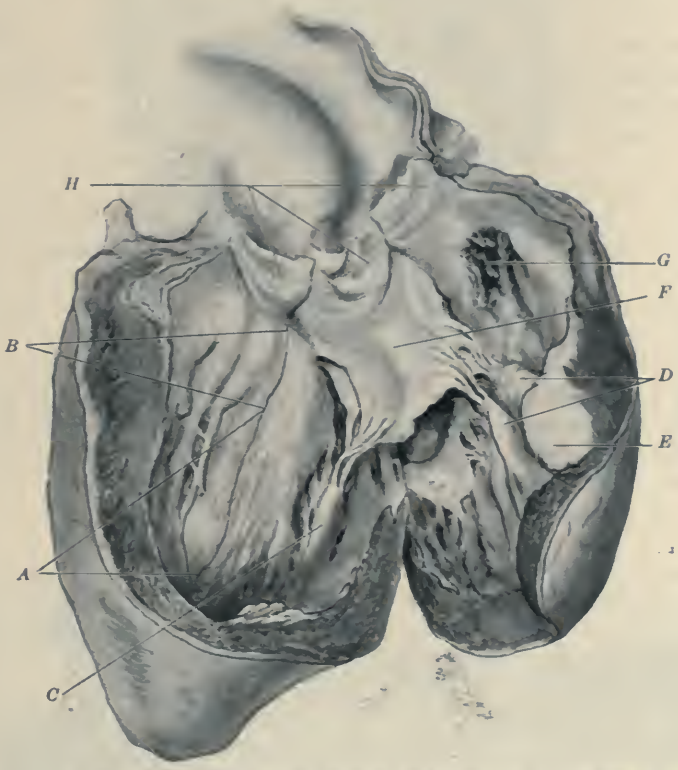


FIG. 4.—The cavity of the left ventricle, showing the gummatous involvement of the wall. *A*, *B*, incision into the gummatous mass, involving the interventricular septum; *C*, *D*, *E*, papillary muscles to which the process has extended; *F*, anterior mitral leaflet, *G*, small clot adherent to the ventricular wall; *H*, aortic leaflets.

All of these nodules consist of a central, firm, homogeneous, yellowish mass, surrounded by dense, grayish, rather translucent tissue. Nowhere within this mass can any tissue be seen of the macroscopic appearance of normal cardiac muscle. At the borders, the demarcation of this mass from the cardiac muscle is comparatively sharp. Upon the posterior superior portion of the endocardium of the left auricle is a thin grayish-red clot, measuring 2 by 1.5 cm., firmly adherent to the endocardium in its central portion. About the

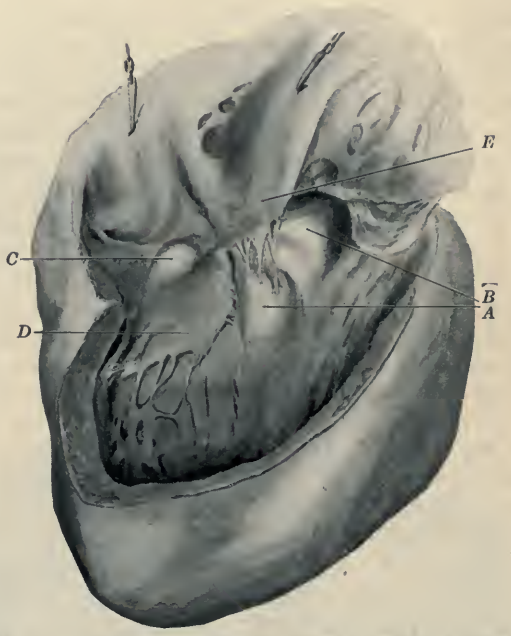


FIG. 5.—The cavity of the right ventricle, showing the extension of the gummatous infiltration from the left ventricle completely through the interventricular septum. *A*, *B*, *C*, gumma presenting on the right ventricular surface of the interventricular septum; *D*, posterior tricuspid leaflet; *E*, middle tricuspid leaflet.

FIG. 6.—Photograph (slightly enlarged) of Section No. 1, with a tracing, showing the course of the bundle of His, from the interauricular septum to its bifurcation. *A*, the bifurcation of the bundle of His; *B*, the course of the bundle; *C*, base of the anterior mitral leaflet; *D*, the interauricular septum; *E*, middle tricuspid leaflet.

middle of the endocardial surface of the left ventricular portion of the interventricular septum is a similar area measuring 0.3 by 0.6 cm. The endocardium under these clots is rough and granular. The left ventricular wall, free from involvement in the mass above described, is 1.2 cm. in thickness. The portions involved in this mass vary from 1.4 cm. to 1.8 cm. in thickness. There are no signs of sclerosis in either coronary arteries or any of their branches as far as they can be followed. Slightly above the aortic leaflets are a few small yellowish areas, pin-head in size. There is no sclerosis and no plaque formation.

The only features of interest in the histological examination of the tissues, excepting those of the heart, are a moderate degree of chronic passive congestion of the spleen, liver, kidneys, pancreas, intestines, stomach, and lung; slight œdema of the lungs; and moderate atrophy of the cortical tissues of the adrenals.

Histological examination of the heart (not including the auriculoventricular bundle of His): The cardiac muscle not involved in the growth above described shows only a moderate amount of fragmentation with slightly decreased prominence of the transverse striations. The portions particularly involved in the pathological process present somewhat varying pictures. In those areas where the process is most advanced there is found centrally a necrotic, homogeneous mass, staining moderately well with eosin, and containing, especially toward the periphery, some nuclear dust. Nowhere within this area is any cell structure preserved. Surrounding this necrotic area is a zone composed primarily of lymphocytes with some polymorphonuclear leukocytes and plasma cells, and a considerable number of young bloodvessels with walls composed of a single layer of endothelium. Toward the periphery numbers of small spindle-shaped cells appear and some larger epithelioid cells, while lymphocytes and plasma cells are still present in small numbers. Young bloodvessels become much more numerous. In a number of areas outside of this zone can be seen one composed of fibrous connective tissue, some of which have undergone hyaline degeneration. In none of these areas are giant cells to be seen. The cardiac muscle immediately surrounding these areas is, in most cases, extensively disintegrated and here and there can be seen a few fibers apparently undergoing hyaline degeneration. The areas in which the process has not proceeded to the stage above described present two pictures. In some of them there is merely a dense infiltration of lymphocytes and polymorphonuclear leukocytes with total disappearance of the normal muscular tissue; in others the normal tissue is moderately well-preserved, but thoroughly infiltrated with lymphocytes, young connective-tissue elements, and newly formed capillaries. The endocardium of the portions of the heart involved in this process is greatly thickened, both the endothelium and the subendothelial layer participating in the thickness,

which is due to a proliferation of endothelial and connective-tissue elements without the signs of an acute inflammatory process. The

FIG. 7.—Photomicrograph of the bifurcation of the bundle of His. *A*, undivided portion; *B*, the branch to the right ventricle; *C*, the branch to the left ventricle.

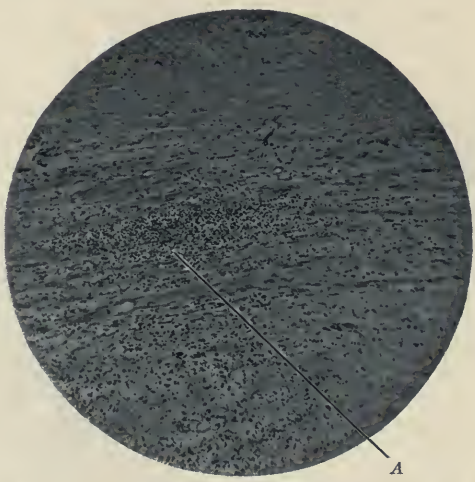


FIG. 8.—Photomicrograph, showing an area of round-cell infiltration in the bundle of His.

pericardium presents no pathological features. A few of the smaller bloodvessels show slight endothelial proliferation. Aside from this, their study reveals no abnormalities.

Diagnosis. Gumma of the heart; acute vegetative endocarditis; chronic passive congestion of the spleen, liver, kidney, intestines, stomach, and lungs; œdema of the lungs; angioma of the liver; bilateral pleural transudate.

Histological Examination of the Auriculoventricular Bundle of His. For histological examination of the auriculoventricular bundle of His, a section of the heart corresponding to the following boundaries was excised: Considering the heart to be placed vertically, with the ventricular septum anteroposteriorly, the anterior boundary corresponded to the middle of the right aortic leaflet; the upper boundary, to a line drawn parallel with the free margin of the aortic leaflets 8 mm. below the uppermost portion of their attachment; the lower boundary, to a line drawn parallel to the upper boundary 1.4 cm. below the lowest point of insertion of the posterior aortic leaflet; the posterior boundary, to the posterior margin of the interauricular septum. The anterior leaflet of the mitral valve and a portion of the median tricuspid leaflet were then cut away from this block. Serial sections in a plane at right angles to the long axis of the heart were cut from this block, commencing at its inferior surface. The sections were 10 microns in thickness. Each sixth section was stained with hematoxylin-eosin; each seventh section with hematoxylin-van Gieson. Subsequently the intervening sections of the first one hundred and fifty were also stained with hematoxylin-eosin.

As the histological findings involving the bundle of His are limited to a series of thirty-nine consecutive sections, we will confine our attention to them. Numbering the uppermost one of these, that is, the one nearest the auricles, 1, the numbers will increase as we approach the apex of the heart. Though in some of the sections above No. 1, portions of the bundle are visible, it is here that it becomes evident throughout its course from the auricular septum to its bifurcation into a right and a left branch. The macroscopic appearance of this section is shown in Fig. 6, in which the course of the bundle, just visible macroscopically in the section, is shown running in a curved direction from slightly above the auriculoventricular septum toward the left ventricular surface of the interventricular septum, then just beneath the endocardium to the point of bifurcation A. Fig. 7 shows the bifurcation into the branch for the right ventricle and the branch for the left ventricle. Though the course of the bundle throughout the first seventeen sections is easily traceable, it is microscopically by no means intact. Especially throughout the undivided portion there is an extensive round-cell and young connective-tissue infiltration. Some of these areas are shown in Figs. 8 and 9. As Section 18 is reached, a much more extensive involvement of the bundle is observed, resulting in a complete solution of its continuity. Here the gumma shown at G in Fig. 10, which is a reproduction of Section 18, has extended

sufficiently to involve the bundle at the point H, Fig. 10, resulting in a complete disappearance of the muscle fibers and their substitution by the infiltrating tissue of the gumma. This interruption in the continuity of the auriculoventricular bundle is shown in Fig. 11. Photomicrographs of the terminations of the two fragments are shown in Figs. 12 and 13. Throughout the remaining sections in which the bundle is visible this interruption persists. Finally, arriving at a level below that of the undivided portion of the bundle, only the right and left branches can be seen, the left lying just beneath and parallel to the endocardium of the left ventricle,

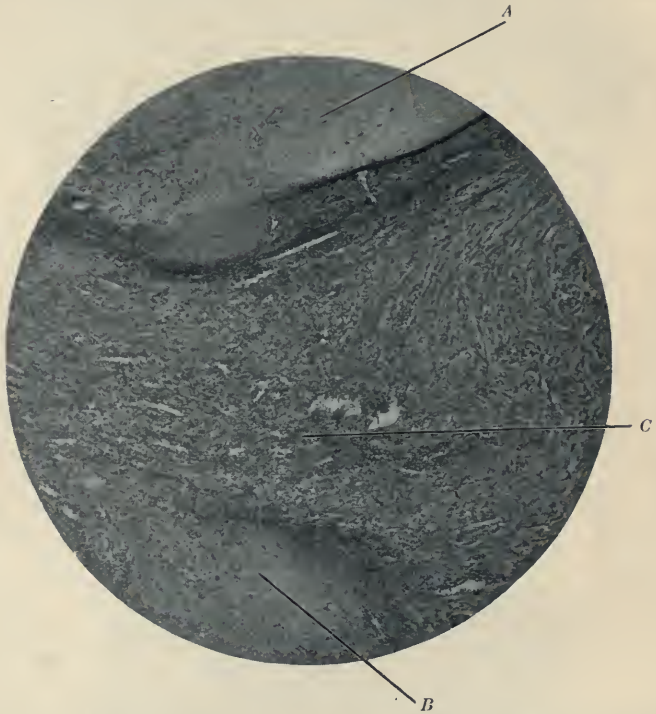


FIG. 9.—Photomicrograph showing an area of round-cell and spindle-cell infiltration in the bundle of His, just as it emerges from the interauricular septum. *A*, auriculoventricular septum; *B*, base of middle tricuspid leaflet; *C*, round-cell and spindle-cell infiltration in bundle of His.

the right showing as a small bundle cut in cross-section lying nearer and nearer to the right ventricular surface of the septum, as we descend toward the apex of the heart.

Though numerous theories have been proposed for the cause of heart-block in the human being, almost all have been without pathological basis. From the recent work in the physiology and anatomy of the heart, we now have every reason to believe that a definite anatomical lesion involving the bundle of His, is responsible for

this condition in man. On account of the absence of examinations for lesions in the bundle of His in the early pathological reports of cases of Adams-Stokes disease, their consideration in the light of our present knowledge can be practically ignored. The findings looked upon as causal in these cases were probably purely coincidental.

A number of cases have been recently reported with more or less definite pathological lesions involving the auriculoventricular bundle. Stengel has reported a typical case in which there were macroscopically fibrous and calcareous processes at the base of the anterior mitral leaflet involving the area traversed by the bundle of His. Schmoll's[39] case showed scar formation in and around the bundle

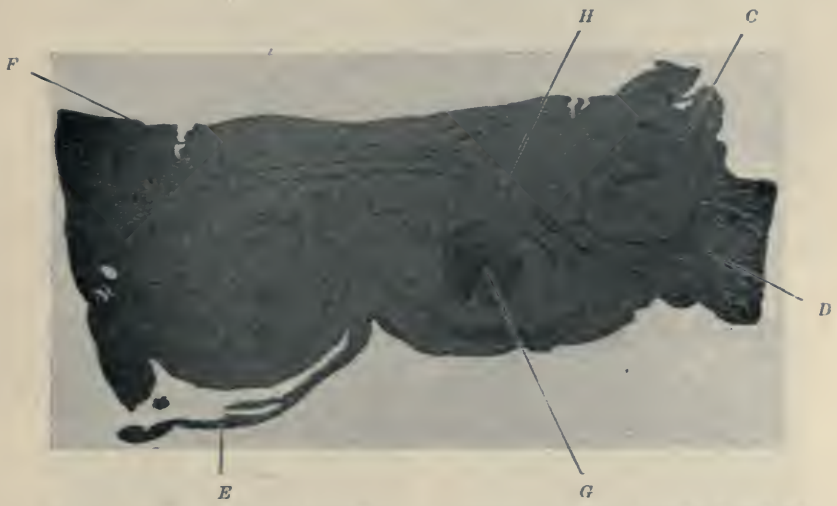


FIG. 10.—Photograph (slightly enlarged) of Section No. 18, with a tracing, showing the location of the interruption in the bundle of His; *H*, location of the interruption in the bundle of His; *G*, the necrotic center of the gumma destroying the bundle at the point *H*, *C*, *D*, *E*, and *F*, as in Fig. 3.

of His leading to atrophy of the muscular elements of the bundle and separation of its fibers from the ventricular muscle. Handford[40] reports a case in which the autopsy revealed gummas, involving the auriculoventricular septum. He does not report the histological examination of the bundle of His itself. The case of Jellick, Cooper, and Ophüls[41] showed anemic necrosis of the muscular septum in the region of the bundle of His consequent upon recent thrombosis of its nutrient arteries. The autopsy of Grünbaum's[42] case dis-

[39] Dent. Arch. f. klin. Med., 1906, lxxxvii, p. 554.
[40] Brit. Med. Jour., December 31, 1904.
[41] Jour. Amer. Med. Assoc., 1906, xlvi, v. 361.
[42] Quoted by Ewart, Progressive Medicine, September, 1906, p. 74.

closed a gumma of the interventricular septum. Keith and Miller[43] report a case which was apparently one of Adams-Stokes disease in which there was found cicatrization of a gummatous mass involving all of the upper portion of the bundle of His and in addition gumma of the coronary sinus, obliteration of the superior vena cava and partial occlusion of the coronary arteries. Sendler[44] saw a case in

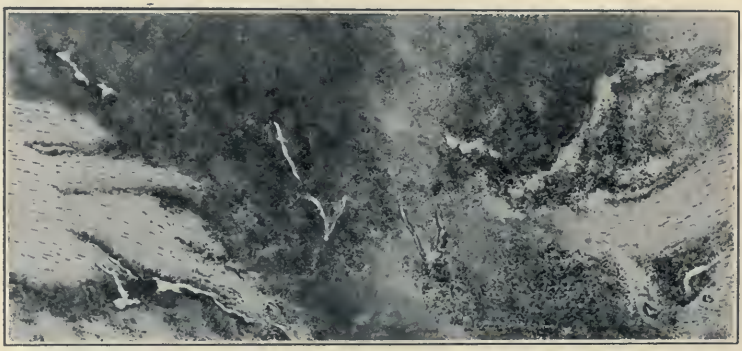
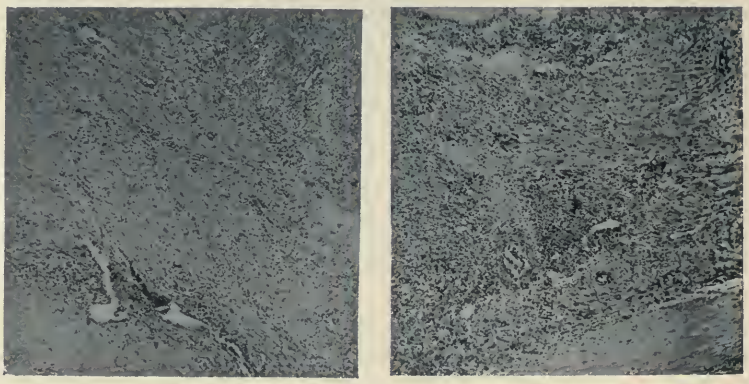


FIG. 11.—The interruption in the continuity of the bundle of His. The two fragments of the bundle are seen entering at the right and left sides of the illustration. Between their two terminations is the infiltrating tissue of the gumma shown at *G*, in Fig. 4. Photomicrographs of the terminations of the two fragments are shown in Figs. 12 and 13.



FIGS. 12 and 13.—Photomicrographs of the terminations of the two fragments of the bundle of His, as shown in Fig. 11.

which a cartilaginous tumor of the interventricular septum was found. The reports of most of these cases have not included the histological examination essential to the determination of the lesion in so delicate a structure as the bundle of His.

[43] Lancet, November 24, 1906.
[44] Cntrbl. f. klin. Med., 1892, p. 642.

The association of syphilis and Adams-Stokes disease appears to have been a peculiarly frequent one. Aside from the cases of Handford, Keith and Miller, and Grünbaum, quoted above, Jacquet, Osler, and Erlanger report cases in which there was clinical evidence in support of the view that syphilis was responsible for the condition. Erlanger and Jacquet mention this frequency of association, but the latter apparently assumes some obscure relationship between the two rather than the actual gummatous involvement of the bundle, as occurred in our case and apparently also in some of the earlier cases reported.

As in all other pathological conditions, the prognosis in Adams-Stokes disease depends upon its cause. First of all, we must clearly bear in mind that all cases of marked bradycardia are not necessarily instances of Adams-Stokes disease. Bradycardia may result from a great number of causes. Thus, it may occur physiologically from hunger, fatigue, pregnancy, and from individual or family idiosyncrasy. Clinically it is met with during the convalescence from infectious diseases, such as pneumonia, typhoid fever, influenza, diphtheria, erysipelas, etc. Riegel has noted the symptom in many cases of gastrointestinal disturbance, gastric ulcer, chronic gastritis, carcinoma, and jaundice. A slow pulse may also be encountered in diseases of the respiratory tract, notably emphysema, and in disease of the heart or bloodvessels—coronary sclerosis, myocarditis, atheroma of the aorta, and embolism of the coronary artery. It occurs also in renal disease—uremia, hematuria. Occasionally it has been noted in diabetes, chlorosis, or other forms of anemia. Bradycardia also occurs in diseases of the nervous system—epilepsy, apoplexy, meningitis, tumors of the brain, diseases of the medulla, and cervical spinal cord, mania, paresis, and melancholia. It has been reported in diseases of the genital system, and of the skin. Finally comes the important toxic group—tobacco, coffee, alcohol, lead poisoning, digitalis, etc.[45] [46]

So much for bradycardia simplex. In order to make a diagnosis of Adams-Stokes disease we must have not only the slow pulse, but also the increased pulsation of the veins, and the nervous symptoms. It seems quite reasonable to suppose from what we now know of the pathology of the bundle of His that minor grades of auriculoventricular dissociation may exist for years without giving rise to marked symptoms. In other words, the degenerative changes in the bundle are so slight in extent, and so slow in progression, that the patient dies from some other cause before the typical symptoms of Adams-Stokes disease develop. Doubtless the combined studies of the arterial and venous pulses which are now being made by different observers with the Jacquet cardiosphygmograph, the

[45] Grob, Deut. Arch. f. klin. Med., xlii.
[46] Babcock, The Heart and the Arterial System, 1903, p. 624.

Mackenzie polygraph, or other instruments, will in the near future throw much light on this and many other hitherto obscure cardiovascular diseases.

Since it has already been shown that several cases of Adams-Stokes disease have been due to gummas involving the bundle of His, heroic doses of the iodides, if resorted to at a sufficiently early stage, may bring about a cure. This has apparently been accomplished in one case reported by Jacquet and Erlanger. In cases in which the lesions are sclerotic or necrotic in character no expectation of recovery can be entertained and they offer practically no hope of other than a fatal issue.

From the accumulated evidence of those cases of Adams-Stokes disease in which satisfactory tracings have been made it seems that the cases were due to heart-block. Now the question arises, May heart-block exist without producing the symptoms of Adams-Stokes disease? Belski and Mackenzie have reported cases of auriculoventricular dissociation without the symptoms of Adams-Stokes disease other than bradycardia. It follows, therefore, that there must be another factor concerned in the production of the symptom-complex. In all probability the ventricular asystole, which is the cause of the syncopal attacks, is brought about by the sudden occurrence of complete heart-block, for as Erlanger has shown, when the bundle of His is suddenly compressed, ventricular activity is in abeyance for a considerable time, that is, for the time required by this structure to inaugurate its own rhythm. This explanation, of course, is applicable only to cases of partial heart-block. Cases such as ours, in which the block is complete, cannot be accounted for in this way. Schmoll has suggested that in the latter event a condition of ventricular depression of conductivity exists, analogous to that which is present in the bundle of His, while the stimulus production goes on normally. If such a state of affairs existed we should expect to find a definite relationship between the rate of the ventricular contractions before and after the block took place. This has actually been noted in a few cases. Thus in His' case the pulse-rate fell from 36 to 18, and later returned to 36. Once more it fell to 12, and subsequently rose to 24, indicating that the original rhythm was undisturbed, but that it required more than the normal number of stimuli to provoke a response. Similar observations have been made by Erlanger, Cornil, and Schmoll, and are, of course, the exact reverse of those noted by Hoffman[47] in cases of paroxysmal tachycardia.

In conclusion, we desire to express our indebtedness to Mr. E. B. Krumbhaar, a student in the University of Pennsylvania, for assistance in the histological examination of the heart.

[47] Ztsch. f. klin. Med., vol. xliii, p. 206

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TRANSIENT PARASITISM IN MAN BY A SPECIES OF RHIZOGLYPHUS.

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and

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In 1906 Dr. Pepper presented before the Philadelphia Pathological Society certain minute ova which he had found in February and March of the same year in the fecal material from a patient in the Philadelphia General Hospital, and tentatively ascribed them to Busk's fluke, basing this opinion upon their size and shape and upon the supposed existence of an operculum at one pole of the eggs. This last feature was never surely determined, although the appearance was such as to have misled several observers of the specimen at the time. In the stool there also existed a number of small arthropods noted by several persons; but these were not mentioned in the communication to the society, because their importance in relation with the ova in question was not appreciated and they were supposed to be merely accidentally

present. The patient from whom the material was obtained was a white man, aged fifty-six years, a plumber, with an indefinite history of lead poisoning and with symptoms regarded as rheumatic in origin. In the blood examination a high grade of eosinophilia was noted, ranging in different observations from 21 to 33 per cent.; and muscle tissue was examined to determine or exclude trichiniasis, but without discovery of trichinellæ. The stools were examined and showed, along with ova of *Trichuris trichiuria*, the eggs and arthropods above mentioned. Repeated examinations of the urine and sputum did not show the presence of any parasites or ova. There were made repeated efforts to dislodge the supposed trematode parasites by means of thymol and magnesium sulphate, but all these attempts proved futile. The stools were carefully searched for days after the vermifuges were given, but no verminous parasites were found. In the course of two months under appropriate treatment his rheumatic symptoms abated and he left the institution; at the time of his discharge still showing the peculiar ova in the feces, but in diminished numbers and with appearance of degeneration in the eggs not previously noted. In 1907 he was readmitted to the hospital, and for several months manifested the symptoms of a very severe and nearly fatal nephritis. During this second sojourn in the hospital the stools were repeatedly examined, but neither ova nor arthropods were found. Subsequently the man died outside the hospital, and as far as is known no autopsy was performed.

Although acting upon the supposition that the ova in question were those of Busk's fluke, and without appreciation at the time of the relations between them and the acarians noticed in the dejecta, Dr. Pepper was never entirely satisfied of the verity of their identification as the eggs of a trematode worm, and held in abeyance final publication of the case.

In August, 1906, Dr. F. W. Schnauss, of the Georgia State Department of Health (at the time located at Albany,

Georgia), sent to Dr. Smith a sample of fecal material containing in large numbers certain ova which he was unable to determine, suspecting their identity with those of *Ascaris texana*, Smith and Goeth. In the laboratory these were at once recognized as the same eggs as those in Dr. Pepper's case. Dr. Schnauss' patient was a white woman, aged forty years, who had for a number of months been losing flesh and strength and who had complained of obscure attacks of pain every few weeks in the left hypochondriac region, followed each time by a severe diarrhea lasting several days. Her physician suspected the existence of tuberculosis, which was not verified by Dr. Schnauss, who was summoned in consultation. Suspecting uncinariasis Dr. Schnauss made an examination of the stools and found the ova mentioned (and, too, the arthropods, although again the relation was not at once realized).

It should be recalled that by the time the fecal material had arrived from Georgia in Philadelphia several days had elapsed, during which interval chance for incubation of the ova had been afforded; and further, that the temperature to which they were subjected in August was probably more favorable for development than in the winter and spring when Dr. Pepper's case was under observation. At any rate in Schnauss' material not only were ova met identical in appearance and size with those in Pepper's material, but in addition numerous ova were encountered with partially and completely formed larval arthropods within the shell; and, too, several stages of extra-oval growth of the acarians were to be seen in the fecal matter. This, of course, at once led to a realization of the true character of the eggs as those of an acarian and to the correction of Dr. Pepper's assumption that they were the ova of a fluke. The eggs, as originally seen in Dr. Pepper's specimens, were of early age, without the same degree of embryonic development. They ranged from 0.11 to 0.17 mm. in length and from 0.075 to 0.078 mm. in transverse diameter, and were constantly of an oval shape.

The shell was thin, hyaline, and transparent, without marking; the contents light yellowish brown, slightly granular, usually somewhat impressed on one side. An operculum could not be clearly demonstrated, but in several examples when treated with sulphuric acid a line appeared at one end in the region where one would expect to find an operculum. In none, however, did this actually open or separate from the rest of the shell, and doubtless it was entirely an artefact. Drawings of the eggs (Fig. 1) before and after the addition of the acid were made by camera lucida, but a photograph was not obtained before the specimens had degener-

Fig. 1

ated. A photograph, however, was made of one of a number of eggs which had been in a centrifuge tube for over a month, the water having in the meantime dried up and been replenished several times (Fig. 2). The resistance of the shell may be appreciated from such a circumstance; but the interior of the egg had shrunken, become almost black and opaque, and had lost all of its original appearance. No records or drawings had been made of the arthropods which were seen in this material, because they were not at the time thought to have any connection with the supposed fluke eggs.

The ova met in the material from Dr. Schnauss' case were of the same size, shape, and general appearance as the

above, but for the most part they exhibited further stages of development of the contents (Fig. 3, of same size as Fig. 1, but photographed at lower power of amplification). Some were entirely comparable with the ova in Dr. Pepper's case, but in all in which there was any distinct development there was noted a dark and relatively opaque area in the material toward one end, doubtless of the nature of yolk substance. The same appearance in the posterior portion of the distinct embryo and larva is to be referred either to the same material or more probably to the developing intestine and hepatic structures. Numerous instances of intra-oval larvæ, with

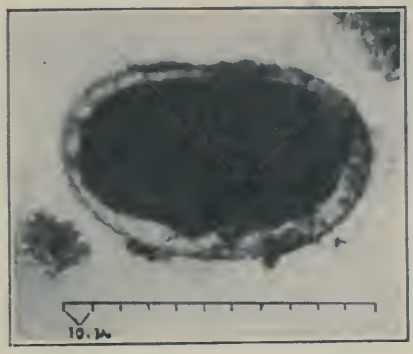
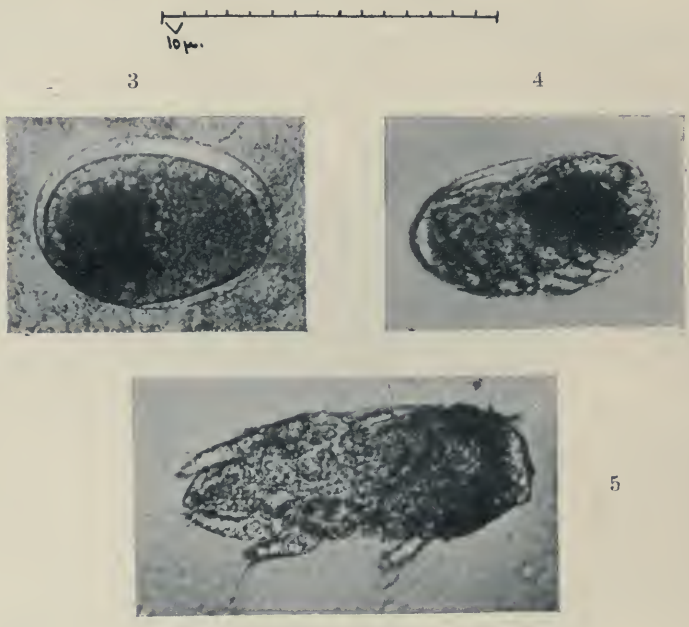


Fig. 2

considerable development of the limbs, were encountered; and some of these (Fig. 4, same amplification as Fig. 3) had become divested of the proper shell of the ovum and were surrounded only by the intermediate membrane. A fully formed and emerged larva is shown at the same degree of magnification as Figs. 3 and 4, in Fig. 5, exhibiting three pairs of legs. A fully developed ovigerous female, with four pairs of legs, measuring 0.250 mm. in length, is shown in Fig. 6 (a tracing made from a photomicrograph, the photograph being rejected for publication because of the faintness with which the limbs of the one side of the body were seen

because of the difficulty of getting the thick-bodied parasite generally in focus). Comparison of this illustration with descriptions available make the writers feel satisfied that the acarian is some form of *rhizoglyphus,* the short legs terminated each with a claw and beset with sparse simple hairs, the simple body hairs, the conical head with pincer-like mandibles (cheliceræ) being characteristics of this genus



Figs. 3, 4, and 5.

of *tyroglyphidæ.* It is either identical or more probably a closely related species to *Rhizoglyphus parasiticus,* Dalgetty.

Mites of the subfamily *tyroglyphidæ* have long been known as occasional and transitory parasites of vertebratæ, rarely of man. They are commonly met living in vegetables and oleaginous material, and in some way are transferred with such substances. Thus workers in raw sugar (or sometimes

in refined sugar), those handling grain or flour, are occasionally afflicted with a dermal inflammation due to the sugar mite or to the flour mite. Among grocers the affection seen about the fingers and hands is known as "grocer's itch." Much the same effect is seen in those who handle vanilla bean from the mite common to the latter.[1] Various skin affections, among others craw-craw, have been suspected of being due to arthropods of this general type; they have been met upon and in the interior of the horns of cattle, and in one case were met beneath a horny growth of the back of a

FIG. 6

woman's hand.[2] The mites found by da Silva Aranjo[3] in the lymph taken from an elephantiasic scrotum and by Magalhaes[4] in the urine of a case of hemetochyluria are

[1] Railliet, Traité de Zoologie, Médicale et Agricole, second ed., Paris, 1895, p. 690.

[2] Moriggia, Atti dell' Accad. delle Scienze di Torino, 1866, i. p. 449.

[3] Gazeta medica da Bahia 1877, ii, No. 11 and 1878, iii, p. 1.

[4] Progresso medico, 1877, No. 4.

believed to have been *Tyroglyphus siro*. Such mites are probably frequently introduced into the alimentary canal along with vegetable and other food (notably cheese), but are pretty surely destroyed long before their passage, and there is no evidence in literature that they reproduce in the intestinal canal, as far as the writers have found. They have been found in the vomit, and Burke[1] has found what are believed to be *Tyroglyphus siro* in the nodules of the buccal mucous membrane of horses in pustular stomatitis. Linnaeus,[2] prior to 1760, gave the name *Acarus dysenteriæ* to a mite which Latreille and other writers after him regard as *Tyroglyphus siro*, found in quantities in the stools of one of his students who was affected with a serious diarrhea; the same mites were also found in large numbers in and upon the wood of a wooden vase from which exclusively this man was accustomed to drink. Lambl,[3] in 1859, met what is supposed to be the same mite in fecal material in the Children's Hospital in Prague. Perrier[4] records a case of the presence of *Glyciphagus domesticus* (de Geer) in the feces.

The writers have not met any recorded instances of *rhizoglyphus* being met in fecal material. Their ordinary habitat is in vegetable material, especially in various bulbs. *Rhizoglyphus parasiticus*, Dalgetty,[5] was originally observed in lesions of the skin of the feet in Indian coolies working in tea

[1] Veterinary Journal, 1882, p. 3; ibid., 1890, p. 229; The Veterinarian, 1886, p. 692.

[2] The writers have not verified this reference, which is given in Blanchard's and Railliet's medical zoologies, in Höfle's Chemie u. Mikroskopie am Krankenbette, Erlangen, 1848 (Anmerkungen, p. 43), and in Braun's Animal Parasites of Man (English edition, London, 1906, p. 376), and elsewhere. Höfle refers to Linnaeus, Amoenit. Academ.: De Exanthem. vivis, 1759, vol. v; Blanchard (Traité de Zool. Méd., Paris, 1890, vol. ii, p. 298) to J. C. Nyander, Exanthemata viva: Linnei Amenitates academicae, v. p. 92, Dissertatio lxxxii; Erlangæ, 1757.

[3] Prager Vierteljahresschrift f. d. prakt. Heilkund, lxi, p. 1; note, p. 45.

[4] C. R. Acad. Sci., Paris, 1896, vol. 120, p. 859.

[5] Jour. Tropical Medicine, 1901, vol. iv, p. 73.

plantations, the affection beginning with blisters between the toes and spreading over the feet, but not extending beyond. They are grayish in color, taking on a greenish-yellow or greenish-brown hue with the food in the alimentary canal. The adult males measure 0.18 mm. in length, the females 0.2 mm. It seems unlikely that the specimens in the two instances here recorded are identical with this species, as the adults are materially larger and the color is grayish, with darker gray blotches in the abdominal part from the contents of the alimentary canal. The details of the structure were unfortunately never sufficiently worked out at the time when material was available to establish the finer points in the anatomy; and the writers deem it impossible to insist upon the specific determination beyond the indication already made that the specimens belong to a species closely allied to *Rhizoglyphus parasiticus*. How these parasites gained access to the stools is entirely conjectural. The intimate admixture of the arthropods and of the ova with the fecal material (even when fresh) suggests that they were actually in the material when it was passed. Had they been merely denizens of the anal verge they would have been largely or entirely confined to the surface of the formed mass. The adult acarians in the Schnauss material were all motionless and apparently dead when it was received in the laboratory from Georgia (several days after its discharge from the host); in the Pepper material it is the recollection of one of us that some of the mites were moving at least slightly, this within a few hours after discharge from the host. The undeveloped condition of the ova in the Pepper case compared with the advanced but varied development in that of the Schnauss case point to the development having been extracorporeal, and, therefore, if the acarians have (as is not impossible when one considers the fact of their discovery in other intracorporeal situations, as the lymph and urine above mentioned) actually been mingled with the feces within the intestine, they are at least not renewed by intra-intestinal propagation, but

must eventually disappear as they die and are discharged, unless fresh numbers are introduced with the ingesta. The exact circumstances of collection of Schnauss' material are not now known, but in Pepper's case the chance of introduction of the arthropods into the feces after passage is excluded; and, as already suggested, the intimate admixture of the parasites with every particle of the fecal sample rather than merely with the surface, and the general care usually observed in obtaining material for examination, render it improbable that this mischance enters into the problem.

Dr. Schnauss had considerable difficulty in procuring his material, and a direct examination of the anus and rectum was denied when he endeavored to obtain it after the nature of the case was reported to him. These mites are not provided with a tracheal system, require but little oxygen, and their life in the intestine could scarcely from this one point be seriously endangered, provided they were able to withstand other influences; but their history of development and their general structure are not adapted to an entozoal existence and they can be but transient parasites. Whether in such circumstances they are capable of producing appreciable effects upon the hosts is unknown, and seems unlikely.

A NEW METHOD OF EXAMINATION OF THE FECES FOR THE OVA OF UNCINARIA. WITH REPORT OF A CASE OF U. AMERICANA AND OF A CASE OF U. DUODENALE.*

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(From the William Pepper Laboratory of Clinical Medicine.)

Having very recently had two cases of Uncinariasis under observation, one U. Duodenale and the other U. Americana, and while making frequent examinations of the feces, it was noted that the ova of these parasites were quite sticky and that this peculiarity (as far as I know not mentioned in any description) could be made use of in searching for these ova.

The methods recommended for finding parasitic ova in the stools include (1) the examination of a small amount of feces mixed if necessary with water on a slide under the microscope; (2) the natural sedimentation of a thoroughly liquefied stool in a tall narrow glass jar and the removal after a few hours with a pipette of some of the middle strata of deposit at the bottom of the jar for microscopical examination; (3) the centrifugalization of a small amount of much diluted feces and the subsequent microscopic search of this sediment.

This latter method, when the washing is frequently repeated and when after each centrifugalization the supernatant dirty water is thrown away and fresh water added, the whole then being shaken up and again placed in the centrifuge, has proved most useful in my hands.

In this way all bacteria, free coloring matter, light vegetable matter, etc., is soon got rid of, and only the heavier particles, including any ova that may be present will remain. After about six repetitions of this eliminative washing, the sediment can be easily and satisfactorily examined under the

* Received for publication Jan. 14, 1908.

low power of the microscope. There is then left no obscuring cloud of bacteria nor fine granular débris, but instead each ovum or muscle fiber or crystal or vegetable fiber stands out sharp and clear.

In endeavoring to remove some ova from a slide under the microscope prepared in this manner, by touching the egg with a very finely drawn out glass tube and thus causing it to be carried up into the tube by capillary attraction, it was found impossible with the ova of Uncinaria, the eggs having stuck to the glass. I have thus frequently transferred from one slide to another the ova of Ascaris Lumbricoides, of Trichiuris Trichiura and of Taenia Saginata and have never seen them adhere at all to the slide. A rather peculiar fact to be noticed in this connection is that the ova of the Uncinaria, although sticking closely to the glass slide, do not seem to adhere to any of the many other constituents of the stool. When a drop of this washed sedimented feces is allowed to stand on a slide for a few minutes and then gently immersed in water and examined microscopically, the eggs are found adhering to the slide while all else has been washed away. If additional drops are placed on the slide and washed off, the slide becomes thickly studded with the eggs as is shown in the accompanying photograph. A ring of asphalt may be used to keep the drop when placed on the slide in bounds and also serves to support a cover-glass. Both the old world and new world variety act in the same way. The ova at all stages in their development behave in the same manner even including those in which a living embryo could be seen moving within the egg. Ova were also seen to develop up to this stage while mounted in this way in water and under a cover-glass, but were not observed to progress further. For demonstration purposes this method has proved very useful.

It has been remarked by nearly all writers that it is much more difficult to find the ova of Uncinaria when the stools are loose than when they are formed and the explanation of this may lie in the fact that perhaps in loose watery stools the ova sink to the bottom, adhere to the vessel in which the

stool is collected, and are thus not to be found in such large numbers in the feces examined.

On the other hand in loose watery stools or those containing mucus the eggs I observed did not adhere so well to the slide.

It is conceivable also that this stickiness might aid in the distribution of the ova, although this is very problematical.

The clinical report of two cases of Uncinariasis is added to demonstrate how widely spread this disease is, and how common it would probably be found to be if systematic examinations of the stools were made even in cities as far north as Philadelphia.

The first case illustrates the extreme value of routine laboratory examinations.

P. J. Italian. Aged twenty-six years. Admitted to the Philadelphia Hospital on 3–28–07. He had been in this country one year spending all of that time working as a laborer building bridges in Pennsylvania. About eight weeks before his admission to the hospital he began to grow weak and short of breath, and to cough and to have pain in his chest and abdomen. On exertion he had marked palpitation. In about a month he had to stop work and went to a hospital where he was in bed for some days and where he was found to have a left-sided pleural effusion which was tapped and about a quart of fluid removed. He then came to the Philadelphia Hospital with practically the same symptoms. The important points of the physical examination on admission were as follows: Fairly well nourished, anemic looking young man. Tongue, pale and moist. Pulse regular and of low tension. At base of left chest small area of almost complete flatness on percussion with loss of fremitus and distant breath sounds. The collodion dressing over the aspiration wound still in place. The spleen was distinctly palpable.

The patient's temperature during the first week he was in the hospital was always above 100° and below 103°, during the second week it was between 99° and 101°. A Widal test on 3–30–07 was negative, and on the same date the leucocytes numbered seven thousand per cubic millimeter; the differential leucocyte count showed normal proportions of the various forms.

4–5–07. The examination of the blood showed Hem. forty per cent. Red cells, two million one hundred and ten thousand. White cells, seven thousand.

On account of the persistence of the fever, and the enlargement of the spleen, and the increasing anemia together with the suspicious signs

existing at the left base, an aspirating needle was introduced on that side, but no fluid was obtained.

4-10-07. The examination of the stools on this day cleared up the case at once. Ova of Uncinaria were found in large numbers. Ten of these eggs were carefully measured and were found to range between 61-78 μ in length by from 40-45 μ in breadth, the average size was 67.8μ-42.4 μ. These measurements led to the mistaken idea that the worms were of the new world variety, or Uncinaria Americana, but on obtaining the worms themselves from the stools later all were found to be Uncinaria Duodenale. The comparative size of these eggs according to various authorities is here quoted:

U. Duodenale, 55-65 μ = 32-45 μ U. Americana, 64-75 μ = 36-40 μ	Braun.
U. Duodenale, 50-60 μ = 30 μ U. Americana, 68-70 μ = 38-40 u	Smith.
U. Duodenale, 52-60 μ = 32 μ U. Americana, 64-76 μ = 36-40 μ	Porto Rico Anemia Commission.

A study of these figures will show why the diagnosis of Uncinaria Americana was made; and demonstrates the unreliability, in some cases at least, of determinations based on the size of the ova.

4-18-07. The patient was given Thymol gr. LX. and about twenty-five adult male and female worms were found in stools, all of these were Uncinaria Duodenale. During the next week Thymol gr. LX. was given on two occasions but only about six or eight worms were found. Eggs still continued in the stools.

14-29-07. Examination of the blood showed red corpuscles, one million seven hundred and forty thousand. White corpuscles, eight thousand four hundred.

5-11-07. Thymol gr. XC. was given and a number of worms were found, bringing the total number recovered from the stools to between fifty and sixty, all of which were U. Duodenale. After this the patient began rapidly to improve in weight and color, and would not remain longer in the hospital. There were still a few ova in his feces when he left on 5-15-07.

The second case, although the presence of Uncinaria had probably but a slight influence upon the patient's general health, is interesting from another standpoint. The abdominal symptoms in pulmonary disease are often confusing and led the surgeons who were called in to open the abdomen in spite of the medical diagnosis of pulmonary abscess.

J. F. Black. Aged twenty-six years. Waiter. Born in North Carolina. Admitted to the Philadelphia Hospital 2-27-07. Service of Dr. Stengel.

Had had chills and fever in 1901. Has been living in Philadelphia for last four years coming to this city from his home in North Carolina. On 2–25–07 had a chill followed by pain in right chest and then cough. On examination the patient was found to have consolidation of the right upper and lower lobe, with all the accompanying signs and symptoms of a croupous pneumonia. He became quite jaundiced. His urine and sputum were very bile tinged. His spleen was not palpable at this time. His pulse was very weak and irregular and altogether the attack was a very severe one. On 3–4–07, the seventh day after the initial chill, the temperature dropped and the patient became much more comfortable and was apparently out of danger. The temperature remained normal until 3–10–07, when it rose suddenly to 102 , and then dropped quickly to normal and the patient that day complained of pain in right axilla, also on 3–11–07 there were two abrupt elevations of temperature and again on 3–20–07. No explanation could be found at the time for these rises. On 3–24–07 his temperature was around 104° all day but was normal on the 25th, and the patient was then found to have chicken-pox; his temperature reached 105° on the 26th. Having recovered from the chicken-pox he left the hospital on 4–2–07.

He reëntered the hospital on 5–14–07, not having been very well since he left; complaining of cough, pain in chest and abdomen and extreme weakness. On examination an area of dulness was found still to be present at base of right lung, with harsh breathing and subcrepitant and bubbling râles. Repeated examinations of the sputum revealed no tubercle bacilli but showed enormous numbers of streptococci, staphylococci and other organisms. A blood culture was negative.

On 5–18–07 the ova of Uncinaria were found in small numbers in the stools. These ova averaged in length 71.5 μ by 37.8 in width and were therefore thought to be from Uncinaria Americana, which was subsequently proved to be the case at the autopsy.

On 5–22–07. Thymol gr. LX. given, but no worms were recovered from the stools. The patient's condition did not warrant another attempt to dislodge the worms.

During this time the patient had a typical hectic temperature ranging daily from 98° or 99° to 103°.

A blood count on 5–17–07 showed three million three hundred and eighty thousand red cells and thirteen thousand three hundred and thirty white cells with eighty-four per cent neutrophiles.

The patient grew weaker, the spleen became enlarged, the signs at the base of the right lung increased, the dulness was not movable, the tactile fremitus and vocal resonance were not lost, and there were no signs of free fluid in the pleural cavity. The abdomen became slightly swollen, tender and rigid, but nothing abnormal could be detected on palpation.

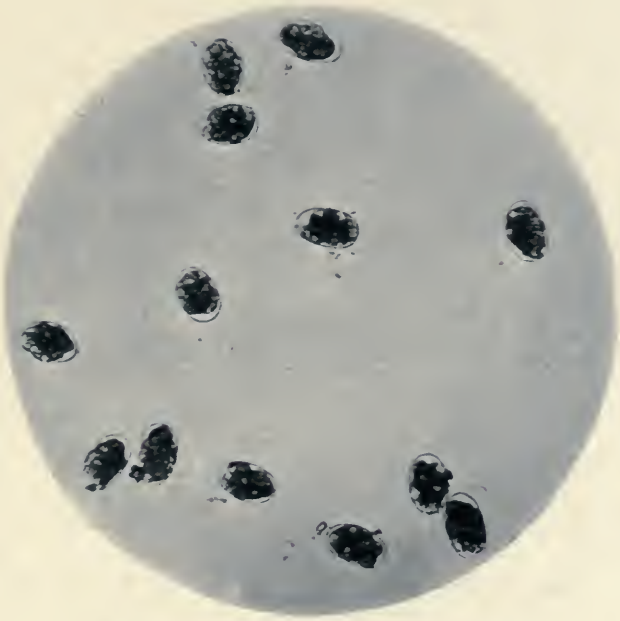
On account of the hectic temperature, leucocytosis, enlarged spleen, increasing weakness, absence of tubercle bacilli in the sputum, taken in

consideration with the signs at the base of the right lung, the diagnosis of pulmonary abscess or interlobular empyema was made. The case was transferred to the surgical wards on 5-29-07 with the request that should the man be thought strong enough and the signs sufficient that the right chest be opened and any purulent collection evacuated and drained. The patient was operated upon the same day. The surgeons, however, thinking the pulmonary signs indefinite and the abdominal ones positive, first introduced an aspirating needle into the right pleura, and not getting any fluid proceeded to open the abdomen under local anesthesia over the gall bladder region. Nothing was found but a small amount of clear fluid in the abdominal cavity so the wound was closed. The patient died five days later.

The intestines and the right lung were removed through the abdominal incision twenty-four hours after death. The lung was bound to the chest by slight easily torn adhesions, the lower lobe had running across it a raised ridge about three inches in length by one inch in breadth, looking like a welt on the skin raised by a very sharp blow of a stick. The crest of this ridge had evidently been adherent to the costal pleura and was yellowish and somewhat ulcerated. On section this area was found to be fairly firm, free from air and beginning to disintegrate and break down. The cause was found to be a large thrombus in one of the large arterial branches supplying this portion of the lung.

Sections from this area, examined microscopically, showed entire disappearance of lung tissue, a mass of round cells and in the center granular débris. Liquefaction was apparently just beginning.

On opening the intestines ten Uncinaria Americana were found, eight of these were females and two males. All were dark in color, were alive, and were not adherent to the mucous membrane. They were found only in the small intestine between one and two yards below the pylorus.



Ova of Uncinaria duodenale. Collected from the feces by the author's method, adhering to glass slide even after gentle washing.

A SUBSTITUTE FOR THE MOVABLE STAGE TO BE USED WITH THE MALTWOOD FINDER.

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In microscopic work, especially in studying blood or bacteriologic slides, some sort of "finder" is a very necessary part of the equipment. Any one who has used the vernier scale which accompanies most movable stages will agree that this is a rather unsatisfactory method of noting down an exact locality on a slide for further examination. The slightest disturbance of the relation existing between microscope and movable stage destroys the value of the reference figures completely. In carelessly covering the microscope with a bell jar, for example, the movable stage may be struck and moved, and all one's past trouble is wasted.

Another objection to registering with the vernier scale is that the same microscope must be made use of each time. For these reasons I have been using the Maltwood finder and find it very much more convenient. This is a finder that has been in use for a number of years but is not widely known. It consists of a heavy glass slide three inches in length, in this respect corresponding precisely with the ordinary slide, on which a network of a large number of small squares, each containing two figures arranged one above the other, so that each square has a different combination, has been

placed (Fig. 1). These squares have been photographed on the slide.

All Maltwood finders are made interchangeable, the squares being placed exactly in the same place on each slide. In using this finder the methods is as follows: If on looking over a slide with the help of a movable stage a cell or some similar object is seen which one desires to examine at some later time, the slide is carefully removed, the Maltwood finder substituted without disturbing the movable stage, and the square which is found in the center of the field on focussing on the finder is noted down. In order to make sure that the proper reading has been made the finder and the slide should be substituted, one for the other several

1 1	1 2	1 3	1 4
2 1	2 2	2 3	2 4
3 1	3 2	3 3	3 4

Fig. 1.—Illustrating a small portion of the Maltwood finder showing the plan of figure combination.

times, when on focussing the same field on the slide and the same square on the finder should appear.

Suppose the reading to have been $\frac{13}{23}$, then later, when the particular field or cell that it is desired to find again is sought, this process is reversed. Put the finder under the microscope and locate the square $\frac{13}{23}$, place it in the middle of the field, then remove the finder and substitute the original slide, again without disturbing the movable stage, and on focussing the looked-for field or cell should be found in view. This takes but very little time and has the advantage that a slide can be sent to any one having such a finder, with the request that he examine such and such a field, giv-

ing the numbers of the particular square to which reference is made.

Having often had the wish to use this finder on microscopes without movable stages I devised a simple little right-angle of brass that could easily be carried in the pocket with the finder and which could be substituted at any time for a movable stage, as the only purpose that the movable stage serves in this connection is to afford an angle into which the slide and the finder will fit.

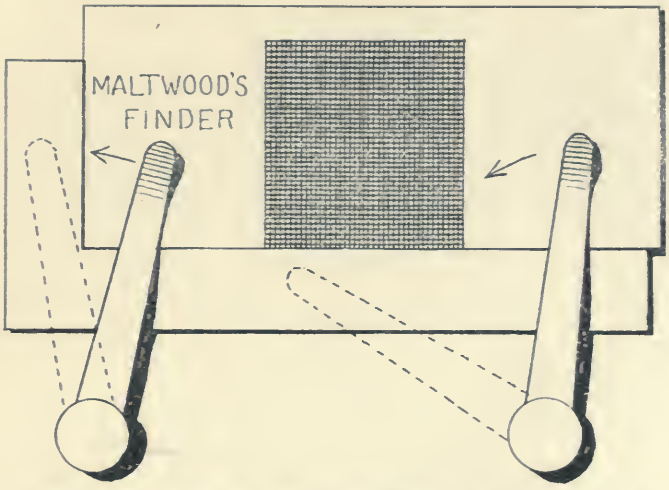

Fig. 2.—Showing brass right-angle devised to take the place of the angle furnished by the movable stage; the Maltwood finder in position. The two clips of the microscope stage are shown, with dotted lines demonstrating how they can be moved from the finder or slide to the brass right-angle in order to hold it steady.

The illustration shows this right-angle and demonstrates how the clips on the microscope can be moved from the finder or slide, to hold the right angle steady, while the slide or finder are being substituted one for the other. The illustration also shows the size of this right angle which has been found to be most serviceable. The strip of brass from which the right angle is cut should be about one-sixteenth of an inch thick.

By means of this simple little device it is a very easy

matter to arrange a demonstration of slides under a large number of microscopes in a very short time, often less than a minute being required for each specimen. In finding particular fields for photomicrographic reproduction this right-angle has proved itself to be very useful.

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A COVER-SLIP HOLDER.

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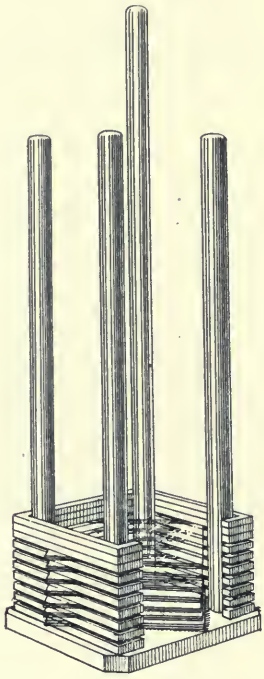
This holder was devised and made to fill the want of a suitable piece of apparatus to hold a large number of cover-slips while staining. It consists of four upright brass posts rising from a flat, square base, each post being securely fastened in a corner of the base, and of some twenty or thirty square bands or hoops of brass fitting snugly around the four posts, part of one side of each band having been cut away. The base should project slightly beyond the four posts, so that the bands when placed over and around the post will rest on it. Cover-slips, either singly or in pairs, with back to back, can be placed between each band, the corners of the cover-slips projecting between the posts. When in position the cover-slips are a sufficient distance apart to allow the stain to run in between them.

The various stains can be kept in glass cylinders just large enough to receive the apparatus and the loaded holder can be lowered into one of these glasses, tilting the glass as far as possible to one side to let the air bubbles run out through the openings in the bands; these openings should preferably be superimposed one above the other. Cover-slips can not fall out after being placed in position, and there is not the slightest tendency for them to get broken.

The holder shown in the cut is for use with ¾ inch square cover-slips; for larger sizes a larger apparatus would be necessary. It would, perhaps, be possible to construct a triangular holder with three posts for staining round cover-slips, but these are seldom used in blood work, the squares being much better for making spreads.

I have stained spreads in this holder with hematox-

ylin and eosin very successfully, and even Wright's stain can be used with good results and with a considerable saving of stain. I have put in one glass, pure undiluted Wright's stain, and in another glass the properly diluted stain, and then have transferred the holder from the first into the second. The stain in these two glasses



Cover-slip holder for staining a large number of cover-slips simultaneously.

can be used again several times, so that it is possible, with but very little stain, to prepare a great many cover-slips. With this apparatus 35 c.c. of solution is sufficient for staining fifty cover-slips simultaneously.

Reprinted from The Journal of the American Medical Association, January 11, 1908, Vol. l, p. 122,

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A CASE OF FATAL HEMOLYSIS FOLLOWING DIRECT TRANSFUSION OF BLOOD BY ARTERIOVENOUS ANASTOMOSIS.*

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AND
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Since the report by Crile[1] in November, 1906, of several cases of severe anemia in which direct arteriovenous anastomosis and transfusion of blood was made use of in the treatment of the anemia the method has been tried, at times with favorable results and at others without much apparent change in the course of the disease.[2] No serious ill effects have been reported so far as having been caused by this method of treatment, and we, therefore, believe that the following report of a case of fatal hemolysis after two transfusions of blood from different individuals should be placed on record in order to show that the procedure is not without danger and that until our knowledge of the hemolytic action of different sera is more exact it should be used with caution.

Patient.—C. J. G., aged 33, white, married, born in England. Referred April 16, 1907, by Dr. Frank Harris, Trenton, N. J., to the Hospital of the University of Pennsylvania, service of Dr. Stengel. Complained of bleeding from gums.

History of Present Illness.—Some time before October, 1906, it was noticed that the patient's complexion, though naturally pale, was becoming paler, though he had been in apparently good health up to that time. Tinnitus aurium, and a very slight intermittent nightly bleeding from the upper gum began

* From the William Pepper Laboratory of Clinical Medicine.
1. THE JOURNAL A. M. A., Nov. 3, 1906.
2. Watts: Johns Hopkins Med. Bul., May, 1907.

at this time. He had been able to be about on his feet, but had gradually grown weaker during this period. Dizziness, palpitation of the heart, and pains in legs were occasionally present. He had gained six pounds in weight in the last ten weeks; for a time he noticed that his vision was dim. The bleeding from the upper gum was at first noticed at night only, but it gradually increased in severity, occurring day and night for ten weeks preceding his admission, though intermittently, and during the last four days preceding admission constant bleeding had occurred. Patient was kept in bed under a physician's care for seven weeks, beginning about Jan. 15, 1907. He grew somewhat better at the end of that time and went to work. On April 13, 1907, bleeding and other symptoms forced him to stop work again. Physicians told him he was losing blood in his urine, and by the bowel (after examination of urine and feces). He had noticed no edema. No hemophilic nor scorbutic history.

Previous Medical History.—Patient had none of the diseases of childhood. Had nervous indigestion six years ago; otherwise has been a very strong man.

Social History.—Patient at 21 years became a machinist, doing hard, manual labor ever since. About 11 years ago he had a sore on his penis, hard and persistent; a rash followed this, and he was treated for six months for syphilis. Was married ten years ago; wife had one miscarriage and one living child, which has coxalgia. He used tobacco and tea moderately, occasionally drank beer, rarely whisky. Had a good home and good food.

Family History.—Father and mother were living and well. Patient had fifteen brothers and sisters. One brother died of apoplexy and one of injury. One sister died of a peculiar (non-anemic) wasting disease. No history of renal, cardiac, or pulmonary disease.

Condition on Admission.—Temperature 98 F.; pulse, 108; respiration 22. Patient walked to the hospital, looking extremely anemic, but not dyspneic or weak.

Physical Examination.—Patient was a dark-complexioned man, fairly well nourished, and with good musculature. Skin uniformly throughout body had a dirty lemon color. No edema nor cyanosis present. Peripheral arteries were soft; pulse of low tension, easily compressible, moderately rapid and quickly receding. No capillary pulse. Lymphatic glands were palpable in axilla and groin and one beneath the jaw. Conjunctivæ very anemic; sclera showed a glistening pearly-white luster; pupils equal; pupillary reflexes normal. Ears showed a waxy-like pallor. Alæ of nose moved with respirations. Lips were very pale and blood stained. Tongue very pale and coated with mucus and blood. Upper gums, especially anteriorly, oozed blood continuously; slight oozing from lower gums. No blue line at edge of teeth; teeth were somewhat decayed at gum margin. Oral mucous membranes very pale. Neck

shows marked pulsations, arterial in type. Thorax rounded and fairly well muscled. Respirations equal on either side, expansion good, breathing costo-abdominal. Lungs were normal as to vocal, tactile fremitus, and resonance, which extended from the sixth right rib to apex anteriorly on right side, and posteriorly to level of tenth dorsal vertebra. Breath sounds were vesicular in type; no râles. Heart: Apex beat extended over several interspaces, but was seen best in fifth interspace, within the left midclavicular line. A feeling suggesting a thrill on palpation. Cardiac dulness: Above third rib; right, 1 cm. beyond right sternal margin; left, about the anterior axillary line, 3 cm. beyond nipple line. A loud first sound, accompanied by a rough, loud murmur, heard best at apex, not transmitted. A systolic murmur was also heard in third interspace, not transmitted to vessels of neck, where a humming sound was heard over their course. The second murmur was the higher pitched. Pulmonary second sound was accentuated. Abdomen was of normal rounded outline; slight panniculus. Liver and spleen were not palpable. Retroperitoneal lymphatic glands were not palpable. Abdomen was generally tympanitic on percussion. Liver dulness extended from right midclavicular, sixth rib, to rib margin. Splenic dulness began at ninth rib in midaxillary line, and soon blended with colonic tympany about the eleventh rib. Limbs were well muscled. Nails bitten and anemic.

Uurinalysis.—Straw colored urine, flocculent sediment; odor, normal; sp. gr., 1016; acid; mucus, plus; leucocytes, plus; erythrocytes, minus; squamous epithelia, plus; a few calcium oxalate crystals; a few bacteria.

Blood.—Hemoglobin, 20 per cent.; r. b. c., 970,000; w. b. c., 3,600. (See chart and table for further examinations.)

Blood Pressure.—Systolic, 120; diastolic, unobtainable. .

Stool Examination.—Formed, hard, dark and tarry, somewhat offensive. Mieroscope showed erythrocytes, and undetermined crystals. Occult blood, very marked positive reaction.

The bleeding continued in small amounts and patient lost ground steadily.

April 24: 2,000 units diphtheria antitoxin were injected in the hope of influencing a possible undiscovered infection, whatever its nature.

April 25: The patient is losing ground daily. Lost several ounces of blood from the mouth last night in spite of various local applications and mouth-washes. Seems paler daily.

It was evident at this stage of the case that the patient was suffering from some obscure type of hemorrhagic disease rather than from any of the more definite forms of blood disease. Careful inquiry failed to disclose any history of hemophilia in his family. Scurvy was negatived by the absence of characteristic change-

in the gums, or deep (intramuscular or subdermal) hemorrhagic effusions or of a suggestive history. The morphology of the blood as well as the blood count excluded ordinary pernicious anemia, and the patient was quite certain that his pallor followed the bleeding from the gums. Had the reverse been the case such persistent bleeding from the mouth could not well be ascribed to pernicious anemia; no such tendency to uncontrollable hemorrhage occurs in that disease. The blood picture more closely resembles that of so-called aplastic anemia, but the fact that the anemia seems to have followed the hemorrhage rather than to have occasioned it caused us to exclude this diagnosis. The possibility of the patient having acute leukemia was considered and the fact that cases have been recorded in which this disease has existed and even terminated fatally with leucocyte counts no higher than those obtained in our case was considered. We felt, however, that the degree of lymphocytosis and the general morphology of the blood did not justify this diagnosis.

For all of these reasons the conclusion arrived at was that the patient was suffering from some type of obscure hemorrhagic disease of unknown etiology. The rapid increase of the anemia with the persistence of bleeding caused us to place the patient under the care of Drs. C. H. Frazier and J. E. Sweet for direct transfusion, the patient's wife offering to furnish the blood.

April 26: Patient passed a very bad night, bleeding continuously from gums. Tinnitus aurium was very severe. Nausea present in high degree. Seemed to be sinking very rapidly. At 5:52 p. m., after anastomosis by Dr. Sweet of the left radial artery of patient's wife with a large vein at left elbow of patient, clamp was removed and transfusion begun. Transfusion ended at 7:25 p. m. Both husband and wife stood operation well. During the operation the patient vomited considerable quantities of dark grumous material.

Blood, 5:50 p. m.

R. B. C.	420,000
W. B. C.	4,200
Hb.	12 per cent.
Pressure	100

Differential Count.

	Per cent.
Polymophonuclear	41
Large mononuclear	0.5
Transitionals	2.5
Lymphocytes	54.5
Eosinophiles	1.5

Blood, 6:15 p. m.

R. B. C.	920.000
W. B. C.	1,800
Hb.	15 per cent.
Pressure	118

Differential Count.

	Per cent.
Polymorphonuclear	28
Transitionals	3
Large mononuclears	0
Lymphocytes	68.5
Eosinophiles	1

Blood, 7:15 p. m.		Differential Count.	
			Per cent.
R. B. C.	1,001,000	Polymorphonuclear	44
Hb.	21 per cent.	Large mononuclear	2.5
Pressure	115	Transitionals	3
		Lymphocytes	49
		Eosinophiles	1.5

Pulse rate, 120-130 throughout operation. (See blood charts and table.)

April 27: Patient passed a fair night. Bleeding from gums almost entirely ceased immediately after transfusion and did not recur. Tinnitus aurium entirely ceased in one ear and was better in the other. Had not vomited since transfusion. Color a great deal better. No jaundice noted.

April 28: Patient continued to feel stronger and much better. Bleeding from gums was merely a trace. Stomach not very retentive. At 5:35 p. m. a vein was exposed in upper left arm by Dr. Frazier. This was found not suitable to the left radial artery of patient's brother-in-law, which was being exposed at same time. Another vein in patient's lower arm was exposed and an arteriovenous anastomosis done by Dr. Sweet. Blood was allowed to transfuse from 6:33 p. m. to 7:37 p. m. Patient visibly reddened during operation. The donor grew somewhat sick at stomach, but otherwise stood the operation well.

Blood before transfusion, 6:30 p. m.: R. B. C., 1,270,000; W. B. C., 2,450; Hb., 21 per cent.; pressure, 122.

Blood after transfusion was begun, 6:55 p. m.: R. B. C., 1,370,000; Hb., 23 per cent.; pressure, 140.

Blood, 7:15 p. m.: R. B. C., 1,580,000; Hb., 29 per cent.; pressure 145.

Blood at end of transfusion, 7:30 p. m.: R. B. C., 1,800,000; Hb., 36 per cent.; pressure, 142.

Blood, differential, 7:30 p. m.: Polymorphonuclears, 11.6 per cent. lymphocytes, 83.3 per cent.; large mononuclear, 0.3 per cent.; transitionals, 0.6 per cent.; mast cells, 0.3 per cent.; eosinophiles, 0.3 per cent.; myelocytes, 0.3 per cent.; microcytes, macrocytes. No nucleated red cells.

10:00 p. m., Blood pressure 142.

Later in the evening the patient lay in a flushed, warm lethargic condition, probably influenced somewhat by morphin given at operation. Much sweating. No jaundice by artificial light. Temperature, 102 F.

April 29: Patient this morning was very jaundiced. Stomach had not been retentive since operation. Expectorates green mucoid material from throat. No bleeding from gums. Temperature rose in afternoon to 104 F. Arm somewhat painful and swollen. Hand edematous. No pus in wounds. Spleen palpable. Urine contained urobilin, hemaglobin, some free blood and many casts. Blood pressure, 115.

After the first transfusion (wife's blood) the urine showed slight reddish discoloration and slight amount of urobilin, suggesting hemolysis, but this had nearly disappeared when the second transfusion (brother-in-law's blood) was undertaken. During the night after this second transfusion the urine changed to a marked bloody character and subsequently showed

a direct proportional relation with the jaundice, oppression, and other evidences of hemolysis. (Details regarding the metabolism and hemolytic features in the urine will be reported by Drs. Stengel and Edsall.)

April 30: Passed a poor night. Jaundice worse. Stomach still not retentive. Temperature still high. Arm condition the same. Mouth very dry, but no bleeding.

May 1: Was in a very low state. Blood pressure, 105. The patient sank rapidly and was removed to his home in Trenton, where he died May 3, 1907.

The patient's temperature during the first ten days he was in the hospital was usually slightly above normal, reaching on one occasion 101 F. The pulse was always higher than normal, ranging from 80 to 120. The respirations ran between 22 and 32. During the last week the patient was in the hospital the temperature, pulse and respirations were higher, the temperature reaching 104 F., the pulse 125 and the respirations 39 and never coming down to normal. An effort was made to determine if the blood serum of the patient was hemolytic to normal red blood corpuscles.

Sterile blood was collected from the patient eighteen and thirty-six hours after second transfusion. The blood was allowed to coagulate and the serum used for the following tests: A 5 per cent. suspension of washed normal red blood corpuscles in 0.85 sodium chlorid solution was prepared. The serum of the patient was mixed with the suspension of red corpuscles in varying proportions. The mixture of serum and corpuscles was kept in an incubator at 37 C. (98.6 F.) for two hours. On removal no evidence of hemolysis was observed. The result was also negative after the incubated mixture had been kept on ice for twenty-four hours. The mixture when prepared as above and an activating substance supplied by adding normal serum, also failed to show hemolysis.

Throughout the patient's stay in the hospital a number of examinations of the blood were made which were of considerable interest. The type, as judged from the study of the stained specimen, was that of a secondary anemia. A remarkable feature was the fact that on only a few occasions were nucleated reds found and then only in very small numbers. These were all normoblasts, and not more than ten or twelve were seen altogether in the many slides examined. Poikilocytosis and polychromatophilia were constant. The leucocytes were normal in appearance.

A study of the table of the various leucocyte counts shows that the absolute number of lymphocytes was practically always higher than that of the neutrophiles, but was never higher than 2,289. The lymphocytes ran at a more regular figure than did the neutrophiles, which

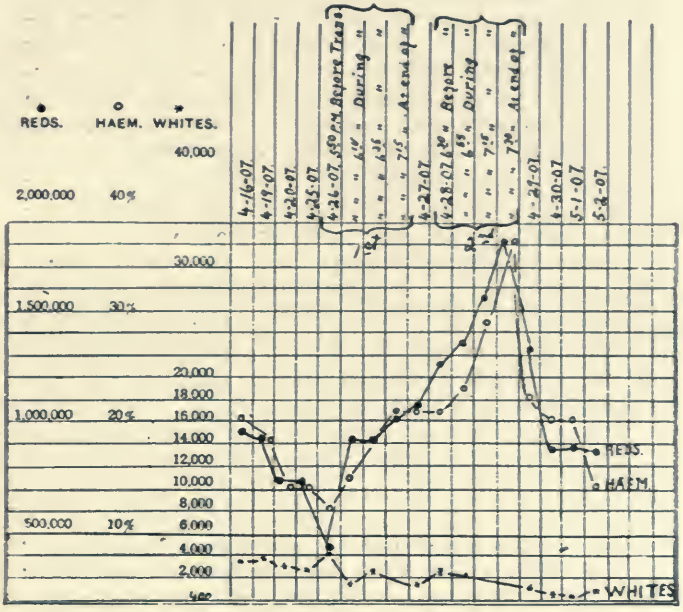

Chart of the patient's blood.

were affected by both transfusions, dropping much below the normal figures. The eosinophiles were normal in number. Very few basophiles were found. Only one myelocyte was seen.

The chart here given demonstrates diagramatically the extreme grade of the anemia, the improvement in the hemoglobin percentage and in the red cell count, following the transfusions, and the rapid drop succeeding the second.

The color index, as can be easily seen, was usually above normal. There was a constant leucopenia, the total count per c.m. dropping May 1, the day before the patient left the hospital and three days after the second transfusion of 400 per c.m. Determinations were made of the hemoglobin, red and white cells before and during

both transfusions, and an effort was made in this way to estimate approximately the amount of transfused blood.

Twelve hours after the second transfusion it became evident that a rapidly increasing hemolysis had developed and this persisted until death. Jaundice set in promptly and deepened until it was intense; the patient's temperature, which was a little higher after the first transfusion than previously, became still more elevated, fluctuating between 100 F. and 104 F. and the rates of the pulse and respiration became correspondingly higher. The urine quickly became blood red and, though at times a little lighter colored, did not change materially to the end. The patient was intensely restless and irritable, all food taken by the mouth and even water was promptly rejected, and the bowel proved equally unretentive. Petechial hemorrhages appeared in various places and there was active and increasing hemorrhage from the mouth and nose. The liver increased in size and was somewhat tender to pressure. The spleen was recorded as being palpable.

There was no doubt of the nature of the condition, which was typically that of intense hemolysis, and it is mainly on account of this event that the case is worthy of publication. It seems to have been too implicitly believed that the transfusion of human blood into another human being is incapable, apart from such accidents as embolism, thrombosis or infection, of causing untoward results and especially that hemolysis will not take place. It is true that Ehrlich and others who have investigated hemolysis in animals have called attention to the fact that iso hemolysins occasionally appear, and Eisenberg has reported some investigations of this question in its relations to the blood of various diseases. Nevertheless there has been no serious doubt of the innocuousness of introducing blood from normal individuals into other normal persons, or those suffering from hemorrhage or disease, providing the technical accidents could be obviated by some such refined procedure as that reported by Crile. The fallacy of this belief is illustrated in the case herewith reported.

When we come to consider the possible cause of the intense hemolysis which destroyed our patient our attention is at once called to the fact that the first transfusion was followed by but a suggestion of hemolysis

TABLE SHOWING ABSOLUTE AND RELATIVE DIFFERENTIAL LEUCOCYTE COUNTS AND TOTAL LEUCOCYTE COUNT PER C.MM. OF BLOOD.

	4-16-07.	4-19-07.	4-25-07.	Before trans. 5:30 p. m. 4-26-07.	During trans. 6:15 p. m.	During trans. 6:35 p. m.	At end of trans. 7:15.	Before trans. 6:30 p. m. 4-28-07	At end of trans. 7:30.	4-29-07.	4-30-07.	5-1-07.
Neutrophiles	1494	1404	767	1722	504	×	....	×	....	570	175	210
Per cent.....	41.5	36.	29.5	41.	28.		44.		11.6	45.3	35.	52.5
L. Mononuc.	108	156	0	21	0	×	....	×	....	20	5	0
Per cent.....	3.	4.	0.	.5	0.		2.5		.3	1.6	1.	0.
Transit.	36	390	52	105	54	×	....	×	....	45	15	4
Per cent.....	1.	10.	2.	2.5	3.		3.		.6	3.6	3.	1.
Lymph.	1872	1911	1742	2289	1224	×	....	×	....	604	305	184
Per cent.....	52.	49.	67.	54.5	68.		49.		86.3	48.	61.	46.
Eosinoph.	90	39	39	63	18	×	....	×	....	16	0	2
Per cent.....	2.5	1.	1.5	1.5	1.		1.5		.3	1.3	0.	.5
Basoph.	0	0	0	0	0	×	....	×	....	7	0	0
Per cent.....	0.	0.	0.	0.	0.		0.		.3	.6	0.	0.
Myelocytes	0	0	0	0	0	×	....	×	....	0	0	0
Per cent.....	0.	0.	0.	0.	0.		0.		.3	0.	0.	0.
Count per c.mm.	3600	3900	2600	4200	1800	2100	....	2450	....	1260	500	400

Blood count of patient.

(evident in some discoloration of the urine and by the presence of a small quantity of urobilin, neither being positively attributable to the transfusion rather than to the patient's disease), and in the second place to the prompt appearance of marked hemolysis after the second transfusion. One receives the impression that the first transfusion may in some manner have caused the formation of hemolytic bodies which after the second transfusion found abundance of vulnerable corpuscles for their operation. We do not feel that there are sufficient data to warrant our expressing any opinion as to the rôle ascribable to second transfusions or to transfusions of blood from more than one individual. It may be recalled, however, that Crile has reported one case of successive transfusions of blood from two brothers of the patient without any hemolysis being noted. Some experiments in animals and studies of sera and corpuscles of man undertaken in this laboratory since the occurrence of our case have thus far failed to throw any light on the matter.

We can not omit mentioning the injection of a dose of diphtheria antitoxin some days previous to the first transfusion, especially as the studies of Theobald Smith, Rosenau and Anderson and others have indicated possibilities of danger in secondary injections. These studies, however, have shown no hemolytic results and have in addition been concerned with secondary injections of the same heterologous serum and not with homologous blood or serum after foreign serum.

The published cases of Crile and others indicate the probable safety of the operation of transfusion in post-hemorrhagic cases, but the results in our own indicate the danger in certain pathologic conditions and the necessity of caution until we are in possession of greater knowledge. At the same time the possibility of benefit may justify transfusion in apparently desperate cases.

Autopsy Notes.—The autopsy was performed by Dr. Pepper, at the home of the patient in Trenton, N. J., on the afternoon of May 4, 1907, the body having been injected with some preservative fluid containing formalin by the undertaker some hours previously. Body of a well-nourished male, extremely anemic in appearance, and exhibiting a fairly intense jaundiced hue of the skin. Subcutaneous fat a bright lemon color. Muscles of the abdominal wall very pale. Numerous, easily broken down but fairly extensive, pleural adhesions throughout the left pleura; no adhesions in the right side. The heart was

large, both auricles being very much dilated; the heart was empty and had been evidently injected with formalin, as the walls of the auricles felt like leather; the right ventricle was dilated. All the valves were normal.

Both lungs showed small subpleural hemorrhages and on section both were riddled with numerous dark-red firm areas, between which the lung tissue was apparently normal and crepitant. The lungs were very dry and these small areas or nodules were undoubtedly hemorrhagic and were so firm that they could be palpated throughout the whole lung. Most of them were about the size of a split pea; a few seemed to have coalesced.

The spleen was normal in size and appearance, on section it was also normal in appearance. The liver was fairly large smooth, light in color, and on section showed no macroscopic evidence of necrosis; it appeared slightly fatty, but otherwise perfectly normal. The gall bladder contained a small amount of bile.

The left kidney was large, thick, fairly firm and rounded; there were a number of small subcapsular hemorrhages. The capsule stripped readily, leaving no trace of the hemorrhages on the kidney. Section of the kidney showed a cortex of normal width; there was no congestion. The parenchyma was clouded and granular in appearance. The right kidney showed exactly the same condition and in addition an area of hemorrhage in the parenchyma about a centimeter in length. The pancreas was normal. The right suprarenal was normal. The stomach contained a small amount of dark brown liquid. The mucous membrane was not ulcerated but was merely dotted here and there with a number of small reddish spots. There did not seem to be any break in the continuity of the mucous membrane at these points. The mesenteric lymph glands were normal in size and appearance. The intestines were not opened. The bone marrow from the middle of the shaft of the right tibia was normal in appearance.

Pathologic Diagnosis.—Severe anemia. Jaundice. Numerous small intrapulmonary hemorrhages. Dilatation of the heart. Acute parenchymatous nephritis with subcapsular ecchymoses.

Microscopic Examination of Tissues.—Lungs: Hemorrhagic extravasation into alveoli, congestion and edema. Number of large epithelial cells containing pigment (Hertzfehlerzellen). Kidneys: For most part the epithelium of the tubules presented normal characteristics. In some areas, chiefly in the convoluted tubules the epithelium was granular, the demarcation between cells obscure, and the nuclei invisible. The lumina of a number of these tubules were filled with granular débris; many others were filled with red blood corpuscles, more or less disintegrated. Glomeruli presented no unusual features. Proportion between interstitial and parenchymatous tissue was normal. In small scattered areas were found

bodies presenting the characteristics of emboli composed of bacteria, but unattended by any inflammatory reaction. Liver: Some deposit of pigment, probably blood pigment, in the liver cells. (No areas of necrosis.) Suprarenal: Moderate congestion. Pancreas, spleen and bone marrow normal.

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THE BACTERIOLOGY OF THE PUERPERAL UTERUS.

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The germ content of the uterus has been controversial ground for years. The question has been investigated by many since the time of Doederlein with the most varied results, to be explained, in our opinion, upon the ground of errors in technique. Probably the earliest investigator in this field was Myerhofer, who, in 1865, employed suction by means of a glass tube. He was always able to demonstrate cocci and bacilli if the case were febrile, but he did not find them in afebrile cases. Doederlein, in 1887, reported a series of 30 cases with normal temperature. In 27 of these the lochia was sterile, while in 3 bacilli were present, streptococci being identified once. He drew the conclusions from his study: (1) That in normal cases the uterine lochia is sterile; (2) that microörganisms are almost always present in severe cases of puerperal infection; (3) that infection is not always due to lack of care on the part of the physician. Von Ott and Czerniewski, in 1888, arrived at the same conclusions, but the latter held that the streptococcus might be present in the lochia of normal cases in rare instances without symptoms.

In contradistinction to the above, we wish to call attention to the statistics contributed by Stolz, who found streptococci in the vaginal secretion of three normal pregnant women, while in a series of women with abnormal vaginal secretion during pregnancy streptococci were present in several instances. In studying the puerperal uterus, he found that on the ninth day, in a series of 156

cases examined during labor, with aseptic precautions, there were 55 positive and 101 negative results, streptococci being found in 11 per cent. of the positive cases.

Neither the duration of the labor, the presence of laceration, the number of examinations during labor, or the operations performed to effect delivery seemed to alter the result. Retention of secundines did, however, increase the bacterial content. In 54 women who had not been examined in labor, and in whom the puerperium was normal, he found that in 10, cultures gave streptococci on the ninth day. In a series of over a dozen women in whom cultures were taken on the third, fourth, fifth, sixth, seventh, and eighth day, in order to determine the time of ascendancy of the germs, it was found that early in the puerperium there might be non-pathogenic organisms in the lochia with absence of any signs of infection; that the puerperium from the third day on did not differ in germ content from the later period (ninth day); that the content on the ninth day was less on the average than earlier. Therefore, he believes that in the latter days of the puerperium the uterus cleanses itself from organisms in a large proportion of cases. As his cases were not selected, there occurred a series of 18 in which, one or more days after the culture, there was a development of fever. In this febrile series, with the exception of 5 cases, there had been found a growth in culture before the appearance of the fever, and in half of the positive findings streptococci were demonstrated. In cases in which, on the earliest culture, streptococci were present, there cannot be a question of having caused the fever by infection at the time of culture, according to the opinion of the author. Doederlein and Franz also conclude that in cases of streptococcic vaginal lochia the taking of a culture is not a harmless experiment, but that the infection is sometimes to be laid at the door of the culture. Doederlein declared that the initial period of freedom from symptoms before the taking of the culture could be explained by the incubation of the organisms, but Stolz denies this. However, he does not deny that the presence of streptococci in the cavum uteri may be the cause of the development of fever, without other reason than the trauma necessitated by the culture. He makes the point that the danger is much less if the culture be taken late in the puerperium, and states that he has never seen any difficulty if he has not cultured in the early days. In studying the examination of the lochia and vaginal secretions on the fourth day, he used a series of 75 cases for the uterine lochia and 65 cases for the vaginal secretion. He found that the uterine lochia was positive in 80 per cent. and that in 36.9 per cent. streptococci were present, while the vaginal secretion in 27 per cent. gave streptococci. Both these series were entirely normal cases. He concludes as follows in regard to the findings of the fourth day: (1) That the vagina always contains organisms,

and the uterus does so in a large proportion of cases; (2) that the presence of streptococci in either situation is possible without symptoms; (3) that the uterus contains fewer germs in unexamined cases than in those examined, but streptococci are to be found in both uterus and vagina in some unexamined cases; (4) that examination with sterile hands during labor has no apparent influence upon the germ content; (5) that aseptic glove operations have no distinct influence; (6) that no actual increase in germ content appears to be dependent upon the duration of labor, but that streptococci are relatively increased.

Finally, we would quote rather extensively from the paper of Little, which appeared while this paper was in preparation. Little came to the following conclusions: (1) Cultures taken immediately after labor are sterile in 92 per cent., or in 96 per cent. if gonorrheal cases be included; bacteria may be present exceptionally, even in the absence of vaginal examinations during labor, and the puerperium may be normal; the bactericidal power of the blood serum may be the cause of a certain number of negative results. (In 10 of his 50 cases it was necessary to introduce the hand into the uterus, and it is impossible to believe that no organisms were carried into the cavity. Of course, the downward flow after labor may also be a reason for negative findings in these cases.) Upon the third day he found sterility present in 62.5 per cent. of 40 afebrile cases, as compared with 40 per cent. sterility in 10 cases in which the temperature reached 100.6° or higher. (2) That the inclusion of cases in which gonococci were demonstrated will increase these averages to 85 per cent. and 50 per cent., respectively. (The author calls attention to the fact that he has included in his febrile series cases in which the temperature rise was obviously not due to any intrauterine cause, and the lochia, being sterile in these cases, or at least in some of them, a decrease in the percentage of the negative results is caused in the afebrile series and of the positive results in the febrile.) (3) That the finding of bacteria in the cervical canal at the completion of labor does not necessarily imply their presence later in the puerperium. (In one instance, in which there was a flaw in the tube, the author found a positive result in the first culture, but a negative one the third day, and admits that this was due to contamination with cervical secretion.)

Conclusions based on the cultures made on the seventh day postpartum were as follows: (1) Absolute sterility in 50 per cent. of the afebrile cases, as compared with 20 per cent. of the febrile. (2) Inclusion of gonococci makes these averages 80 per cent. and 50 per cent., respectively. (3) Bacterial findings differ more markedly according as the case is febrile or afebrile than by clinical characteristics. (In 5 of this last series positive results were obtained in cases which had been sterile at both previous cultures.

From 3 of these 5 cases a diplococcus was obtained which resembled, and was probably identical with, the diplococcoid forms so frequently observed in the cervix and vagina, and the author thinks it may have been due to contamination, since he admits that it is impossible to get an absolutely trustworthy result by his method at this stage. In the 2 remaining cases the organisms were gonococci.) It is to be noted that in 20 cases showing bacteria on the seventh day of the puerperium the gonococcus was the organism in 12, and, further, that only 2 of the 10 febrile cases had sterile lochia on the seventh day; the streptococcus found in one instance on the third day had disappeared on the seventh day. (4) The uterus has the power of self-cleansing, and so the presence of organisms on any day of the puerperium does not mean their continued presence, and the author believes that the results given by Stolz, who found fewer organisms late in the puerperium that an at earlier period, are to be thus explained.

The gonococcal findings in his complete series of cases were demonstrated in 2.5 per cent., 25 per cent., and 30 per cent., respectively, on the first, third, and seventh days. His general conclusions as regards the effect of interference during labor are as follows: (1) Laceration of the cervix and the perineum have no bearing upon the germ content of the lochia; and (2) vaginal examinations have but slight effect (4 out of his 6 afebrile cases not examined during labor showed bacteria in the lochia, Bacillus coli communis being found once and the gonococcus three times; while 1 afebrile case was examined six times in labor and no organisms were ever found in the lochia.)

Operations to effect delivery resulted in this series as follows: In his febrile series there was one woman who had been delivered by forced accouchement who showed gonococci in the lochia; while a second one, upon whom version had been performed, was the case of streptococcic infection. There were 8 others operated upon in the series, and of them, 3 were positive (version, low forceps, and induced labor, of each, 1 case); 3 other cases showed gonococci (2 low forceps and 1 bag induction); of 2 cases, 1 gave on the third day a variety of Bacillus dysenteriæ, while the other gave Micrococcus aureus and Bacillus pseudodiphtheriæ on the seventh day (the first was a midforceps operation, and the latter a case of version). The former of these last 2 is considered to have been a contamination at the time of culture.

General Conclusions.—In 50 cases studied by Little the uterus was found to be sterile in 92 per cent., 50 per cent., and 44 per cent. on all three days. If gonococci be included, the above averages are 96 per cent., 72 per cent., and 67 per cent. The puerperium is to be noted as normal in 40 and febrile in 10 cases of this series. In the normal cases there was absolute sterility in 92.5 per

cent., 62.5 per cent., and 50 per cent., as compared with the febrile series, in which 90 per cent., 40 per cent., and 20 per cent. were found to be sterile. Including the gonococcic cases, these latter figures would be 95 per cent., 85 per cent., and 70 per cent., and 100 per cent., 50 per cent., and 50 per cent. The author considered his results as positive if bacteria were found only in smear preparations or only in cultures, as well as when present in both. It is likely, therefore, that a certain number of positive results were due to contamination and that the uterus is really sterile in a larger number of cases than these percentages would indicate. Streptococcus was present but once—a febrile case, on the third day; absent, however, on the first and seventh days. Finally, for purposes of completeness, the following schedule of results is worth including, this being taken from Little's article:

						Per cent.
Von Ott	in	9	cases	found lochia sterile	in	100
Czerniewski	"	57	"	"	"	98
Doederlein	"	30	"	"	"	90
Doederlein	"	250	"	"	"	83
Vogel	"	15	"	"	"	80
Franque	"	10	"	"	"	80
Kronig	"	63	"	"	"	79
Thomen	"	9	"	"	"	66
Walthard	"	20	"	"	"	65
Stahler	"	55	"	"	"	64
Franz	"	10	"	"	"	0
Burckhardt	"	14	"	"	"	7
Stahler	"	19	"	"	"	16
Wormser	"	100	"	"	"	16
Stolz on the fourth day				"	"	19.6
Vogel	in	15	"	"	"	34
Schauenstein	"	100	"	"	"	36
Stolz on the ninth day				"	"	65

The importance of definite and certain knowledge on this whole question cannot be overestimated, because of its bearing upon the general question of puerperal septic infection and more particularly upon the frequency of auto-infection. If some investigators are correct in their findings of pathogenic organisms in a great proportion of normal cases after delivery, it is very evident that the value of this method as an aid to diagnosis is nothing; and, moreover, that auto-infection is one of the most common causes of puerperal sepsis, instead of being, as is the general opinion at present, one of the most rare happenings. Even if the extreme position of Stolz with regard to the frequency of positive findings be found untenable, proof that the ascent of organisms after the first few days into the cavity of the uterus is a usual or even a moderately frequent event will render useless any further consideration of this matter, since the import of positive findings in any given case will be beyond determination.

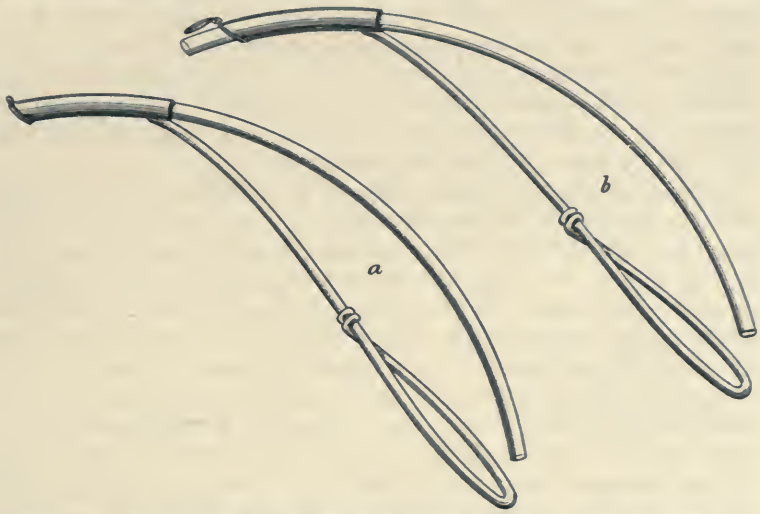
The probability that streptococci would be satisfied to act as saprophytes within the uterine cavity after delivery being to us a

matter of grave doubt, together with the fact that in normal cases used for demonstration of the method before the class, the laboratory reported pure streptococcic cultures, turned our attention forcibly to the question of the technique employed in the clinic for the collection of the lochia. It being a matter of common knowledge that the lower vagina in most cases is the seat of bacterial activity, and that in a goodly number the same condition prevails in the cervix and upper portion of the vagina, we felt that the method employed, while as careful as any then known to us, demanded modification if it was to be worth doing at all. At this time the ordinary Doederlein tube was employed, sterilized by boiling, and its introduction was performed with the usual aseptic precautions. Realizing that introduction without contamination from the cervix was certainly impossible, if done several days after delivery, and that it was improbable at any time, it was assumed that a positive culture obtained in a normal case simply meant that there was bacterial growth somewhere below the internal os uteri; while those in which this method gave negative results simply gave evidence of both a sterile endometrium and an absence of contamination in the vagina and cervix. Our attention, therefore, was directed toward a modification of the technique which would render possible the collection of uterine lochia without the risk of contamination from the lower canal.

After some experimentation it was decided that there had been several weak points in the technique which we had been in the habit of using, and the method upon which the present findings are based was evolved. Its most important element (see figure) is the use of a slightly curved cervical speculum, the distal end being closed by a hinged cap. A handle of convenient length is attached to render its introduction more easy. We do not claim originality for this idea, as, although at the time the fact was unknown to us, various forms of protective specula have been employed by others. We believe that our instrument will be found to be the simplest as well as the most trustworthy. To enable us to use the speculum, we discarded the typical Doederlein tube and adopted one with a uniform curve and of small caliber, easily obtained from any manufacturer.

The method in detail is as follows: The patient is placed in the lithotomy position and the external genitalia are carefully cleansed with tincture of green soap, water, and mercuric bichloride. A Sim's speculum is inserted, the cervix is grasped by a double tenaculum, and its vaginal portion cleansed with cotton and bichloride solution. The metal tube, with cap closed, is then inserted into the uterine cavity. This tube is sterilized by pressure and wrapped in two coverings, in order that the operator may remove it from the inner one without contaminating his hands. The glass tube is placed within the metal one before sterilization and is not removed

from the latter until the culture has been completed. The cap is opened by pushing the glass tube into the cavity of the uterus, a piece of sterile rubber tubing is attached to the proximal end of the glass tube, and as much lochia as possible is sucked into the glass tube by means of a hard rubber syringe. The glass tube is then withdrawn until its distal extremity is engaged within the metal tube and then both are simultaneously removed from the patient. The ends of the glass tube are sealed with wax and the tube is sent to the laboratory. The points of paramount importance, in our opinion, are the presence of the cap upon the distal end of the sheath tube and the sterilization of the tubes by pressure instead of by boiling. We also feel that the simultaneous introduction of both tubes is very important and that their simultaneous removal is but little less important.



Curved cervical speculum for taking intra-uterine cultures: *a*, tube with cap closed ready for insertion; *b*, after insertion, showing the open cap and the projected inner tube for collecting the secretions.

As important as the collection of the uterine lochia is the technique employed in the laboratory. The danger of outside contamination, especially from the tube itself, must be recognized. For this reason the tube was washed with a bichloride solution, the ends broken off, and the contents placed in a sterile Petri-dish, cultures being made from this upon the following media: (1) Agar-agar stroke plates; (2) glycerin agar stroke plates; (3) serum agar stroke plates; (4) bouillon tubes; (5) litmus milk tubes for anaërobic cultures by Wright's method; (6) glucose agar for anaërobic cultures. In addition, cover slip preparations were made, two being stained with Löffler's stain and two with Gram's stain.

At times this routine method was deviated from because of the

lack of serum agar. This medium was used for the demonstration of the gonococcus. It has been our experience in studying the gonococcus that in the secretions in which the organism could not be demonstrated microscoically no growths occurred upon the special medium used for its cultivation, and that often it could be found in the stained specimen without growth upon the artificial medium, owing to the overgrowth of a mixed culture. For this reason we do not believe that our results as to the presence of the gonococcus are vitiated by the occasional omission of this form of medium. In this series the presence of the gonococcus was remarkably infrequent. We believe this to be due to the technique, which eliminated cervical contamination and proved conclusively to our minds an already formed opinion that gonorrheal endometritis is a much rarer condition than is generally thought. We do believe, however, that this organism is present and persists for a long time in the cervix, often acting as the forerunner of septic infection. Two of the cases in this series showed the presence of the gonococcus; the streptococcus was also found. The frequency with which the gonococcus has been found by other observers we believe to be due to cervical contamination.

In determining the qualifications of a normal case, we have differed from some of the other investigators in this field. We have taken no note of lacerations of either the cervix or the perineum, the duration of the labor, the number of vaginal examinations, the parity of the woman, or the presence of evanescent temperature, unless the latter has been shown clearly to be dependent upon pathological conditions in the generative tract. In other words, we have classified a case as normal if there has been no instrumental interference in labor, if the hand has not been introduced into the uterus, if gauze has not been introduced into the uterus or vagina, and if no douches have been given, if there has been no retention of considerable portions of the placenta or membranes, and if no alteration of the odor or appearance of the lochia has occurred. In short, we use the term normal as descriptive of the most common parturient state. We believe that by so doing we are likely to reach more valuable conclusions than by more closely restricting ourselves in our selection of cases for study, since the important fact for determination is the bacterial content of the uterus in the type of case most usually met with in actual practice.

With regard to the value of the intra-uterine culture as an aid to diagnosis, we feel that it is a method which should not be neglected in the routine study of infected cases, at least in institutions having the advantage of well equipped laboratories of bacteriology. The technique as regards asepsis is more exacting than that required for successful blood culture, since the vagina and cervix, with their bacterial flora, must be traversed in obtaining the intra-uterine culture. If a suitable technique be followed, we are confident that

the results, as a whole, will well repay the time spent in the procedure; but we do not desire to be understood as affirming our belief that the method is, as it was formerly thought, a sovereign means of diagnosticating the presence or absence of infection in all cases. We have, for instance, four records not included in this paper, in which in cases afterward proved to be septic, the intra-uterine findings were negative. That such an occurrence will take place as a matter of course, more or less often in a series of examinations of septic cases, must be evident to anyone who will consider the varied manifestations of septic processes during the puerperium. On the other hand, the relative rarity of this negative finding in the presence of septic infection offers valuable evidence as to the general utility of the method.

Taken in connection with the studies upon the bacteriology of the blood which have been made in our clinic, we feel justified in making the following statements: (1) If both blood and intra-uterine cultures are negative, the temperature is due to some intercurrent condition; (2) if the intra-uterine culture is positive, but the blood culture is negative, we consider the infection to be still local in its manifestations; and (3) if the intra-uterine culture is negative but the blood culture is positive—a very unusual condition—we are justified by our general conclusions in considering that the case is one of general infection, the local endometrial condition having been either sterile from the first or having become so gradually after the general infection developed.

It will be noted that we have classified 6 cases as normal which have given cultures in the lochia, and that we have explained the growth in them by errors in technique. We feel that this demands a fuller explanation in order that we may be entirely intelligible. It is necessary that it be clearly understood in the first place that these 6 cases do not include by any means all the cases in which there was a departure from the method described in the first part of this paper. In each instance any such departure was noted at the time the culture was made, and these are the only cases associated with technical error in which a growth was obtained. In the greater number of cases, however, in which accidental departures from the technique occurred, without cultural results, the variation was trivial, being simply noted for reasons of scientific accuracy. In the 6 cases mentioned the variations in the method were of a nature to give expectation of the probability of vaginal or cervical contamination. It is also quite true that the same, or as grave, errors were made in a few cases which did not show positive results in the culture; and this emphasizes our claim that, while a technique as rigid as ours may not aways be necessary to obtain satisfactory results in each individual case, still, if error has been made in technique, it is manifestly unfair to consider positive findings as evidence of intra-uterine infection.

NORMAL CASES—CULTURES TAKEN IN THE FIRST, SECOND, AND THIRD PERIODS.

Number.	Case number.	First period: First to third day.			Second period: Fourth to seventh day.			Third period: Eighth to thirteenth day.			Remarks.
		Aërobic.	Anaërobic.	Microscopic.	Aërobic.	Anaërobic.	Microscopic.	Aërobic.	Anaërobic.	Microscopic.	
1	1	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
2	2	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
3	5	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal except for one temperature of 102° on the sixth day (a few hours after culture) falling at once to normal.
4	7	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
5	25	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Student introduced hand into vagina to deliver placenta; otherwise a normal case. On third culture three attempts made before tube passed.
6	56	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
7	57	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
8	58	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
9	61	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
10	62	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Dead foetus delivered at home: otherwise normal.
	34	See error in technique.			Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Labor normal. Error made at first culture—whereby vaginal secretion obtained.

NORMAL CASES—CULTURES TAKEN IN THE FIRST AND SECOND PERIODS.

11	13	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal. Febrile temp. once because of congested breasts.
12	27	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal. One febrile temp.
13	28	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal.
14	41	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal.
15	42	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal.
16	43	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal.
17	65	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal.
18	6	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Normal.

Normal Cases—Cultures Taken, in the First and Third Periods.

19	9	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.
20	14	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.
21	15	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.
22	22	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.
23	59	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.
24	69	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Steri e.	Negative.	Normal.
25	70	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.
	51	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.
	20	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Normal.

Normal Cases—Cultures Taken in the First Period Only.

26	19	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Normal.
27	60	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Normal. Temperature febrile second and third day.
28	29	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Normal.
29	31	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Normal.
30	44	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Normal.
31	38	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Abortion at 6 months. Breech delivered—Wiegand.
32	39	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Normal.
33	64	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Prolapse of cord (no version). Otherwise normal.
34	4	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Normal.

Normal Cases—Cultures Taken in the Second and Third Periods.

35	10	....	....	....	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Tuberculosis. Irregular febrile temperature.
36	16	....	....	....	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Normal.
	55	....	....	....	Sterile.	Sterile.	Negative.	See error in technique.			Normal.

NORMAL CASES—CULTURES TAKEN IN THE SECOND PERIOD ONLY.

Number.	Case number.	First period: First to third day.			Second period: Fourth to seventh day.			Third period: Eighth to thirteenth day.			Remarks.
		Aërobic.	Anaërobic.	Microscopic.	Aërobic.	Anaërobic.	Microscopic.	Aërobic.	Anaërobic.	Microscopic.	
37	47	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Normal.
38	48	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Normal.
39	49	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Normal.
40	53	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Slight phlegmasia.
41	37	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Normal. Temperature once 101.2°
42	52	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Normal.
43	66	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Normal.

NORMAL CASES—ERRORS IN TECHNIQUE WITH POSITIVE FINDINGS.

44	34	Mic. pyog. aur., Bac. xeroides, Mic. magnus.	No obligatory anaërobe.	Gram positive micrococci and bacilli.	See normal cases: Cultures taken in first, second, and third periods.						The first culture was taken as a demonstration. The tube became blocked and was accidentally withdrawn and vaginal secretion inspirated.
45	20	See normal cases: Cultures taken in first and third periods.			....	....	....	Mic. pyog. alb.	No obligatory anaërobe.	Gram positive micrococci.	On last culture, tube was introduced without speculum. This growth considered vaginal or cervical contamination.
46	51	See normal cases: Cultures taken in first and third periods.			....	....	....	Mic. pyog. aur.	No obligatory anaërobe.	Gram positive micrococci.	The last culture was taken by resident physician and mistake in technique was made.
47	24	Streptococcus, Bac. coli com.	No obligatory anaërobe.	Gram positive micrococci. Gram negative bacilli.	....	....	....	....	....	....	Attempt to pass tube failing, it was withdrawn and passed by the aid of vaginal touch. Case normal clinically.
48	54	....	....	....	Mic. pyog. alb.	No obligatory anaërobe.	Gram positive micrococci.	....	....	....	Tube boiled and passed without speculum.
49	55	....	....	....	....	....	....	Mic. pyog. alb. bac.	No obligatory anaërobe.	Gram positive micrococci.	Tube passed without speculum; cervix not cleansed; cap opened in vagina.

ABNORMAL CASES OBSTETRICALLY—FORCEPS.

50	45	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Low Sawyer forceps.
51	18	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	....	....	....	Simpson forceps. Slight fever on third day.
52	63	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Simpson forceps. Bad cervical tear. Much clotted blood in vagina at first examination. Vaginal discharge foul. Intra-uterine douche several times before last culture. Leukocytes, 14,000. Blood culture, negative
53	40	Sterile.	Sterile.	Negative.	....	....	....	....	....	....	Low forceps. Temperature never febrile.
54	50	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Simpson forceps. Temperature never febrile.

ABNORMAL CASES OBSTETRICALLY—DOUCHES; MANUAL REMOVAL OF THE PLACENTA; VERSION; INTRA-UTERINE PACK

55	23	Sterile.	Sterile.	Negative.	....	....	....	Sterile.	Sterile.	Negative.	Temperature never febrile. Intra-uterine douche before cultures.
56	17	Mic. pyog. alb.	No obligatory anaërobe.	Gram positive micrococci.	....	....	....	Sterile.	Sterile.	Negative.	Adherent placenta. Manual removal. Normal temperature.
57	35	....	....	....	Sterile.	Sterile.	Negative.	Sterile.	Sterile.	Negative.	Placenta previa with version. Gauze pack. Irregular fever. Lochia foul. Complete tear. Child macerated. Blood culture negative.
58	46	....	....	....	Sterile.	Sterile.	Negative.	....	....	....	Intra-uterine pack.

ABNORMAL CASES OBSTETRICALLY—CRANIOTOMY.

59	30	Mic. pyog. alb., Bact. coli com.	No obligatory anaërobe.	Gram positive micrococci. Gram negative bacilli.	Mic. pyog. alb. Bact. coli com.	No obligatory anaërobe.	Gram positive micrococci. Gram negative bacilli.	....	....	....	Never febrile. Craniotomy. Fetid discharge. Probable muscular rupture of uterine wall.
60	11	....	....	..	Mic. magnus. Mic. pyog. aur.	No obligatory anaërobe.	Gram positive micrococci.	....	....	....	Craniotomy for hydrocephalus Normal temperature.

Intercurrent Disease—Typhoid Fever

Number	Case number.	First period: First to third day.			Second period: Fourth to seventh day.			Third period: Eighth to thirteenth day.			Remarks.
		Aërobic.	Anaërobic.	Microscopic.	Aërobic.	Anaërobic.	Microscopic.	Aërobic.	Anaërobic.	Microscopic.	
61	33	....	....	....	....	....	....	Sterile.	Sterile.	Negative.	Douche before admission. Blood culture. Bac. typhosus.

Gonorhœal Cases.

62	12	Mic. pyog. aur.	No obligatory anaërobe.	Gram positive micrococci. Gonococci.	Mic. pyog. aur.	No obligatory anaërobe.	Gram positive micrococci. Gonococci.	....	....	....	Child developed ophthalmia neonatorum. Never febrile.
63	26	Sterile.	Sterile.	Gonococci.	....	....	....	Sterile.	Sterile.	Gonococci.	Douche before second culture. Febrile after first culture. Diagnosis: Gonorrheal rheumatism and breast abscess.
64	67	Streptococcus.	No obligatory anaërobe.	Gram positive micrococci. Gonococci.	Sterile.	Sterile.	Negative.	....	....	....	Normal temperature.

Septic Cases.

65	3	Sterile.	Sterile.	Negative.	Streptococci	No obligatory anaërobe.	Gram positive micrococci.	....	....	....	Blood culture showed streptococcus pyogenes. Febrile third to fourteenth day. Breast congested. Many intra-uterine douches.
66	68	Streptococcus.	No obligatory anaërobe.	Gram positive micrococci. Gonococci.	Streptococci	No obligatory anaërobe.	Gram positive micrococci. Gonococci.	....	....	....	Febrile 3 days. Manual extraction placenta. Purulent cervical discharge. Diagnosis puerperal endometritis.
67	21	....	....	....	....	....	....	Streptococcus.	....	Gram positive micrococci.	Blood culture: Steptococcus pyogenes.

To consider these 6 cases from the standpoint of actual the error occurring in each case:

Case XXXIV.—The first culture showed Micrococcus aureus and magnus and Bacillus xeroides. The case was used for demonstration, the tube accidentally slipping, whereby vaginal secretion was inspirated.

Case XX.—First culture sterile; second culture gave Micrococcus albus. Here the variation consisted in the omission of the Sim's speculum in the introduction of the tube, it being guided into the cervix by the finger in the vagina.

Case LI.—In this case the first culture was sterile, while the second, taken by an assistant, showed a growth, Micrococcus aureus. In both instances the variation in technique was identical, the vaginal speculum being omitted. From our knowledge of the ease of contamination, we consider that this second culture was contaminated by lack of care upon the part of a man inexperienced in the method. We admit that this contention is not proved.

Case XXIV.—But one culture was made, and this gave the streptococcus and the colon bacillus. In this instance the Sim's speculum prevented sufficient depression of the tube to enable it to pass, so the former was discarded and the tube was passed by guidance of the finger. During the short time elapsing between the introductions, the tubes were both placed in the instrument tray, which was an additional source of possible infection.

Case LIV.—Tube was introduced by guidance of a finger in the vagina. In addition, the tube was sterilized by boiling instead of by pressure.

Case LV.—Tube was introduced, as in the last case, and, in addition, the cap of the metal tube opened while it was in the vagina during the introduction.

It is to be noticed that the omission of the Sim's speculum was noted in each instance in which in a normal case a growth was recorded. In two instances there were other factors present which would have been sufficient to cause contamination—in one case the protective cup was open during introduction, while in the other both tubes lay for several minutes in an instrument tray the sterility of which during that period must be considered doubtful.

Because of difficulties inherent to the work it was not possible, and, indeed, it did not seem desirable, to culture each case upon the same day of the puerperium, so we have divided the cultures into three periods. We have further divided the whole list of cases under various headings, as follows:

A. Clinically normal cases:

1. Cultures during first period (first to third day), 34 in number; all sterile.
2. Cultures during second period (fourth to seventh day), 29 in number; all sterile.

3. Cultures during the third period (eighth to thirteenth day), 18 in number; all sterile.

B. Clinically normal cases with errors in technique and positive results:

1. Cultures during first period, 2 in number.
2. Cultures during second period, 1 in number.
3. Cultures during third period, 3 in number.

(All of these cases, with one exception, in which but one culture was taken, showed negative results from other cultures made without error.)

C. Clinically abnormal cases:

(*a*) Forceps (in excavation or at outlet), 5 cases.

1. Cultures during first period, 4 in number; all sterile.
2. Cultures during second period, 3 in number; all sterile.
3. Cultures during third period, 1 in number; all sterile.

(*b*) Douches (intra-uterine), 1 case:

1. Cultures during first period, 1 in number; sterile.
2. Cultures during third period, 1 in number; sterile.

(*c*) Manual removal of placenta, 1 case.

1. Cultures during first period, 1 in number; growth.
2. Cultures during third period, 1 in number; sterile.

(*d*) Craniotomy, 2 cases:

1. Cultures during first period, 1 in number; growth.
2. Cultures during second period, 2 in number; growth.

(*e*) Version for placenta prævia (macerated fœtus):

1. Cultures during second period, 1 in number; sterile.
2. Cultures during third period, 1 in number; sterile.

(*f*) Uterine packing:

1. Cultures during second period, 1 in number; sterile.

D. Intercurrent disease:

Typhoid fever (blood positive).

1. Cultures in third period, 1 in number; sterile.

E. Gonorrhœa:

1. Cultures during first period, 3 in number; all positive.
2. Cultures during second period, 2 in number; 1 positive.
3. Cultures during third period, 1 in number; positive.

One case, positive in the first and third periods, was unassociated with other organisms. In this case blood examinations were negative, but a mammary abscess and gonorrhœal rheumatism were complications.

The second case, positive in the first and second periods, was associated with Micrococcus aureus in both cultures; while the third case, positive at the first culture and associated with streptococci, was negative in the second period and also sterile at this time.

F. Septic cases (3):

1. Cultures during first period, 2 in number; positive.
2. Cultures during second period, 2 in number; positive.
3. Cultures during third period, 1 in number; positive.

(Cultures not taken of third case during first or second period.) Blood cultures were positive in 2 of the above cases, and were not taken in the third case.

GENERAL CONCLUSIONS.

1. The uterine lochia is sterile in normal cases throughout the puerperium.
2. Streptococci are never present within the cavum uteri without causing symptoms.
3. In a few instances non-pathogenic germs may be found in cultures in afebrile cases, but there is every reason to believe that their presence is really the result either of contamination during the extraction of the lochia or of their introduction during obstetric manipulation.
4. Ascendance of the gonococcus is an event of comparative rarity, though the frequency of this organism would of itself give reason to expect otherwise.
5. Infection of the endometrium is an ever present danger in culturing within a few days of delivery.
6. A study of the bacterial content of the puerperal uterus is of great importance as a subsidiary means of diagnosing septic infection following delivery.
7. As nearly as may be, a technique should be adopted which will prevent contamination during the removal of the lochia in order to avoid a vitiated result.

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THE BACTERICIDAL PROPERTY OF MILK.[1]

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It has been the experience of many observers in the study of the relative number and increase of bacteria in unheated and pasteurized milk, that the microörganisms increase more rapidly in the latter than in the former. This phenomenon might be due to one of two factors: either an antagonistic action of one species of microörganisms toward another in a favorable medium containing a mixed bacterial flora, as is usually the case in raw milk and not in the heated milk, or an inhibitory or bactericidal property of milk which is destroyed at 68° C., the pasteurizing temperature, or to both of these.

Since the time that Buchner discovered the bactericidal power of blood serum which he attributed to a ferment (alexine), followed by the demonstration of this activity in ascitic and hydrocele fluids and in the urine, and the finding of antitoxin in the milk of mothers suffering with diphtheria, it has been the effort of several investigators to determine the presence or absence of such a property in the milk of

[1] Read before the Philadelphia Pediatric Society, May 9, 1905.

lower animals. This work has been more or less stimulated by clinical observations, for it was found that infants nursing upon sterilized, and probably upon pasteurized, milk did not exhibit the same powers of resistance as did those fed at the breast or upon raw milk. There has been a tendency to attribute this to an inherent property of fresh milk which is theremolabile and consequently destroyed at the sterilizing and pasteurizing temperatures.

Because of the failure of chemistry to measure the quantity and nature of ferments in the blood, the most natural method for their demonstration in milk was the same as had been employed in the earlier work upon the blood. Fokker[1] performed a series of experiments with the view of testing the increase of acidity and the rapidity of coagulation in specimens of the same milk, heated and unheated. He obtained what he considered sterile milk, although apparently he did not make control cultures to confirm this, and seeded specimens of the raw and sterilized article with rapidly forming lactic-acid organisms originally obtained from milk. He found that acid formed and coagulation was produced much more rapidly in the sterilized milk than in the raw milk, and consequently concluded that the latter possessed an inhibitory activity similar to that of blood serum. He believed that the lactalbumen of the milk possessed this germicidal activity which when heated not only lost the property but became a favorable culture medium similar to the albumen of the blood serum and to egg albumen. Basenau[2] criticises Fokker's work as the result of his own experiments. Using the Bacillus bovis morbificans, he compared its relative growth upon fresh milk and upon bouillon. He concluded that not only did milk possess no bactericidal property, but that it was just as favorable a medium for the growth of this organism as was bouillon. To our minds, Basenau's work was in-

[1] Centralblatt f. Bakt. und Parasitkunde, Nr. 31.
[2] Archiv f. Hygiene, vol. xxiii, 1895.

sufficient, for it only tested the comparative culture properties of fresh milk and bouillon for one organism, and did not determine its relative growth upon heated milk.

Hesse[1] experimented with the Bacillus typhi and the Vibrio choleræ. He concluded that fresh cow's milk is not only no nutritive medium for the Vibrio choleræ, but that the organism rapidly dies in it; that the destruction begins the instant the organisms are introduced and is almost complete in twelve hours at a temperature of 15° to 20° C., and in from six to eight hours at a temperature of 37.5° C.; that the destruction is independent of the acid content of the milk or of the germ content and their metabolic products, but is rather a living activity of milk which is destroyed at 100° C.; that cow's milk possesses the same property toward the Bacillus typhi. Basenau's[2] work, however, led him to draw exactly opposite conclusions. He inoculated a specimen of cow's milk almost free from bacteria, and at the same time a specimen containing a large mixed bacterial flora, with cholera organisms. He found in the former specimen that the vibrio increased much more rapidly than it did in the latter specimen. He also found that the organism remained alive for at least thirty-two hours both at 37.5° C. and at 20° C. Therefore he believed that the apparent bactericidal activity claimed by Hesse was due to the acid forming microörganisms normally found in milk, and that the gradual disappearance of the vibrio was due to the increase of acidity. von Heim[3] also found that the Vibrio choleræ was demonstrable six days after inoculation and possessed developmental activity in raw and self-soured market milk.

Moro[4] was unable to demonstrate any germicidal activity in cow's or mother's milk, but did find that the blood serum of breast-fed children possessed a greater bactericidal power

[1] Zeitschrift f. Hygiene und Infectkrankheiten. Band, xviii, 1894.
[2] Loc. cit.
[3] Arbeiten aus dem Kaiserliche Gesundheitsamte, Band v.
[4] Archiv f. Kinderheilkunde, Band, xxxiii.

than that of those artificially fed. Cozzolino[1] tested the growth of the Bacillus coli communis in cow's, goat's, ass', and mother's milks. He attempted to sterilize the milks at a low temperature by heating them an hour each day for eight days at 55° to 58° C., at which temperature the lact-albumen was not coagulated. The sterilization, however, was not complete since the bacterium mesentericus vulgatus and a sarcina remained in small amounts. He observed with great regularity a marked destruction of the bacterial content in women's milk and a more transient and variable inhibition in other milks. After forty-eight hours the phenomenon disappeared. Klem[2] and Ellenberger[3] both found that ass' milk was a poorer medium for organisms than the other milks. They considered that it must possess a bactericidal property, since it could be obtained germ-free so easily. On this account, Ellenberger recommended its use in the gastro-intestinal catarrh of nursing children. Schlegel found that ass' milk remained sterile twenty-four hours after milking, and drew the same conclusion as did the preceding authors.

Klimmer[4] found that the ordinary milk bacteria increased very quickly in both ass' and cow's milks, and was unable to demonstrate any bactericidal activity in them against the Bacillus coli communis or the Bacillus typhi.

Richtet found that fresh milk by the addition of a definite quantity of lactic acid forming organisms coagulated sooner than sterilized milk treated in the same manner. This directly opposed the findings of Fokker,[5] who explained it as a probable property of the serum albumen of sterilized milk, whereby it might act as an inhibitory agent to the bacteria of one species, while it was a favorable medium for others. Following this line of investigation Sommerfeld[6] attempted to determine the

[1] Archiv f. Kinderheilkunde, Band, xxxiii.
[2] Jahrbuch f. Kinderheilkunde, Band xliii.
[3] Archiv f. Anatomie und Physiolog. Abtheil., 1899, Separatabzug.
[4] Archiv f. Kinderheilkunde, Band xxxvi.
[5] Loc. cit.
[6] Centralblatt f. Bakteriologie und Parasitenkunde, Nr. 37.

question by isolating the lactglobulin and lactalbumen by passing the milk through a Pukal stone filter and testing their germicidal activity. He performed six experiments with the Bacillus typhi and the Bacillus coli communis, and concluded that the soluble albumens of the milk had no germicidal activity either at room or incubator temperature.

Basenau, whose work has already been mentioned, also attempted to determine whether or not the milk while in the cistern of the udder had an inhibitory action upon bacteria, and at the same time endeavored to determine whether animals suffering with a bacterial disease secreted the organism in the milk. He found that animals suffering with such a disease do not secrete the organisms in the milk, although they may be demonstrated in the circulating blood, until the animals exhibit marked clinical symptoms of the disease. In these experiments, as already stated, he was unable to discover any appreciable inhibition of milk upon bacteria.

Finally, Hunsiker,[1] after a very carefully planned and exhaustive set of tests to determine the practical value of a germicidal property of milk as regards the keeping quality of the market product, concluded that freshly drawn milk of most cows contains varying germicidal qualities; that the degree of the germicidal action varies greatly in the milk of different animals, and sometimes in the milk of the same animal taken at different milkings; that the bactericidal influence differs at different temperatures, appearing to be greatest, while it lasts, at 70° F., being less pronounced but of longer duration at lower temperatures; that at 70° F. the maximum duration was twelve hours, the average being from three to six hours; that heat is detrimental to this germicidal agent, milk subjected to a temperature of 149° F. for forty minutes losing all such activity.

This *resume* of the literature upon the subject places one in the position of doubt, because of the apparently contradic-

[1] Cornell University Agricultural Experiment Station, 1901, Bulletin 197.

tory conclusions. We believe that the varying results are due to different conceptions of the question and the consequent variation in the methods. None of the investigators employed an absolutely sterile milk and was enabled thereby to exclude the question of bacterial antagonism. Some compared the growth of a single organism in fresh milk containing a mixed bacterial flora with the growth in sterile bouillon, without determining its growth in heated milk. Others compared the growth of a mixed bacterial flora in fresh and heated milk without testing the growth of the same in sterile bouillon. While this omission is not of so serious import as the former, yet one is unable to exclude the question of bacterial antagonism or temporary inhibition which might be due to osmosis. To our minds, conclusions drawn from such experiments are of little value.

With these errors in mind we attempted to make examinations along the same line as we had been using in determining the bactericidal power of blood serum. In order to accomplish this it was necessary first of all to obtain sterile milk. The temperature we believed should be the optimum for the microörganisms used, and in testing such organisms they must be used individually and in pure culture. In this way we attempted to exclude the possibility of bacterial antagonism and the inhibitory effect of temperature upon bacteria themselves.

The method employed in obtaining the milk was as follows: A sixteen-ounce bottle was fitted with a rubber cork containing openings for and fitted with two glass tubes, one for the intake of milk, the other for the air outlet. The latter was plugged with raw cotton while to the other was attached rubber tubing of the proper size and length. At the end of this tube was attached a German-silver milking cannula which was placed in a test tube securely stoppered with raw cotton. This apparatus was then sterilized at thirty pounds' pressure. The udder and teats of the cow (which from her life history had always been perfectly healthy and free from udder

infection) were thoroughly cleansed with soap and water, then with alcohol followed by a 1 to 2000 solution of bichloride of mercury, and finally with sterile water. About half the milk

Fig. 1

was stripped from each quarter of the udder and the teats again sterilized, especial attention being given to the meatus. The cannula was introduced into the teat, care being taken to

avoid air contamination, and the milk was drawn quickly into the bottle, which was then stoppered with sterile raw cotton.

The milk was then divided among flasks, 25 c.c. to each. Several of these flasks were set aside at incubator, room, and refrigerator temperatures as controls.

One set of flasks was kept at room temperature for the "raw-milk" specimens, another set heated at 55° C. for thirty minutes, another set heated at 68° C. for twenty minutes, another set heated at 100° C. for thirty minutes, and another frozen solid and then quickly melted. After all of the specimens had been brought to room temperature, series composed of two flasks of each specimen were separately inoculated with the following microörganisms: Streptococcus pyogenes, Micrococcus aureus, Bacillus coli communis, Bacillus acidi lactici, and Bacillus subtilis. One set of inoculated flasks was kept at incubator, the other at refrigerator temperature. Counts were made immediately after inoculation at the end of four, eight, twelve, and twenty-four hours, and the percentage of increase or decrease was noted. The specimens kept at refrigerator temperature showed widely varying results as to their bacterial content. As this was true in the bouillon as well as the milk cultures, we concluded that any inhibition exhibited in these specimens was due to temperature and not to any property of the milk. Therefore we have not incorporated these counts in our report.

The following tables (I, II, III, IV, V), showing the numerical variations and changes in the physical characteristics of the specimens, and the charts (I, II, III, IV, V), indicating graphically the *percentage* variations, show the result of our investigations.

TABLE I.—*Streptococcus.*

	Immediate count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated .	3,630	3,520	None	None	3,140	None	None	11,700	None	None	12,120,000	None	None	Very Slight	None	Very Slight	None	Very Slight	None
Heated 68° .	3,240	4,060	None	None	5,450	None	None	16,840	None	None	13,938,000	Slight	None	Slight	None	M'k'd	Slight	M'k'd	M'k'd
Heated 55° .	3,550	2,770	None	None	2,940	None	None	4,040	None	None	12,362,400	None	None	Slight	None	Iner'd	Slight	M'k'd	M'k'd
Heated 100°	3,220	3,570	None	None	11,950	None	None	226,000	None	None	18,786,000	Slight	None	M'k'd	None	Com-plete	M'k'd	Com-plete	½
Frozen . .	2,890	2,680	None	None	3,040	None	None	12,090	None	None	15,392,000	Slight	None	Slight	None	M'k'd	M'k'd	M'k'd	M'k'd
Bouillon . .	3,240	3,400	..	..	3,580	..	..	12,200	..	..	19,998,000	..	..	..	..	..	..	..	..
Sterile water	1,880	1,020	..	..	140	..	..	10	..	..	Less than 10	..	..	..	..	..	..	..	..

TABLE II.—*Staphylococcus.*

	Immediade count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated .	8,860	7,180	None	None	10,240	None	None	19,800	None	None	1,302,920	None	None			None	None	None	None
Heated 68° .	9,840	11,460	None	None	81,100	None	None	104,940	None	None	3,030,000	Slight	None	Same as 24th hour	Same as 24th hour	Iner'd	Beg'ng	M'k'd	Adv'd
Heated 55° .	8,400	8,760	None	None	10,620	None	None	43,800	None	None	1,515,000	None	None			Slight	None	Iner'd	Beg'ng
Heated 100°	7,070	15,260	None	None	54,000	None	None	266,400	None	None	8,665,000	Slight	None			M'k'd	Adv'd	M'k'd	Adv'd
Frozen . .	7,200	10,860	None	None	10,200	None	None	30,140	None	None	1,575,000	Very Slight	None			Iner'd	None	M'k'd	Slight
Bouillon .	11,700	11,760	..	..	17,000	..	..	36,600	..	..	24,240,000	..	..	..	..	..	..	..	..
Sterile water	5,430	7,100	..	..	5,780	..	..	470	..	..	Less than 10	..	..	..	..	..	..	..	..

TABLE III.—*Bacillus Coli Communis.*

	Immediate count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated	3,800	2,350	None	None	249,000	None	None	480,000	None	None	90,000,000	Very Slight	None	No noticeable change from the 24-hour specimens	No noticeable change from the 24-hour specimens	Slight	None	No noticeable change from the 96-hour specimens	No noticeable change from the 96-hour specimens
Heated 68°	3,150	6,600	None	None	400,000	Slight	None	2,970,000	Slight	None	95,000,000	M'k'd	None			M'k'd	Beg'ng		
Heated 55°	4,110	4,860	None	None	400,000	None	None	720,000	None	None	89,890,000	Very Slight	None			Slight	None		
Heated 100°	4,210	78,000	Slight	None	2,000,000	Incr'd	None	3,000,000	Incr'd	None	98,000,000	M'k'd	None			M'k'd	M'k'd		
Frozen	..	..	..	..	.....	..	..	.....	..	..	.....	..	..			..	..		
Bouillon	4,570	5,880	..	..	2,000,000	..	..	3,000,000	..	..	96,960,000	..	..			..	..		
Sterile water	3,120	2,100	..	..	1,200	..	..	750	..	..	Less than 10	..	..			..	..		

TABLE IV.—*Bacillus Subtilis.*

	Immediate count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated	340	360	None	None	55,200	None	None	600,000	Slight	None	2,000,000	M'k'd	M'k'd	Complete	¼	Complete	¾	Complete	Complete
Heated 68°	300	560	None	None	199,800	Slight	None	576,000	M'k'd	Slight	4,423,800	M'k'd	M'k'd	Complete	¾	Complete	Complete	Complete	Complete
Heated 55°	390	400	None	None	750,000	Slight	None	780,000	M'k'd	Slight	2,424,000	M'k'd	M'k'd	Complete	¼	Complete	¾	Complete	Complete
Heated 100°	320	1880	Slight	None	792,000	M'k'd	Slight	2,880,000	M'k'd	M'k'd	5,717,000	Complete	½	Complete	Complete	Complete	Complete	Complete	Complete
Frozen	300	360	None	None	18,300	None	None	240,000	Slight	None	2,020,000	M'k'd	M'k'd	Complete	¼	Complete	¾	Complete	Complete
Bouillon	400	680	..	..	6,060	..	..	180,000	..	..	3,000,000	..	..	..	..	..	..	..	..
Sterile water	389	30	..	..	Less than 10	..	..	Less than 10	..	..	Less than 10	..	..	..	..	..	..	..	..

TABLE V.—*Bacillus Acidi Lactici.*

	Immediate count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated .	1,740	1,850	None	None	273,000	None	None	600,000	None	None	43,026,000	Slight	None	Slight'	None	M'k'd	Beg'ng	Slight increase over the 96-hour specimens in same ratio	Slight increase over the 96-hour specimens in same ratio
Heated 68° .	1,630	18,740	None	None	720,000	Slight	None	4,000,000	Slight	None	60,600,000	M'k'd	None	Incr'd	Beg'ng	M'k'd	Adv'd		
Heated 55° .	1,550	6,640	None	None	244,800	Slight	None	2,970,000	Slight	None	44,601,000	Slight	None	Slight	None	M'k'd	Beg'ng		
Heated 100°	2,170	72,000	Slight	None	2,000,000	Incr'd	None	4,000,000	M'k'd	None	116,352,000	½	None	¾	Beg'ng	Complete	Adv'd		
Frozen . .	1,080	2,600	None	None	278,000	None	None	534,000	None	None	30,300,000	Slight	None	Slight	None	M'k'd	Beg'ng		
Bouillon . .	2,220	51,600	..	..	1,750,000	..	..	2,000,000	..	..	43,632,000	..	..	..	..	..	..		
Sterile water	1,490	1,150	..	..	910	..	..	140	..	..	Less than 10	..	..	..	..	..	..		

Streptococcus Pyogenes. At the end of four hours the bacterial content of the unheated milk had decreased 3.5 per cent., that of the milk heated to 55° C., 20 per cent., that of the frozen milk 7 per cent., while the pasteurized and

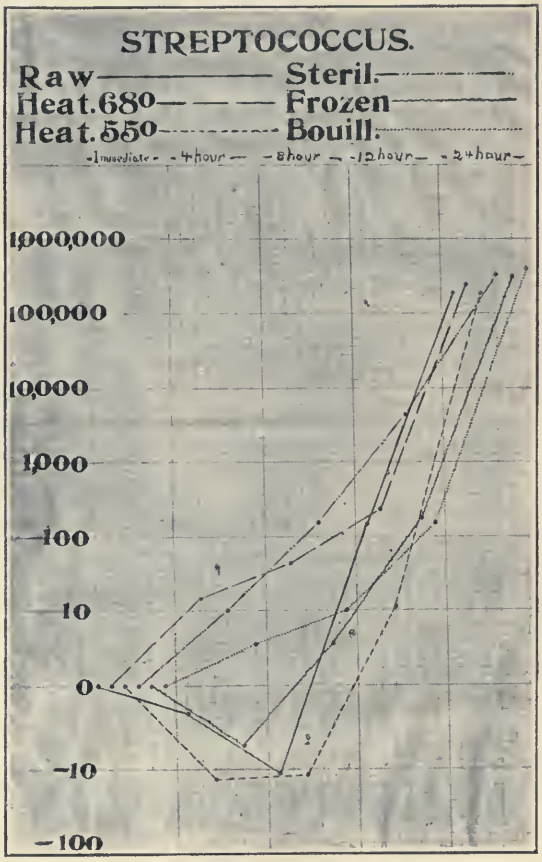

Chart I

sterilized milks had an increase in their bacterial content of 25 per cent. and 10 per cent. respectively, the bouillon control increasing 6 per cent. At the end of eight hours this wide variation in the percentages of increase disappeared.

We conclude, therefore, that against the Streptococcus pyogenes, raw sterile milk possesses an actual germicidal activity which is destroyed by heating at or above 68° C.

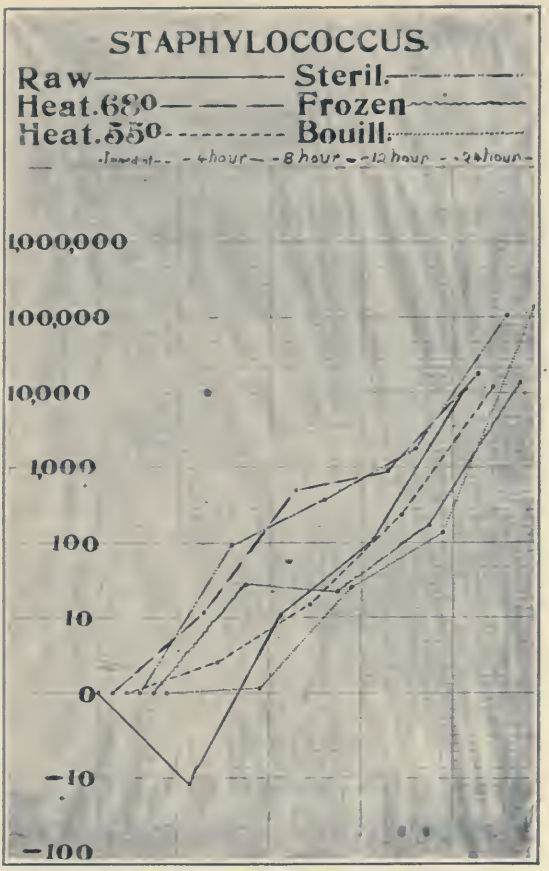

Chart II

Staphylococcus Aureus. At the end of four hours the number of bacteria in raw milk had decreased about 20 per cent.; the milk heated to 100° C. showed an increase of 100 per cent. in bacterial content; in that heated to 68° C. there was an increase of between 10 per cent. and 20 per cent.; in

that heated to 55° C. there was found an increase of 4 per cent., while in that frozen there was an increase of 40 per cent. The bacterial increase in the bouillon control was 1 per cent. Therefore we conclude that against the Micrococcus aureus

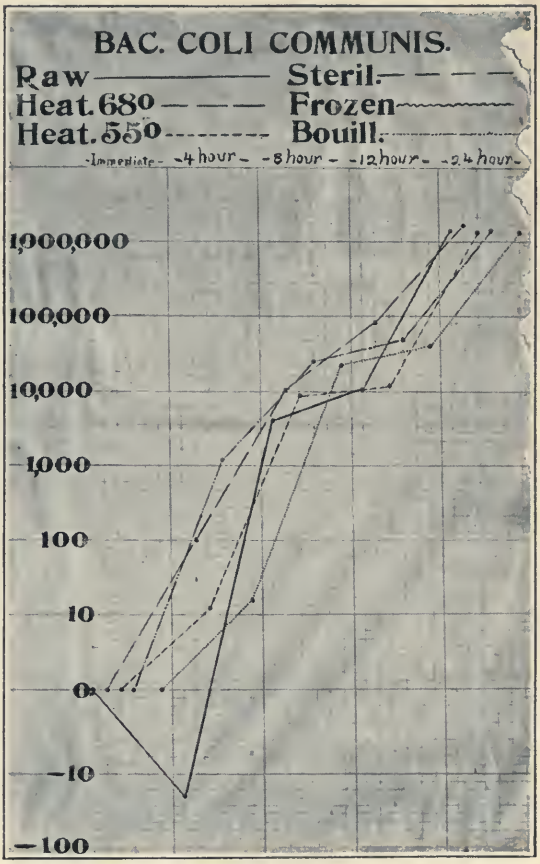

Chart III

raw sterile milk possesses an actual germicidal activity; which is destroyed by heating at or above 55° C. or by freezing, that milk so treated is a better medium for the growth of the micrococcus than bouillon; that at the end of eight hours

the germicidal activity disappears and the micrococcus develops in the same ratio in the different specimens.

Bacillus Coli Communis. At the end of four hours this organism decreased 40 per cent. in the count in raw

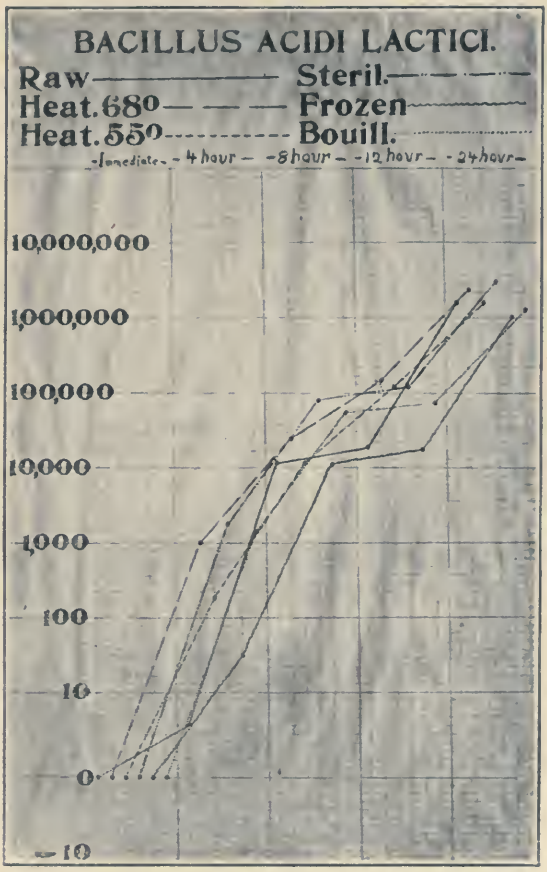

Chart IV

sterile milk, while it increased 10 per cent., 25 per cent., 100 per cent., and 2000 per cent. respectively in the counts in the milk heated at 55° C., the bouillon control, the milk heated at 68° C., and the milk heated at 100° C. At the

end of eight hours the bacterial content increased rapidly, the raw milk, however, showing the smallest ratio of increase. At the end of twenty-four hours there was very little difference in the percentages of increase in the various specimens. From

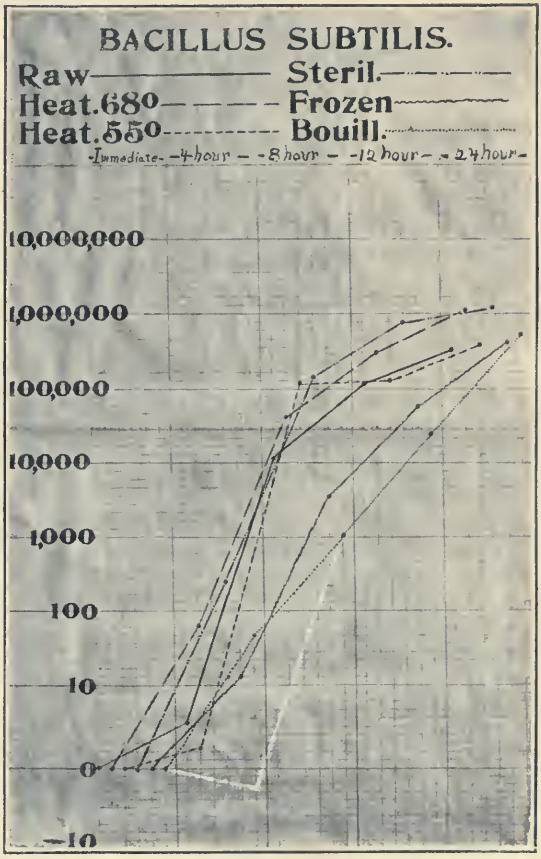

Chart V

this we conclude that against the Bacterium coli communis, raw sterile milk possesses an actual germicidal activity which is destroyed by heating at or above 55° C., and which is lost at the end of eight hours.

Bacillus Acidi Lactici. At the end of four hours this organism showed an increase of 6 per cent., 55 per cent., 250 per cent., 1000 per cent., 3500 per cent., and 2500 per cent. respectively in the bacterial content of the raw sterile milk, the frozen milk, the milk heated at 55° C., the milk heated at 68° C., the milk heated at 100° C., and the bouillon control. We conclude, therefore, that against Bacillus acidi lactici, raw sterile milk possesses only an inhibitory activity, which lasts from four to eight hours, and which is destroyed by freezing and heating at or over 55° C.

Bacillus Subtilis. At the end of four hours this organism showed an increase of 5.5 per cent., 2.5 per cent., 20 per cent., 85 per cent., 450 per cent., and 60 per cent. respectively in the bacterial content of the raw sterile milk, the milk heated at 55° C., the frozen milk, the milk heated at 68° C., the milk heated at 100° C., and the bouillon control. Hence we conclude that against the Bacillus subtilis, raw sterile milk possesses an inhibitory activity which lasts from four to eight hours, and which is destroyed by heating at or above 68° C.

Each of the organisms used in this experiment were isolated from milk by Dr. D. H. Bergey, to whom we are indebted for the subcultures.

One thing is noticeable in comparing the results obtained with the different organisms, namely, that toward those organisms which are pathogenic, and to which the cow is especially open to infection, the milk exhibits an actual germicidal activity, while toward the non-pathogenic organisms there is only an inhibitory activity. This condition we know exists in the human blood serum, *i. e.*, toward those organisms to which the human race is ever open to infection there is an actual germicidal activity; for example, against the Bacillus typhosus, the Bacillus coli communis, the Streptococcus pyogenes, and the Micrococcus aureus, while the saprophytic organisms are apt to flourish in undiluted serum. This makes us feel that the degree of bactericidal activity

present in any specimen of milk must depend upon the degree of resistance in the animal, and that, therefore, in examining a number of specimens taken from different cows one must expect to find a great variation in results. In the herd from which the cow used in this experiment was selected, there had been a persistent under infection due to the Streptococcus pyogenes and the Micrococcus aureus, which had attacked about 80 per cent. of the animals. Therefore this cow with about twenty others may have possessed sufficient resistance to overcome the infection to which they were subjected daily. To the Bacillus coli communis all animals are open to infection; so we are readily able to understand the possibility and probability of this cow's blood serum containing a considerable number of antibodies for the three pathogenic organisms used in the experiment, which were secreted to some degree in the milk.

In this experiment we feel that we have eliminated the question of bacterial antagonism, which we considered might have played an important part in the results obtained by others; and our next step was an attempt to determine, if possible, the effect of one organism against another in specimens of milk subjected to different degrees of heat. For this purpose we obtained milk in the same manner as in the previous experiment, from another healthy cow in the same herd. Similar series of specimens were made, and the Bacillus acidi lactici and the Bacillus subtilis were singly used as before; and also for comparison a mixture of the two (equal amounts of a suspension of each organism being employed) was introduced into a third series of specimens.

The following tables (VI, VII, VIII) and percentage charts (VI, VII, VIII) show our results:

TABLE VI.—*Bacillus Acidi Lactici.*

	Immediate count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated .	4,900	14,900	None	None	11,970,000	Very Slight	None	56,560,000	Slight	None	304,304,000	M'k'd	Beg'ng	No marked change from 24-hour specimens except that digestion advanced					
Heated 68° .	3,760	91,800	None	None	25,200,000	M'k'd	None	93,930,000	M'k'd	None	360,360,000	M'k'd	Beg'ng						
Heated 55° .	3,460	15,000	None	None	5,040,000	Slight	None	69,690,000	M'k'd	None	336,336,000	M'k'd	Beg'ng						
Heated 100°	5,200	240,000	Slight	None	27,300,000	M'k'd	None	72,720,000	M'k'd	None	390,390,000	M'k'd	Beg'ng			"		"	
Frozen . .	1,520	6,120	None	None	5,040,000	Slight	None	80,800,000	M'k'd	None	320,320,000	M'k'd	Beg'ng						
Bouillon . .	4,320	586,000	..	..	20,160,000	..	..	19,392,000	..	..	225,825,000	..	..						
Sterile water	5,520	3,360	..	..	26,040	..	..	1,840	..	..	20	..	..						

TABLE VII.—*Bacillus Subtilis.*

	Immediate count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated .	110	2,600	None	None	2,772,000	Slight	None	22,300,800	Complete	Very slight	39,039,000								
Heated 68° .	150	6,800	None	None	4,032,000	M'k'd	None	17,392,000	Complete	Very slight	57,057,000								
Heated 55° .	230	1,260	None	None	3,428,000	M'k'd	None	13,332,000	Complete	Very slight	43,243,200								
Heated 100°	170	13,020	Slight	None	1,008,000	M'k'd	None	25,452,000	Complete	Very slight	56,056,000								
Frozen . .	210	300	None	None	1,008,000	M'k'd	None	14,544,000	Complete	Very slight	40,000,000								
Bouillon . .	180	12,000	..	..	2,327,000	..	..	6,484,200	..	..	9,609,600								
Sterile water	130	Less than 10	..	..	Less than 10	..	..	Less than 10	..	..	Less than 10								

Advanced | Advanced | Complete digestion of coagulum | " | " | " | "

TABLE VIII.—*Bacillus Acidi Lactici* + *Bacillus Subtilis.*

	Immediate count.	4th hour.			8th hour.			12th hour.			24th hour.			48th hour.		96th hour.		120th hour.	
		Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Count.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.	Coagulation.	Digestion.
Unheated .	3,360	9,000	None	None	3,780,000	None	None	56,560,000	Very slight	None	168,168,000	Complete	Advanced		One-half coagulum digested		"		"
Heated 68° .	1,680	25,000	None	None	13,440,000	Slight	None	98,475,000	Complete	Beg'ng	268,268,000	Complete							
Heated 55° .	2,100	12,000	None	None	4,284,000	Slight	None	93,930,000	Complete	Beg'ng	228,228,000	Complete							
Heated 100°	2,480	120.000	None	None	25,200,000	Slight	None	66,599,400	Complete	Beg'ng	300,000,000	Complete							
Frozen . .	1,380	2,160	None	None	3,528.000	Slight	None	60,600,000	M'k'd	None	285,285,000	Complete							
Bouillon . .	2,900	239,400	..	..	30,240,000	..	.	78,780,000	..	..	276,276,000	..							
Sterile water	2,920	1,840	..	..	1,180	..	..	260	..	..	30	..							

The milk of this cow, although showing a similar activity against these two organisms, does not exhibit the same degree of inhibition as did the milk from the first cow. This we can explain only as being due to a lesser degree of resistance

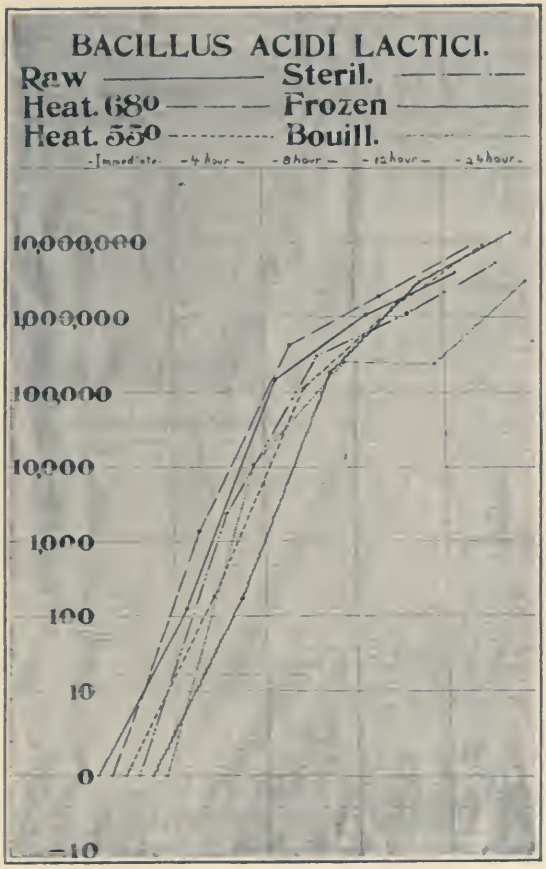

Chart VI

upon the part of the second animal as compared with the first. This variability of the milk of different cows was especially noticed by Hunsiker in his experiments. However, when we compared the results obtained in the series inoculated

singly with those from that inoculated with the mixed cultures, we found an interesting condition which we consider a definite indication of bacterial antagonism. The tables do not show this so strikingly as did the cultures. After the

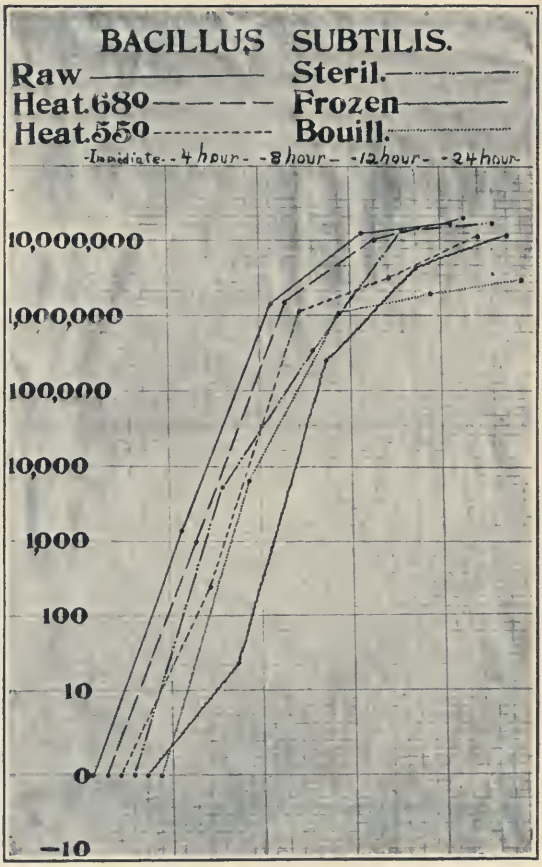

Chart VII

first four hours there was a rapid increase in the number of Bacillus acidi lactici and a decrease in the number of Bacillus subtilis. As the subsequent cultures were made in necessarily increasing dilutions, the number of subtilis colonies to

each plate became rapidly scarcer, until in the twenty-four-hour plates none was present. At the same time the physical characteristics of the specimens varied greatly. In the series seeded alone with Bacillus acidi lactici there was, at

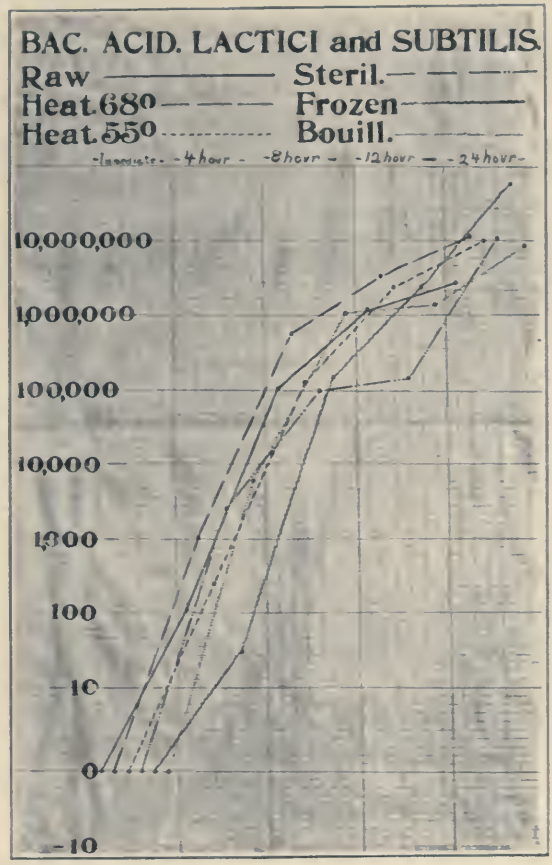

Chart VIII

the end of the forty-eighth hour, marked coagulation with moderate digestion of the coagulum; in the series seeded alone with Bacillus subtilis there was complete coagulation and complete digestion of coagulum; in the series with mixed

culture coagulation was complete, but only one-half of the coagulum digested. This undoubtedly indicated some difference due, not to the heating of the milk but to the antagonistic effect of one organism on the other.

We see this illustrated also by an examination of the percentage tables. At the end of four hours the percentages of increase were as follows:

	B. acidi actici. Per cent.	B. subtilis. Per cent.	Average. Per cent.	Mixed. Per cent.
Raw	200	2500	1350.0	150
68° C. . . .	2500	4500	3500.0	1000
55° C. . . .	350	450	400.0	450
100° C. . . .	4500	7500	6000.0	4500
Frozen . . .	300	45	175.5	55
Bouillon . .	10,000	8500	9750.0	8000

The average percentage of increase of the two series inoculated singly as compared with the percentage in the series with mixed cultures is higher with one exception (that of the milk heated to 55° C.). Notwithstanding this one discrepancy we feel justified in emphasizing the importance of considering bacterial antagonism in studying their growth upon milk subjected to different conditions, and again point this out as the possible explanation of the varied conclusions of the different investigators of this subject.

CHANGES IN THE CHEMICAL AND PHYSICAL CHARACTERISTICS OF MILK.

An examination of the tables seems to indicate at first sight that the increase of acidity and the production of coagulation go hand in hand with the bacterial increase. Our acid determinations were made at the end of twenty-four, forty-eight, and one hundred and twenty hours, while the bactericidal or inhibitory activity of the milk lasted, at the most, eight hours. At the end of twenty-four hours, however,

the relation of the points of acidity to the bacterial content was almost parallel. What role the germicidal activity plays in the production or the prevention of increased acidity, therefore, we are unable to say as far as our acid estimations are concerned; but a more careful examination of our results as regards the bacterial content and coagulation in the various specimens during the eight-hour period favors the view already expressed by Hunsiker,[1] that during the period in which the bactericidal property of milk is manifest acid production and coagulation do not take place in direct proportion to the bacterial content. Take for example the experiment with the Bacterium coli communis. At the end of four hours the specimen heated at 100° C. containing 78,000 organisms per c.c. showed slight coagulation, while the raw milk at the end of eight hours with a count of 249,000 bacteria per c.c., and at the end of twelve hours with a count of 480,000 bacteria per c.c., remained unchanged. Again, the specimen heated at 68° C. with a count of 400,000 bacteria per c.c. at the end of eight hours began to curd, while the specimen heated at 55° C. with exactly the same bacterial content remained unchanged.

An analysis of the above indicates that the phenomenon of coagulation depends in part upon some other factor or factors than bacterial increase, since in one specimen it occurred when only 78,000 bacteria per c.c. were present, while in another it was absent even when the bacterial count was as high as 480,000 per c.c.

Coagulation and probably increased acidity took place first in the specimen heated to 100° C., then in that heated to 68° C., next in that heated to 55° C., and finally in the raw sterile milk. This seems to indicate that heating at or over 68° C. destroys some property of milk which controls or prevents coagulation. We have already concluded that subjection to this temperature destroys the inhibitory activity

[1] Loc. cit.

of milk against bacteria; the higher the degree of heat the more noticeable the destruction. Heating to 55° C., however, seems to injure the bactericidal activity, but apparently does not destroy the property exhibited by unheated milk of resisting the process of coagulation even in the presence of a high bacterial content.

When we examined the specimens of raw sterile milk set aside as controls, we found an interesting phenomenon. Specimens kept at room temperature began to curd at the end of three weeks. In specimens kept at 37.5° C. coagulation took place on the tenth day. In the specimens kept at refrigerator temperature, no change was noticed at the end of six weeks, after which time they were unfortunately destroyed by an accident.

We therefore notice that coagulation occurs in absolutely sterile milk and the phenomenon, therefore, does not depend solely upon bacteria. Sterilized milk does not coagulate, hence heat must destroy some thermolabile element or elements in milk which bring about coagulation. Why then is it that the raw sterile product coagulates independent of microörganisms, and yet more slowly than the sterilized product when seeded with the same organisms? Whether this phenomenon may be explained as due to some distinct activity of milk or to some change in its chemistry which permits the bacteria to form the proper metabolic products for coagulation, we can only surmise.

The process of acid curding depends upon the precipitation of casein. Casein exists as a salt of calcium held in suspension as a finely divided colloid. When acidified it is liberated and being insoluble is precipitated. The spontaneous coagulation of milk, which was established as a fact by Meissner and more carefully studied by A. Levy, is thus explained, the acid being furnished by the destruction of the colostrum cells. This clotting, however, is not similar to the formation of a more solid coagulum by bacterial ferments. That boiled milk does not undergo spontaneous

coagulation may be, that as with rennet curding takes place only in the presence of soluble calcium salts. Boiled milk has been shown to separate the casein and calcium oxide, precipitating the latter, thereby destroying one of the necessary factors of coagulation. The acid formed by the bacteria in much greater quantity, because of a more favorable medium, however, may produce with this precipitate a soluble compound necessary for the formation of a clot, which fact might explain the more rapid curding of heated than unheated milk independent of the relative bacterial content of each.

Whatever the explanation, this observation, we believe, adds weight to our contention that the heating of milk, both at sterilizing and pasteurizing temperature, destroys some of its vital characteristics. How important they are to the food value of this product, clinical observation alone can tell.

The following table indicates acidity in terms of decinormal Na.O.H. We realize that estimations made without numerous controls are of little value, but we incorporate them in this report because they give some indication of the effect of bacterial metabolism upon acidity. Unfortunately no estimations of the acidity of the raw sterile milk were taken at the time coagulation was first noticed.

TABLE IX.

Streptococcus.

		24 hours.	48 hours.	120 hours.
Raw milk .	10.00	10.00	10.00	10.50
Raw . . .	10.00	13.00	15.00	33.75
68° C. . .	10.00	14.00	20.00	51.25
55° C. . .	10.00	13.00	18.75	34.25
100° C. . .	10.00	15.00	25.00	57.25
Frozen . .	10.00	14.50	20.00	42.50
Bouillon . .		5.00	7.50	5.00

Staphylococcus.

		24 hours.	48 hours.	120 hours.
Raw . . .	10.00	12.50	13.75	16.25
68° C. . .	10.00	14.00	15.25	30.00
55° C. . .	10.00	13.50	14.50	25.00
100° C. . .	10.00	15.50	22.50	47.25
Frozen . .	10.00	13.50	18.75	27.50
Bouillon . .		6.00	6.25	5.00

Bacterium Coli Communis.

		24 hours.	48 hours.	120 hours.
Raw . . .	10.00	13.00	45.00	52.50
68° C. . .	10.00	35.00	48.75	65.00
55° C. . .	10.00	13.50	45.00	62.50
100° C. . .	10.00	28.50	53.75	72.50
Bouillon . .		3.00	5.00	5.00

Bacterium Subtilis.

		24 hours.	48 hours.	120 hours.
Raw . . .	10.00	13.00	17.50	25.00
68° C. . .	10.00	14.00	25.00	48.00
55° C. . .	10.00	13.50	22.50	28.75
100° C. . .	10.00	15.00	27.50	55.00
Frozen . .	10.00	13.50	22.50	27.50
Bouillon . .		5.00	5.00	62.50

Bacterium Acidi Lactici.

		24 hours.	48 hours.	120 hours.
Raw . . .	10.00	22.50	55.00	50.00
68° C. . .	10.00	45.00	62.50	60.00
55° C. . . .	10.00	42.50	62.50	56.25
100° C. . .	10.00	47.50	72.50	60.00
Frozen . .	10.00	42.50	62.50	52.00
Bouillon . .		7.50	12.50	37.50

Bacillus Acidi Lactici.

		24 hours.	48 hours.
Raw . . .	9.75	37.00	57.00
68° C. . .	9.75	43.50	60.00
55° C. . .	9.75	37.50	58.00
100° C. . .	9.75	50.00	72.00
Frozen . .	9.75	37.50	60.00
Bouillon . .		8.00	

Subtilis and Acidi Lactici.

		24 hours.	48 hours.
Raw . . .	9.75	15.00	19.00
68° C. . .	9.75	20.00	26.00
55° C. . .	9.75	18.50	22.50
100° C. . .	9.75	23.00	30.00
Frozen . .	9.75	18.00	22.00
Bouillon . .		6.00	6.25

Subtilis.

		24 hours.	48 hours.
Raw . . .	9.75	15.00	19.00
68° C. . .	9.75	20.00	26.00
55° C. . .	9.75	18.50	22.50
100° C. . .	9.75	23.00	30.00
Frozen . .	9.75	18.00	22.00
Bouillon . .		6.00	6.25

This subject can be of very little importance from the practical standpoint of keeping milk, but it emphasizes the necessity of looking upon the pasteurization or sterilization of milk with disfavor, realizing that at the present time it is an evil necessity under certain conditions. The opinions of clinicians as to disturbances of nutrition in children fed upon sterilized and probably upon pasteurized milk, seem to be supported by the results of such an experiment as we have performed, since it shows that, while the germicidal activity of milk is only short-lived, yet its presence and the fact that destruction occurs at the pasteurizing temperature indicate that milk so treated is robbed of some important constituent or constituents. That antibodies and antibacterial ferments are taken up as such by the human economy through the digestive tract, seems to us highly improbable; but we do believe that anything that will destroy antibacterial activity must necessarily destroy the chemical equilibrium of milk, thereby lessening its food value. It is easy enough to measure the fats, proteids, and sugar in the milk, but to estimate its elusive ferments and other living constituents which make

mother's milk a so much more desirable food product than cow's milk has not yet been attained by chemistry.

Conclusions. 1. Freshly drawn milk possesses a bactericidal activity toward certain microörganisms, and an inhibitory activity toward others.

2. This activity is destroyed at 68° C. and materially injured at 55° C. It varies in different cows and lasts from six to twelve hours.

3. Coagulation and acidity of milk do not depend solely upon the bacterial content. They are influenced by natural properties of milk which are soon overshadowed by the metabolic products of bacteria.

4. Sterile cow's milk freshly drawn is acid to phenolphthalein and increases very slowly in acidity independent of bacterial metabolism, due probably to the destruction of colostrum cells.

5. Results obtained in testing milk with mixed bacterial floræ are influenced by bacterial antagonism.

A COMPARISON OF THE VON PIRQUET, CALMETTE AND MORO TUBERCULIN TESTS AND THEIR DIAGNOSTIC VALUE.*

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When we decided to investigate the relative and individual merits of the newer methods of diagnosing tuberculosis, the literature did not contain the almost innumerable reports upon these procedures that are current to-day. But we feel that this in no sense detracts from whatever merit this communication may have, since we are now enabled not only to report on the results of our own investigations, but also to point out their relationship to the work which has already been done, which may add something in the general consensus to the clearing up of this undeveloped question. The tests which we have applied have been:

1. The conjunctival test of Calmette and Wolf-Eisner in one hundred and fifty-eight cases.
2. The scarification test of von Pirquet in one hundred and fifty-nine cases (using both human and bovine tuberculin in twenty-four cases).
3. The ointment test of Moro in one hundred and fifty-four cases.
4. The subcutaneous test in eighty-five cases in confirmation of the others.

PREPARATION OF TUBERCULINS.

It has seemed to us very important to point out that all the tuberculins which we have used in carrying out these tests have been prepared in one laboratory by the same method, and in order to make our results of value in comparison with others, to express briefly the method of preparation of our various solutions.

PREPARATION OF TUBERCULIN ORIGINAL (T. O.) (KOCH'S OLD TUBERCULIN).

A culture of the human type of the tubercle bacillus was grown at incubator temperature on glycerin beef broth for a period of six to eight weeks, or until the culture had covered the entire surface of the media.

*From the William Pepper Clinical Laboratory, University of Pennsylvania. Read before the Association of American Physicians, Washington, D. C., May 13, 1908.

The flasks containing the culture were then placed in a steam sterilizer for three hours, after which they were removed and the contents, including the growth of the tubercle bacilli and the beef broth, poured into a common vessel. This material was then sterilized in streaming steam for another period of two hours, it being considered that this prolonged exposure of the organisms to the streaming steam had some value in extracting the intracellular product of the tubercle bacilli. The organisms were then removed, first by filtration through paper and afterward by double filtration through a Berkefeld filter of the fine flow. The filtrate, which contained the toxins which had been liberated during the growth of the organism, as well as those extracted during the period of sterilization, was then evaporated over a water bath to one-tenth its original volume. This evaporated tuberculin was again passed through a Berkefeld filter, placed in bottles and sterilized by the intermittent method.

For the bovine tests, the tuberculin was prepared in the same way, substituting the bovine for the human culture.

PREPARATION OF THE TUBERCULIN PRECIPITATE (T. P.) FOR THE CONJUNCTIVAL REACTION.

Two volumes of 95 per cent. alcohol were placed in a tall cylinder and to this was slowly added one volume of concentrated tuberculin original. As soon as the precipitate, which forms early, had settled to the bottom of the cylinder, the supernatant liquid was decanted and the precipitate collected on a hard filter with the aid of a suction pump. It was afterward washed with 70 per cent. alcohol until the filtrate ran clear. It was dried in vacuo over sulphuric acid until perfectly dry; then it was broken up in a mortar into fine powder. This powder was then dissolved in normal saline solution to whatever strength was desired.

PREPARATION OF THE TUBERCULIN OINTMENT.

Equal parts by weight of tuberculin original and anhydrous lanolin were mixed together as follows: The lanolin was heated in a mortar until liquid. The mortar was then placed in an ice pack and the tuberculin slowly added, stirring vigorously with the pestle until the entire mass had become solidified. In this manner an even distribution of the tuberculin throughout the lanolin was obtained.

For use in the conjunctival test, the tuberculin was put up in small sealed capillary glass tubes, after the well known form used for vaccine containers, each tube containing three drops of the strength solution desired. The purpose in having three drops in each tube is to enable the

operator to remove one drop to wash away the possible spicules of glass which might adhere to the tube, the second drop being instilled and the third remaining behind to prevent the forcing out of any spicules of glass which may have come from the other end of the tube.

The solutions used for the cutaneous test were put up in bulk, as was also the tuberculin ointment.

STRENGTH OF SOLUTIONS USED.

In the application of the eye test, we have used a 0.5 per cent. strength in the great majority of cases. Occasionally, in the application of a second test to the original control eye, we used 1 per cent. strength; in a small group of older children, we used a 0.75 per cent. solution, while in children under two years of age, we used a 0.3 per cent. solution. A 10 per cent. solution of tuberculin original was used in the scarification tests, both human and bovine, and a 50 per cent. strength in the ointment tests.

TECHNIC.

Eye.—The rubber bulb was slipped over the end and placed in the middle of the capillary tube, after which both ends of the tubes were wiped off with alcohol and the ends broken by the fingers covered with sterile cotton, after which the bulb was placed in its proper position. The history of the patients as to previous eye conditions having been ascertained, the eyes were inspected to eliminate inflammatory lesions, and notes recorded descriptive of the general appearance. The lower lid of one eye (the other serving as a control) was then drawn downward and one drop of the solution placed in the lower inner portion of the conjunctiva. The lid was held in this position until the solution was well diffused throughout the conjunctival sac.

Scarification.—After the thorough cleansing of the upper arm with soap and water, followed by alcohol, three-minute scarifications, just deep enough to produce slight redness without drawing blood, were made at distances of about 5 cm. from each other in the length of the arm. One drop of the 10 per cent. solution was then placed on each of the upper and lower areas, by means of a sterile dropper. To the middle scarification, which served as a control, nothing was applied in the earlier cases, while in the later groups, one drop of the same solution minus the tuberculin, was used. The solutions were then rubbed carefully into the scarifications for a few moments, after which the arm was exposed until the solutions had dried.

Ointment Test of Moro.—The directions of its originator were followed in its application. After carefully inspecting and recording the

appearance of the abdominal surface and without any preliminary treatment of the abdomen, there was applied, either to the epigastric region, or more frequently to the submammary region, about 15 grains of the ointment. With a rubber finger cot or rubber glove, the ointment was gently rubbed into a circular area of from 6 to 7 cm. diameter for forty-five seconds. Over another area on the abdomen the same lanolin as that used in the combined ointment was applied in the same manner to serve as a control. The surfaces were then exposed to the air for twenty minutes. The ointment was not removed and no protective dressing was applied.

As our purpose was to determine the degree of uniformity of the various reactions, we used practically the same dosage for all cases and the same technic in their application throughout our work. We believe, however, that much smaller doses will yield equally satisfactory results, and that variations in the method of applying the scarification and ointment tests may be used advantageously. We are convinced, from the use of these latter tests, in cases not included in this group, that a smaller scarification for the cutaneous test and a less prolonged exposure after the application of the tuberculin is advisable, and that the removal of the excess of the ointment at the end of twenty minutes will limit the reaction to a smaller area in that it will avoid the spreading of the ointment when the clothing is replaced.

THE REACTION.

The principle of the reaction resulting from the application of these tests is, of course, the same in all. When an individual develops tuberculosis there occurs a hypersensitiveness of his tissue cells to the poisons of the tubercle bacillus, a condition for which von Pirquet has suggested the term "Allergie" (allergistic reaction); that is, the altered reaction which the human organism shows to micro-organisms or substances with which it is already acquainted, a reaction, in other words, in an organism with an acquired immunity. When, therefore, the tuberculin solutions are brought into contact with the various portions of the body, these reactions manifest themselves by the phenomena about to be described.

When a drop of tuberculin solution is instilled into the eye of an immunized individual, in from four to twenty-four hours there occurs an injection of the palpebral conjunctiva, semilunar fold, caruncle and orbital conjunctiva, which varies in intensity in different individuals, is usually attended by lachrymation and moderate fibrinous or fibro-purulent exudation, which may go on to profuse suppuration, attended by very marked swelling of the external, as well as of the internal tissues

of the eye (Figs. 1, 2 and 3). This condition ordinarily reaches its maximum in twenty-four to forty-eight hours, after which it gradually fades, its final complete disappearance bearing definite relationship to the severity of the reaction.

Following the application of the scarification test, in from five to twenty hours, there develops immediately adjacent to the scar, a pinkish areola, which rapidly extends in an outward direction until its maximum is reached (from twenty-four to seventy-two hours) at which time there usually exists a central deep pink zone of varying diameter surrounded by a pale pink, indefinitely marginated area, generally more or less circular in shape. The central zone is elevated and indurated and in the severer reactions may be covered with minute vesicles, which occasionally coalesce (Figs. 4 and 5). This cutaneous reaction persists for varying periods of time, from four or five days to two weeks, depending on its degree of severity.

The reaction to the ointment test manifests itself by the development in a time varying from ten hours to three days, of a papulovesicular eruption, at the site of application, and may vary in the number of papules from one to several hundred. The appearance of the eruption is characteristic, the most minute papules having a vesicular appearance, a pinkish color, and an erythematous areola. The papules vary in diameter from 0.5 to 3 or 4 mm., the erythematous areola sometimes measuring from 6 to 8 mm. In the more profuse eruptions these areolas may coalesce, giving a more or less pinkish hue to the entire area (Figs. 6, 7 and 8). In its severer types it usually persists for a week or ten days, after which the pigmented appearance may persist for several weeks, finally disappearing by a process of desquamation.

In describing the physical characteristics of these reactions, for the sake of clearness and uniformity, we have indicated three degrees for each, between which extremes we are enabled to classify all of our cases. In this classification we have followed closely the suggestion of Baldwin for the eye test and have used for the expression of these various degrees the single, double and triple plus marks which he has recommended.

In the interpretation of the eye reaction our single plus mark indicates all manifestations from a moderate redness of the inferior palpebral conjunctiva or of the semilunar fold or the caruncle up to a fairly marked injection of all of these tissues, with or without slight lachrymation or fibrinous exudation. The double plus mark covers the cases in which there occurs in addition to the above, mild capillary injection of the orbital conjunctiva, giving rise to a pinkish hue, some swelling of the caruncle, semilunar fold and palpebral conjunctiva, attended with lachry-

I. CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	Pos. + Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
1	J. F.....	4	General nutrition poor; rachitis, adenoids, anemia.	Conj.....	0.5.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
2	J. McG....	5	Good health.	Conj.....	0.5.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
3	R. C.....	3	General nutrition poor.	Conj.....	0.5.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
4	A. H.....	5	General nutrition good.	Conj.....	0.5.....	+	19	+.....	None	Neg.....	None.....	None.	The Scar. and Oint. tests were applied but the child was removed from the Home before reactions had time to appear.
				Scar.....	.....	..	..	.....	.....	.....	"	"	
				Oint.....	.....	..	..	.....	.....	.....	"	"	
				S. Cut.....	.....	+	..	+.....	.....	.....			
5	M. McG..	3	General nutrition fair.	Conj.....	0.5.....	−	..	−					
				Scar.....	.....	−	..	−					
				Oint.....	.....	−	..	−					
				S. Cut.....	.....	−	..	−					
6	G. B.....	3	General nutrition fair.	Conj.....	0.5.....	+	22	+.....	None	Neg.....	None.....	None.	
				Scar.....	.....	+	23	++(15x15) ..	"	"	"	"	
				Oint.....	.....	+	51	++(28).....	"	"	"	"	
				S. Cut.....	.....	+	....	+					
7	T. S.....	3	General nutrition fair; slight adenitis.	Conj.....	0.5.....	+	32	++.....	None	Neg.....	None	+	
				Scar.....	.....	+	29	++ (10x10) .	"	"	"	+++	
				Oint.....	.....	+	29	+ (11).....	"	1 papule.....	"	+++	
				S. Cut.....	.....	+	....	+.....	.....	.....	"		
8	L. R.....	4	Rachitis; general nutrition fair.	Conj.....	0.5.....	+	21	++.....	Photophobia....	Neg.....	Unilateral conj. severe for 1 week after test.	++	
				Scar.....	.....	+	48	++ (12x12) .	None	"	None.	++	
				Oint.....	.....	+	112	+ (14).....	"	"	"	++	
				S. Cut.....	.....	+	....	+.....	.....	.....	"		

9	M. M.....	5	General nutrition fair.	Conj.....	1st dose 0.5 2nd " 0.75	+	48	++.....	None	Neg.....	None	+	
				Scar.....	.....	+	48	++ (20x20) .	"	"	"	+	
				Oint.....	.....	+	48	++ (25).....	"	"	"	+	
				S. Cut.....	.....	+	....	++.....	.....	.....	"		
10	W. C.....	4	General nutrition fair.	Conj.....	0.5.....	+	23	+++.....	Photophobia....	Neg.....	None.....	+	
				Scar.....	.....	+	24	++ (19x10) .	None	"	"	+	
				Oint.....	.....	+	24	+ (3).....	"	"	"	+	
				S. Cut	.....	+	....	++			"		
11	E. E.....	6	General nutrition good.	Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
12	W. P.....	3	General nutrition fair; adenitis.	Conj.....	0.5.....	+	28	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	24	+ (6x6)	"	"	"	+	
				Oint.....	.....	+	48	++ (30).....	Itching.....	"	"	+	
				S. Cut.....	.....	+	....	++.....	.....	.....	"		
13	J. P.....	3½	General nutrition fair; rachitis.	Conj.....	0.5.....	+	50	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	24	+ (3x4)	"	"	"	+	
				Oint.....	.....	+	24	+ (4)..... ...	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	.....	"		
14	D. M.....	3	General nutrition fair.	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	28	+.....	"	"	"	+	
				Oint.....	.....	+	48	++ (20).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	.....	"		
15	G. Y.....	4	General nutrition fair.	Conj.....	1st dose 0.5 2nd " 0.75	+	22	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	24	+ (6x6)	"	"	"	+	
				Oint.....	.....	+	22	+ (4).....	"	"	"	+	
				S. Cut.....	.....	+	....	++.....	"	.....	"		
16	J. K.....	3	General nutrition good; rachitis.	Conj.....	0.5.....	+	32	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	40	+++ (25x20)	"	"	"	+	
				Oint.....	.....	+	40	++ (30).....	"	"	"	+	
				S. Cut.....	.....	+	....	++.....	"	.....	"		
17	W. C.....	6	General condition fair.	Scar.....	.....	+	28	++ (15x10) .	None	Neg.....	None.....	+	
				Oint.....	.....	+	52	+ (10).....	Itching.....	"	"	+	
				S. Cut.....	.....	+	....	++.....	.....	.....	"		
18	J. G.....	4	Rachitis; adenoids.	Conj.....	.....	+	24	++.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	24	+ (3x3)	"	"	"	+	
				Oint.....	.....	+	41	+ (18).....	"	8 Papules.....	"	+	
				S. Cut.....	.....	+	....	+++.....	"	.....	"		
19	A. K.....	7	General nutrition fair.	Conj.....	1st dose 0.5 2nd " 0.75	+	23	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	42	++ (10x10) .	"	"	"	+	
				Oint.....	.....	+	42	++.....	Itching.....	1 Papule.....	"	+	
				S. Cut.....	.....	+	....	++.....	.....	.....	"		
20	T. C.....	5	General nutrition good.	Conj.....	0.5.....	+	24	+++.....	None	Neg.....	None.		
				Scar { Human	.....	+	48	+.....	"	"	"		
				Scar { Bovine	.....	+	48	+.....	"				
				Oint.....	.....	+	48	+ (13).. ...	Itching.....	"	"		
				S. Cut.....	.....	+	....	++.....	Inguinal glands enlarged l. side..	"	"		

1 (CONTINUED). CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	+| Pos. Neg.	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
21	R. F.....	7	General nutrition fair.	Conj.....	0.5.....	+	24	++.....	None	Neg.....	None.....	+	
				Scar { Human		+	48	++.....	"	"	"	+	
				Scar { Bovine	.....	+	48	+.....	.....	"	"	—	
				Oint.....	.....	+	48	++ (50).....	Itching.....	"			
				S. Cut.....	.....	+		+.....	Inguinal glands enlarged l. side..	"	"	+	
22	J. K.....	7	General nutrition fair.	Conj.....	0.5.....	+	24	+.....	None	Neg.....	None.		
				Scar { Human	.....	+	48	++ (25x25).	"	"	"		
				Scar { Bovine	.....	+	48	++ (20x20).	"	"	"		
				Oint.....	.....	+	....	+++ (100).					
				S. Cut.....	.....	+	....	+.....	Slight enlargement inguinal glands, left.				
23	A. P.....	6	General nutrition good.	Conj.....	0.5.....	+	25	++.....	None	48 hrs. O. S. same as O. D.	None.....	—	
				Scar. { Human	.....		120	+ (8x13)	"	Neg.....	"	—	
				Scar. { Bovine	.....	+	120	.....	"	....	"	—	
				Oint.....	.....	+	73	+ (1x7)	"	"	"	—	
				S. Cut.....	.....	—	....	++ (30).....	.....	.....			
24	J. S.....	7	General nutrition fair.	Conj.....	0.5.....	+	48	+.....	None.....	In 48 hrs. same as other eye..	None.	+	
				Scar. { Human	.....	+	24	+ (5x5)	"	.....	"	—	
				Scar. { Bovine	.....	+	24	+ (3x3)	.....	.....			
				Oint.....	.....	+	48	+ (20).....	"	Neg.....	"	—	
				S. Cut.....	.....	+	....	+.....	.....	.....	"		
25	C.	3	Pertussis with broncho-pneumonia.	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	None	Neg.....	None	.....	Both eyes instilled: both reacted.
				Scar.....	.....	+	24	++ (20x15)..	"	"	"		
				Oint.....	.....	+	24	++.....	"	"	"		
26	M. M....	5	Bronchopneumonia.	Conj.....	0.5.....	+	48	+					
				Scar. { Human	.....	+	36	+ (5x15).					
				Scar. { Bovine	.....	+	36	+ (5x5).					
27	J. S	3	Pertussis.	Conj.....	0.5.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
28	L. M.....	2/3	Bronchopneumonia.	Conj.....	0.3.....	—	....	—					
				Scar.....	.....	—	....	—					
29	W.	2½	General nutrition fair.	Scar.....	... .	—	....	—					
				Oint.....	.....	—	....	—					
30	J. S.....	1⅓	General nutrition poor.	Conj.....	0.3.....	—	....	—					
				.....	.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint									

31	R. C.....	1 1/6	General nutrition poor.	Conj.....	0.3.....	—	....	—.....	None	Neg.....	None.		
				Scar.....	.....	+	23	+ (10x10)....	"	"	"		
				Oint.....	.....	+	48	+ (15).....	"	"	"		
32	C.....	1 1/6	General nutrition fair.	Conj.....	0.3.....	+	27	++.....	None	Neg.....	None.		
				Scar.....	.....	+	23	++ (20x10)..	"	"	"		
				Oint.....	.....	+	49	+ (8).....	"	"	"		
33	A. W....	2	General nutrition poor.	Conj.....	0.3.....	+	24	+.....	None	Neg.....	None.		
				Scar.....	.....	+	48	+ (10x18)....	"	"	"		
				Oint.....	.....	+	48	+++ (250+)	Itching.....	"			
34	T. R.....	1 1/4	General nutrition fair.	Conj.....	0.3.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
35	A. C.....	2 1/2	General nutrition good.	Conj.....	0.3.....	—	....	—					
				Scar.....	.....	—	..	—					
				Oint.....	.....	—	....	—					
36	J.....	3	General nutrition good; rachitis.	Conj.....	0.5.....	+	96	++.....	None	Neg.....	None.		
				Scar.....	.....	+	48	+ (10x10)....	"	"	"		
				Oint.....	.....	+	48	+ (8).....	"	"	"		
37	L.....	2	General nutrition fair.	Conj.....	0.3.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
38	E. C.....	4	General nutrition good.	Conj.....	0.5.....	+	20	+.....	None	Neg.....	None.....	—	
				Scar. { Human	.....	+	48	++ (17x15)..	"	"	"	+	
				Scar. { Bovine	.....	+	48	++ (10x12)..	"	"	"		
				Oint.....	.....	+	48	+ (16).....	"	"	"	—	
				S. Cut.....	.....	+	....	+.....	"	"	"	+	
39	T. G.	6	Slight cervical adenitis; adenoids.	Conj.....	0.75.....	—	....	—.....	None	Neg..	None.....	—	
				Scar.....	.....	+	26	+ (10x10)....	"	"	"	—	
				Oint.....	.....	+	....	+ (8).....	"	"	"	—	
				S. Cut.....	.....	+	....	.....	"	"	"	—	
40	K. S.....	4	General nutrition poor.	Conj.....	0.75.....	+	25	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	30	+.....	"	"	"	+	
				Oint.....	.....	+	48	+ (15).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"	"		
41	B. F.....	6	General nutrition good.	Conj.....	0.75.....	+	36	+.....	None	Neg..	None.		
				Scar.....	.....	—	....	—.....	"	"	"	—	
				Oint	....	+	....	+ (5).....	"	"	"	—	
				S. Cut.....	....	+	....	+.....	"	"	Inguinal glands, both sides, enl'rged and tender.	—	
42	M. S.....	7 1/2	General nutrition fair.	Conj.....	0.5.....	+	28	++.....	Pain in Eye.....	Neg..	None.....	+	Bovine showed a few scattered papules.
				Scar. { Human	....: . : ..	+	48	+.....	None	"	"	+	
				Scar. { Bovine	.....	+	48	++ (15x15)..	....	"	"	+	
				Oint.....	.....	+	72	+++.....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"	"		
43	A. H.....	4	General nutrition fair.	Conj.....	0.75.....	+	31	+++.....	None	Neg.....	None.....	—	
				Scar.....	.. ..	+	24	++.....	"	"	"	+	
				Oint.....	.....	+	48	+.....	"	"	"	—	
				S. Cut.....	.....	+	....	+.....	"	"	Inguinal glands slightly enlarged.	—	

1 (Continued). CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculou .	Test Applied.	Dose. Per cent.	+ − Pos. Neg.	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
44	F. C.....	2	General nutrition good.	Conj.....	0.3.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
45	A. G.....	2	General nutrition poor; rachitis.	Conj.....	0.3.....	+	28	++	None	Congested.....	None.		
				Scar.....	... .	+	24	++ (15x15)..	"	Neg..	"		
				Oint.....	.....	+	24	+ (11).....	"	"	"		
46	A. C :...	3	General nutrition poor; rachitis.	Conj.....	0.3.....	+	28	++++.....	None	Neg.....	None.		
				Scar.....	....	+	23	++++ (20x20)	"	"	"		
				Oint.....	.....	+	48	+++ (50)...	"	"	"		
47	W.....	2	General nutrition poor	Conj.....	0.3.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	...	−					
48	T. K.....	2	General nutrition fair.	Conj.....	0.3.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
49	A. W	5	General nutrition fair.	Conj.....	0.75.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
50	K. S.....	6	General nutrition poor.	Conj.....	1st dose0.5 2nd " 0.75	+	20	+.....	None	Neg.....	None.....	+	
				Scar.....	... .	++	....	+ (6x6).....	"	"	"	−	
				Oint.....	.....	++	....	+ (6).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"			
51	E. K.....	6	General nutrition poor.	Conj.....	0.5....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
52	J. L.	5	General nutrition good.	Conj.....	0.75.....	+	30	+.....	None	Neg.....	None.....	−	
				Scar.....	.....	+	49	+ (6x4).....	"	"	"	−	
				Oint.....	.....	+	48	+ (17).....	"	"	"	−	
				S. Cut.....	.....	+	....	+.....	"	"			
53	D.A. (Col)	6	General nutrition poor.	Conj.....	0.5..... ..	−	....	−					
				Scar. { Human / Bovine	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					

54	S. M.....	7	General nutrition fair; adenitis.	Conj.....	0.5.....	+	27	+.....	None	Neg.....	None.....	+
				Scar. { Human	.....	+	23	+++ (30x20)	"	"	"	+
				Scar. { Bovine	.....	+	48	+ (7x5).....	"	"	"	−
				Oint.....	.....	+	48	+++ (50)...	"	"	"	−
				S. Cut.....	.....	+	....	+.....	"	.....	"	−
55	M. C.....	6	General nutrition fair; adenitis	Conj.....	0.5.....	+	24	+++.....	None	Neg.....	None.....	−
				Scar.....	....	+	25	+ (10x10)....	"	"	"	−
				Oint.....	.....	+	29	+ (7).....	"	"	"	−
				S. Cut.....	.....	+	....	+.....	"	"	"	
56	M. D.. ..	7	General nutrition poor.	Conj.....	0.5.....	+	26	+.....	None	Neg.....	None.....	−
				Scar. { Human	.....	+	53	++ (10x15)..	"	"	"	+
				Scar. { Bovine	.....	−	....	−.....	"	"	"	−
				Oint.....	.....	+	120	+++ (60)...	"	"	"	−
				S. Cut.....	....	+	....	+.....	"	"	"	
57	C. J.....	5	General nutrition good.	Conj.....	0.5.....	−	....	−.....	None			
				Scar. { Human	.....	−	....	−				
				Scar. { Bovine	.....	−	....	−				
				Oint.....	.. ..	−	....	−				
				S. Cut.....	.....	−	....	−				
58	A. C.....	5	General nutrition poor; adenitis.	Conj.....	0.75.....	+	25	+++.....	Photophobia....	Neg.....	None.....	+
				Scar.....	....	+	25	++ (15x17)..	None	"	"	+
				Oint	.....	+	46	+ (5).....	"	"	"	−
				S. Cut.....	.....	+	....	+.....	"	"	"	
59	M. C.....	3	General nutrition poor; rachitis.	Conj.....	0.5.....	+	32	+++.....	Photophobia....	Neg.....	{ Phlyct keratitis, central corneal ulcer 8 days after	
				Scar.....	.....	+	28	+++ (25x22)	None	"		
				Oint.....	.....	+	52	+++ (250+)	Itching.....	"		
60	M. F.....	4	General nutrition fair.	Conj	0.75.....	+	25	+++.....	Photophobia & pain in eye.....	Neg.....	{ 5 phlyctenulæ about 8 days aft. test. Recovery and relapse.	
				Scar.....	.....	+	20	++ (20x15)..	None	"		
				Oint.....	.....	+	24	+++ (250+)	"	"	None.	
61	G. B.....	7	General nutrition poor.	Conj.....	0.5.....	+	23	+.....	None	Neg.....	None.	
				Scar. { Human	.....	+	48	++ (18x17)..	"	"	"	
				Scar. { Bovine	.....	+	48	+ (10x10)....	"			
				Oint.....	.....	+	96	+++ (100)..	"	"	"	
62	A. P.....	6	General nutrition fair.	Conj.....	0.5.....	+	28	+++.....	Photophobia....	Neg.....	{ Phlyctenulæ 9 days after test; recovery and recurrence.	
				Scar. { Human	.....	+	28	+++ (25x25)	None	"		
				Scar. { Bovine	.....	+	28	+ (15x15)....	.....	.....		
				Oint.....	.....	+	28	+++ (100)..	"	2 papules.....		
63	E. McF..	5	General nutrition fair.	Scar. { Human	.....	−	....	−.....				
				Scar. { Bovine	.....	−	....	−.....				
				Oint.....	.....	−	....	−.....				
64	V. C.....	4	General nutrition fair.	Conj.....	0.75.....	+	30	+++.....	Pain in Eye.....	Neg.....	None.	
				Scar.....	.....	+	21	+++ (28x28)	None	"	"	
				Oint	.....	+	48	++ (20).....	"	"	"	
65	M. K.....	7	General nutrition fair.	Conj.....	0.5.....	+	26	++.....	None	Neg.....	None.....	+
				car. { Human	.....	+	50	+++ (30x30)	"	"	"	+
				car. { Bovine	.....	+	50	++ (10x15)..	"	"		
				Oint.....	.....	+	26	+ (8).....	"	"	"	+
				S. Cut.....	.....	+	....	++.....	"	"	"	+

1 (Continued). CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	Pos. + | Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
66	M. Y.....	6	General nutrition fair.	Conj.....	0..5.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
				S. Cut.....	.....	—	....	—					
67	H. G.....	4	General nutrition fair.	Conj.....	0.75.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
				S. Cut.....	.....	—	....	—					
68	L. F.....	7	General nutrition good.	Conj.....	0.5.....	+	29	++.....	None	Neg.....	None.....	+	Mother dead of tuberculosis.
				Scar. { Human	.....	+	48	+++ (30x20)	.....	.....	.....	+	
				Scar. { Bovine	.....	+	48	++ (10x12)..	.....	.....	.....	+	
				Oint.....	.....	+	96	+++ (100)..	.....	.....	.....	+	
				S. Cut.....	.....	+	....	++.....	.....	.....	.....	+	
69	J. de H..	5	General nutrition fair; rachitis.	Conj.....	1st dose 0.5 2nd " 0 75	+	23	++.....	None	Neg	None.....	+	
				Scar	.....	+	28	++ (20x17)..	"	"	"	+	
				Oint.....	.....	+	52	+ (7).....	"	"	"		
				S. Cut.....	.....	+	..	+++..:	"	.....	"		
70	A. D.....	6	General nutrition fair; (enlarged tonsils).	Conj.....	0.5.....	+	24	+.....	None	Neg.....	None.		
				Scar.....	.....	+	20	+.....	"	"	"	+	
				Oint.....	.....	+	28	+ (14).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	.....	"		
71	M. H.....	4	Bronchitis; general adenitis.	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	....	+.....	"	"	"	+	
				Oint.....	.....	+	24	+ (4).....	"	"	"	++	
				S. Cut.....	.....	+	...	++.....	"	.....	"		
72	J. K.....	5	Rachitis.....	Conj.....	1st dose 0 5 2nd " 0.75	—	: ..	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
				S. Cut.....	.....	—	....	—					
73	M. W.....	3	General nutrition poor; rachitis.	Conj.....	0.5.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	...	—					
				S. Cut.....	.....	—	....	—					
74	S. M.....	5	General nutrition fair.	Conj.....	.....	+	28	+++.....	Photophobia....	Neg.....	{ Phlyct. conjunc.		
				Scar.....	.....	+	73	++ (14x14)..	None	"	{ corneal ulcers 10		
				Oint.....	.....	+	24	+ (3).....	"	"	{ days after test.		

75	M. D....	3	General nutrition fair.	Conj..... Scar..... Oint.....	.....	+	23 43 22	+..... +..... + (12).....	None..... " ..... Itching.....	Neg..... " ..... "	None. ..... " "	.....	Unilateral simple conjunc. 6 days after, lasting 1 week. Eye had practically returned to normal.
76	F. M.....	4	General nutrition fair; rachitis.	Conj..... Scar..... Oint.....	0.5.....	+ — +	24 28	+..: ..... —..... ++ (30).....	None ..... " ..... Itching.....	Neg ..... " ..... "	None. " "		
77	C. C.....	5	General nutrition fair.	Conj..... Scar..... Oint.....	0.5.....	— — —	....	— — —					
78	D. W....	2½	Athrepsia.	Conj..... Scar..... Oint..... S. Cut.....	0.5.....	— — — —	....	—..... — — —	.....	.....	.....	.....	Mother had tuberculosis when infant was born.
79	R. S.....	5/6	General nutrition poor; adenitis.	Conj..... Scar..... Oint..... S. Cut.....	0.5.....	— — — —	....	— — — —					
80	J. D.....	2	Acute bronchopneumonia.	Conj..... Scar..... Oint.....	0.5.....	— — —	....	— — —					
81	W. F....	3½	Acute cervical adenitis.	Conj..... Scar..... Oint.....	0.5.....	— — —	....	— — —					
82	J. L.....	1½	General nutrition poor.	Conj..... Scar..... Oint..... S. Cut.....	0.5.....	— — — —	....	— — — —					
83	E.D.(Col)	1½	General nutrition poor.	Conj..... Scar..... Oint..... S. Cut.....	0.5.....	— — — —	....	— — — —					
84	M. H.....	1¼	Enterocolitis ...	Conj.....	0.3..... ..	—	....	—.....					
85	G. C.....	5	Fair health	Conj.....	0.5.....	+	24	++.....	None	Neg.....	Sev. conjunctivitis appearing 96 hrs.; continuing 2 weeks.		
86	S. W.....	1½	Mild rachitis ...	Conj.....	0.3.....	—	....	—.....	.....	.....			
87	E. I.....	3	Fair health	Conj.....	0.5..	+	21	+.....	None	Neg.....	None.		
88	A. K.....	6	Good health	Conj.....	0.5.....	+	36	+.....	None	Neg.....	None.		
89	W. G.....	10	Acute articular rheumatism.	Conj.....	1.....	+	18	+.....	Recurrence of joint pain.....	Slight inflammation.	None.		
90	K. O'D .	8	Bronchopneumonia	Conj.....	1.....	+	29	+.....	None	Slight inflammation.	None.		
91	H. T....	8	Chorea & acute rheum. and endocarditis.	Conj.....	1.....	+	24	+.....	None.....	Neg.....	None.		
92	J. McK..	10	Typhoid fever ..	Conj..... ..... Scar..... Oint.....	1..	— — —	....	—..... — —	.....	.....	.....	.....	Conj. test applied at height of fever. Other tests in afebrile stage.
93	A. H.....	9	Lobar pneumonia	Scar..... Oint.....	....	— —	....	— —					

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	Pos. + Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
94	H. S.....	2 1/6	Bronchopneumonia.	Conj.....	1st dose 0.5	−	. ..	−.....	.....	Neg,.....	.....	.....	2 conj. tests made during febrile period. The others in afebrile period.
					2nd " 0.75					"			
				Scar.	.....	+	23	++ (12x12)..	None	"	None.		
				Oint.	.....	+	23	++ (20).....	"	"	"		
95	K. McD..	2½	Bronchopneumonia.	Conj.....	0.5.....	−	....	−.....	.....	.....	.....	.....	Eye test applied during febrile period; others during afebrile period.
				Scar..... ...	.....	−	....	−					
				Oint...	.....	−	....	−					
96	P. W....	2	Pertussis complicated by bronchopneumonia; tetany.	Conj.....	0.5.....	−	....	−					
				Scar...	.....	−	....	−					
				Oint.....	.....	−	....	−					
97	E. W.....	1⅘	Pertussis with extreme secondary anemia.	Conj.....	0.5.....	+	24	++.....	None	Neg.....	None.	.....	This child reacted in the presence of extremely marked anemia.
				Scar.....	.....	+	24	++ (10x15)..	"	"	"		
				Oint.	.....	+	24	+++ (100)..	"	"	"		
98	M. H....	1½	Cervical lymphadenitis (acute).	Conj.....	0.3.....	+	....	++.....	None	Neg.....	None.		
				Scar.	.....	+	24	++ (20x15)..	"	"	"		
				Oint.	.....	+	48	++.....	"	"	"		
99	W. M....	7/12	Bronchopneumonia.	Conj.....	0.3.....	−	....	−					
100	J. B. H..	⅓	Acute otitis media; marasmus.	Conj.....	0.3...	+	....	+.....	None	Neg.....	None.		
101	S. C.....	4	Bronchopneumonia.	Conj.....	0.75.....	−	....	−.....	....	.....	.....	.....	Tests were applied within 8 days of death.
				Scar.....	.....	−	....	−					
				Oint...	.....	−	....	−					
102	F. W....	2	Bronchopneumonia with pertussis.	Conj.....	1st dose 0.5	−	....	−					
					2nd " 0.75								
				Scar.	....	−	....	−					
				Oint.	.....	−	....	−					
103	J. C.....	1½	Bronchopneumonia.	Conj.....	1st dose 0.5	−	....	−.....	.....	.....	.....	.....	Child anemic and emaciated. Test applied 3 days before death.
					2nd " 0.75								
104	M. N.....	2½	Follicular enteritis.	Conj.....	1st dose 0.5	−	....	−.....	.....	.....	.....	.....	Post mortem showed no evidence of tuberculosis.
					2nd " 0.75								
105	J. M.....	1½	Pertussis.....	Conj.....	0.5.....	−	....	−.....	.....	.....	.....	.....	Post mortem showed no evidence of tuberculosis.
106	K. B.....	1½	Marasmus	Conj.....	0.5.....	−	....	−...	.....	.. ..	.....	.....	Post mortem showed no evidence of tuberculosis.
107	W. H.....	7	Typhoid Fever..	Conj.....	1.....	+	24	++.....	None	Neg.....	None.	.....	Eye test during height of fever; scar. and oint. during convalescence.
				Scar.	.....	+	....	+.....	"	"	"		
				Oint.	.....	+	....	++:	"	"	"		
108	L. S.....	6	Acute articular rheumat. with acute endocarditis.	Scar.	.....	−	....	−					
				Oint.	... .	−	....	−					
109	T. F.....	2	Typhoid fever, otitis media, multiple neuritis.	Conj.	0.5.....	−	....	−					
				Scar.	....	−	....	−					
				Oint.	....	−	...	−					
110	M. K....	4	General nutrition fair.	Conj.:	0.75.....	+	24	++.....	None	Neg.....	None.....		
				Scar, ...	.....	+	48	++ (15x15)..	"	"	"	+	
				Oint.	.....	+	43	+.....	"	"	"	−	
				S. Cut.....	.....	+	....	++.....	"	"		−	

mation and fibrinous or fibropurulent discharge. The triple plus mark indicates all grades of reaction from the foregoing up to the most severe, as described in the above general description of the eye reaction.

In the description of the cutaneous reaction, the single plus mark indicates any degree of hyperemia up to a diameter of 10 mm. The double plus mark indicates all degrees of hyperemia having diameters of from 10 to 20 mm. and the triple plus mark, all reactions having diameters of more than 20 mm.

In the case of the ointment reaction the single plus mark indicates an eruption of from one to twenty papules; the double plus mark, from twenty to sixty papules, and the triple plus mark, fifty or more papules.

MATERIAL USED.

Practically all our patients were under 8 years of age and all but twenty-six of them were inmates of St. Vincent's Home, an institution with a population of about 400, composed of foundlings, orphans and destitute children. The cases in the home were tested in routine by wards, irrespective of the conditions from which they were suffering, and in the great majority of instances, without any knowledge of their physical condition prior to or at the time the tests were applied. We purposely deferred the physical examination of these children until after the tests had been applied, for two reasons, first, in order to be unbiased in our interpretation of the results, and second, in order to make ourselves especially vigilant in searching for tuberculous lesions in those who reacted. We had the children under absolute control throughout the entire period that the tests were being made, a special nurse having been employed for their exclusive care.

The accompanying tables, which record our results, are self-explanatory.

SUMMARY OF TABLES.

In addition to the cases designated in the tables, we have applied the test to seventeen infants ranging in age from four weeks to five months. All three tests were applied to six of them, the scarification test to all, and the ointment to but fourteen. Inflammatory conditions of the abdomen interfered with the application of the eye and ointment tests to the entire group. The results were entirely negative. Tuberculosis was not suspected in any of the cases and in about half of them the condition of nutrition was fair; in the remainder poor.

Of the 134 patients resident in St. Vincent's Home, 95 were clinically non-tuberculous, 27 had suspicious signs of either pulmonary or glandular tuberculosis, and 12 were definitely tuberculous. Of the 95

clinically non-tuberculous patients, 59, or 62.1 per cent., reacted; of the 27 suspicious patients, 23, or 85.1 per cent.; and of the 12 tuberculous, all, or 100 per cent.

Of the 26 patients outside of St. Vincent's Home, 15 were clinically non-tuberculous, 1 suspicious, and 10 tuberculous. Of the clinically non-tuberculous patients 5, or 33⅓ per cent., reacted. The 1 suspicious subject failed to react and, of the 10 tuberculous patients, 9, or 90 per cent. reacted. The one suspicious case in this latter group was probably one of tuberculous meningitis; the patient was tested within the last twenty-four hours of life. The one tuberculous patient who failed to react had advanced pulmonary tuberculosis and was anemic and emaciated.

Taking the two groups together, there were 110 clinically non-tuberculous, 28 suspicious and 22 tuberculous. Of the clinically non-tuberculous, 64, or 58.2 per cent. reacted positively; of the suspicious patients 23, or 82.1 per cent. reacted positively, and of the tuberculous 21, or 95.4 per cent. reacted positively.

If to these groups are added the 17 infants who were non-tuberculous clinically, and all of whom failed to react, the only change that occurs is in the non-tuberculous column in which the percentage of positive reactions is reduced from 58.2 to 51.2 per cent.

One thing that is especially noticeable in these results is the high percentage of positive reactions among the inmates of St. Vincent's Home. This result is in no sense surprising, since the institution is enormously overcrowded, and, until very recently, from the early winter until the late spring, its inmates have been housed with the windows closed and the wards sometimes overheated and sometimes underheated, depending largely on the external temperature. Scattered throughout the various wards there are a number of definitely tuberculous children and a fairly large number that might be suspected of tuberculosis, who would act as especially effective foci in a community of individuals with as marked lowering of the general nutrition as these children show.

OBSERVATIONS OF REACTIONS.

Following in the footsteps of others, we studied our earlier cases from hour to hour, to determine the time of beginning, the maximum point of and the length of duration of the reactions, but, finding that there was nothing to be gained from these frequent observations, we later abandoned them. We are satisfied if observations are made at the end of twelve hours, twenty-four hours, and forty-eight hours, and after this time, the cases are kept under general supervision, that no reactions will be overlooked and all essential information will be obtained. The mildest

cutaneous and ointment reactions will never be missed and we have never observed an eye reaction which did not persist long enough to be discovered during such observation periods.

Nevertheless, even in our later cases, we had observations made at fairly frequent intervals, in order to get a general idea of the course of the various reactions. The earliest onset of the conjunctival reaction occurred two and one-half hours after instillation and the latest forty-eight hours after instillation. In two cases the onset of the cutaneous reaction occurred five hours after its application, and in two cases it did not appear until the forty-eighth hour. The earliest onset of the ointment reaction was ten hours after it was applied and the latest seventy-two hours.

The earliest maximum conjunctival reaction was eleven and one-half hours after instillation and the latest ninety-six hours. The average was twenty-eight hours. For the cutaneous reaction, the earliest was twenty hours and the latest one hundred and twenty hours, the average being thirty-six hours. For the ointment test, the earliest was twenty-two hours, the longest one hundred and twenty hours, and the average forty hours.

As to the length of duration of the various reactions, our observations are accurate only insofar as they show that in one case the conjunctival reaction ceased in nineteen and one-half hours and that in several instances it did not entirely disappear for a period varying from seven to nine days; that the shortest duration of the cutaneous reaction was forty-eight hours, and that it sometimes persisted for more than ten days; and that the shortest duration of the ointment reaction was forty-eight hours and the longest more than ten days, it always having faded in color and most of the papules having disappeared at this time.

CONTROL TESTS.

The controls were practically negative in all cases, except in a few eye cases, to be referred to, in one scarification case, and in eleven of the ointment cases. In each of the latter two this was due to contamination from the inoculated areas. The control in the scarification cases was the middle scar, about 5 cm. from each of the others. Whilst the solution was drying, the child evidently transferred some of it to the control with its fingers. In the case of the ointment it was not removed from the abdomen and consequently when the undershirt was replaced it spread the ointment beyond the limits to which it had been applied, in some cases extending to the control areas.

SUBJECTIVE SYMPTOMS.

Very few of the children complained of discomfort from the reactions, none from the cutaneous. In fourteen of the ointment cases there was evidence of itching. In the conjunctival cases complaint of pain in the eyes was made in six cases; photophobia and recurrence of joint pains occurred in one case of rheumatism and photophobia was noted in thirteen other cases. One of the patients who reacted positively to the subcutaneous test complained of pain at the site of injection; another with chronic tubercular arthritis of the knee had an access of pain in this joint and severe abdominal pain (possibly due to a stirring up of tuberculous mesenteric glands) and a third patient had enlarged painful and tender inguinal glands with pain at the point of injection.

DILATATION OF THE PUPILS.

Apropos of the observation of Blum that dilatation of the pupils followed from one and one-fourth to one and one-half hours after the instillation of the eye, we made observations in the last twenty cases tested and found the pupil of the instilled eye dilated in five cases, contracted in four, and without change in eleven. At various times, in our routine examinations, we had noted dilatation or contraction of the instilled pupils twelve hours or more after instillation. This phenomenon is interesting; especially our observation that sometimes the instillation is followed by contraction instead of dilatation.

We have no satisfactory explanation to offer, although it is possible that the inconstant pupil effects of the instillation of tuberculin depend not alone on any inconstant strength or concentration of the solution used, but on individual peculiarities of the eyes. Whether local irritation produced by the drug, greater in one instance and less in another, may be accountable for these pupil phenomena, is a subject for further investigation.

UNIFORMITY OF REACTION.

In about sixty of our cases the conjunctival test was applied from one to three weeks before the scarification and ointment tests. In the remainder of the cases the three tests were applied at the same time.

The conjunctival, scarification and ointment tests were all applied in 132 cases. In 122 of these all of the tests reacted positively. In the ten remaining, the conjunctival test was negative four times when both of the others were positive and positive once when both of the others were negative. The scarification test was negative four times when one or both of the others were positive, and the ointment three times. It will

be seen from these figures that there was almost absolute uniformity as to reaction with these three tests.

As to the relative degrees of reaction in the individual cases, the ointment test gave the most marked reaction in 35 cases, the conjunctival in 32 cases, and the scarification test in 24 cases. This result is very interesting in connection with the statements in the literature regarding the comparative sensitiveness of the conjunctival, scarification and ointment tests.

Wolff-Eisner, for instance, apparently working with weaker solutions, expresses the opinion that the scarification test is more sensitive than the conjunctival, and that it shows latent foci which are not revealed by the conjunctival unless repeated and that the cutaneous reaction is positive in one-half of all cases, while the conjunctival is positive in but one-sixth.

Feer found the conjunctival test very uncertain with a 0.5 per cent. solution, and frequently negative in cases which were positive to a 25 per cent. solution applied cutaneously.

Morelli, in 100 cases of pulmonary tuberculosis, obtained 98 positive reactions to the scarification and but 86 to the conjunctival test. In 22 cases of tuberculosis other than pulmonary, he obtained 72 per cent. of positive reactions to the scarification and 63 per cent. to the conjunctival. In 96 cases of non-suspected tuberculosis, he obtained 21 per cent. of positive reactions to the scarification, and 11 per cent. to the conjunctival test.

Stadelmann's figures correspond with Wolff-Eisner's, and they share the belief that the conjunctival reaction indicates an active tuberculous process, while the cutaneous suggests inactive or latent foci. A few investigators have found the reactions more uniform and Calmette inclines to the belief that tuberculous lesions are more frequently found by the conjunctival than by the scarification test.

Wolff-Eisner attempts to explain the greater sensitiveness of the scarification test by a difference between the abortive power of the skin and conjunctiva; the absorption in the skin being less, the concentrated tuberculin remains where it is applied until the cells, which, owing to the latent nature of the foci, have not reacted to tuberculin for a long time, regain their power to react under the influence of the prolonged stimulation, whereas in the conjunctiva, where absorption is rapid, the contact is not long enough to stimulate the formation of antibodies.

On the basis of our results, we can not share in this opinion, and, because of the almost absolute uniformity of reaction with the three tests, we believe that the apparent lessened sensititiveness of the conjunctiva is to be accounted for on some other basis. There must be some

satisfactory way to account for the differences which have been obtained by different investigators, and we suggest that it probably depends on the use of solutions of varying strengths which, in the case of the tuberculin precipitate, is due to defective technic in its preparation. In the description which we have given of this procedure, we have pointed out that the precipitate which forms after the concentrated tuberculin original has been added to the alcohol, should be separated from its supernatant liquid as soon as possible. If this is not done, the proteids of the peptones and beef extract contained in the media will be precipitated out and collected with the tuberculin. It is very evident that percentage solutions made from such a precipitate would be much weaker than corresponding percentage solutions prepared from a pure tuberculin precipitate. It is not unlikely also that the effect of too prolonged contact of the alcohol with the precipitated tuberculin may have the effect of denaturizing, and thus in part destroying the activity of the tuberculin, which is a proteid body.

We believe, therefore, that the differences in results which have been obtained can be obviated if proper care is practiced in the preparation of the solutions which are used, and that, as far as children are concerned, as has been shown by our results, there will be practically absolute uniformity of reaction to the various tests. The demonstration of this uniformity of reaction we consider one of the most important results of our investigation, since it shows that none of the three tests has any advantage, insofar as the sensitiveness to reaction is concerned. It then becomes a question as to which of the three is most desirable from other standpoints.

Before beginning the application of the conjunctival test, we had no knowledge of any serious results from its use. It is unquestionably much easier of application than the other tests, and it probably yields results a little more quickly, but it has the great disadvantage of producing a decidedly uncomfortable lesion, and it is not infrequently followed by serious inflammations of the eye, which not only produce great physical discomfort and require weeks of active treatment, but which may permanently affect the vision and even lead to its complete destruction. In our series we have had two cases of severe purulent unilateral conjunctivitis, six of severe recurring phlyctenular conjunctivitis, one of which developed corneal ulcers, and one case of keratocyclitis with a large central corneal ulcer. Permanent disturbance of vision is sure to follow in this last case from the central scar, even should the associated lesion, which at present is in a very unpromising condition, clear up eventually.

These results are by no means unique, many similar observations having been made. Thus Webster and Kilpatrick, Moro, Feer, Schenck, Eppenstein and Gaupp, in their reports, refer to ten cases of phlyctenules; Van Durme and Stocke report five and Schenck and Seifert and Krause and Hertel many of the same condition. Ebstein, de Lapersonne and Eppenstein report eight cases of keratitis; Heymann one case of iritis; Renon one case of kerato-iritis; Simonin one case of corneal ulcer; Buch one case of conjunctival hemorrhage; de Lapersonne two cases of iridocyclitis; Cassoute one case of serious eye trouble, causing loss of vision, and Barbier the case of a child in which an old bilateral keratitis, healed for one year, was stirred up by the instillation of tuberculin, continued for two months, and caused almost complete destruction of the sight of one eye. We have had a number of verbal reports of eye complications, some relating to very serious conditions, and we are sure they are much commoner than the references we have communicated would indicate.

While we are willing to admit the assertion of Calmette that many of the complications may be due to the reaction-inflammation paving the way for the development of preexisting or superadded infectious organisms, we do not feel that this in any sense justifies the test. In fact, we are strongly of the opinion that any diagnostic procedure which will so frequently result in serious lesions of the eye, irrespective of the way in which it produces them, has no justification in medicine, especially since there are other diagnostic tests of equal if not superior value, which are applicable to the same class of cases and not attended with the same disturbing results. We refer to the scarification and ointment tests. As to the relative merits of these two tests, we feel that the ointment offers the advantage of eliminating any denudation of the surface of the skin, thus lessening the danger of infection.

We have had no complaint and have noted no evidence of discomfort during the reaction to the scarification test and nothing other than itching during that to the ointment test. We have seen no complications from either, although we note in the literature that tuberculide (v. Pirquet); lichen scrofulosorum (Ferrand and Lemaire, von Pirquet, Baginsky and Siccard, Oppenheim); scrofuloderm (Moro and Doganoff); and lymphangitis with swelling of the epitrochlear glands (Wolff-Eisner, Kronig) have followed the scarification reaction, and lichen scrofulosorum (Moro) the ointment reaction.

In addition to this, Feer quotes Pfaundler, Moro and Doganoff as having "frequently observed phlyctenules" appear on the cornea ten or fifteen days after the application of the scarification test, which they attributed

to a special hypersensitiveness of the entire organism. Feer communicates two instances of his own, occurring in 344 applications of the cutaneous test, in one of which the conjunctival test had been applied ten days previously. It is not stated in his quotation whether the conjunctival test had been previously applied to the cases of the authors above mentioned. It would seem likely, from the period elapsing between the application of the conjunctival test and the occurrence of the phlyctenules in Feer's second case that the phlyctenules were attributable to the conjunctival rather than to the cutaneous test.

Wolff-Eisner refers to the occurrence of phlyctenules after the application of the scarification test, but, in making the statement he is evidently quoting from the observations of others. In any event, it is manifest from the reports in the literature that complications of this nature occur much more frequently after the eye test than after the scarification test. It is entirely reasonable that it should be so, since the direct application of the solution to the eye not only brings the conjunctival tissue in contact with a larger dose of the tuberculin, but produces an inflammatory lesion which renders the tissues of the eye more vulnerable to infectious organisms, which may be in the eye and which are undoubtedly responsible for many of the severe concomitant symptoms in these cases.

In our own cases the eye complications occurred in all but two before either the scarification or ointment tests had been applied. In these two the three tests were applied at the same time, and in them we have credited the results to the eye test.

If sensitization of the entire organism follows the application of the scarification test, as the authors quoted suggest, it is not surprising that phlyctenules should follow, since their occurrence has been noted after the subcutaneous test. In one of our own cases (Case 62), phlyctenules developed nine days after the subcutaneous injection, the conjunctival scarification and ointment tests having preceded the subcutaneous by more than one month.

It is very probable that the dosage used in the scarification test, the absorptive power of the skin in different individuals, as well as the manner of applying the test, especially the nature of the scarification, may have some bearing on this question. Generally speaking, we do not believe it probable that a systemic reaction is likely to follow the application of either the scarification or ointment tests. Thus the drop of 10 per cent. tuberculin which we applied to the skin in carrying out the scarification test was equal to 0.01 c.c., which contained exactly 0.001 gm. of tuberculin. The drop containing this 0.001 gm. was only in small part in contact with the point of scarification, the greater bulk of it being scat-

tered around its borders. Unless, therefore, it was absorbed by the unbroken skin, the absorptive properties of which we know to be but slight, the amount of actual tuberculin taken up by the tissues generally must have been exceedingly small; and when we realize that one-half of the total quantity of tuberculin contained in this drop was injected subcutaneously in several children who had reacted cutaneously without producing symptoms of systemic reaction, we feel that the chance of its occurrence after the cutaneous test must be extremely slight, or that if it does occur it represents an extraordinarily high degree of sensitiveness.

Furthermore, we believe that in the uninjured skin to which the ointment in the amount used, 0.15 gm. equivalent to 0.075 gm. of tuberculin, is applied, absorption of tuberculin sufficient to produce anything beyond a local reaction can not possibly occur.

LATE REACTIONS.

There is a certain peculiarity of the reaction, pointed out by Stadelmann, which is worthy of consideration and which seems to be common to all, namely, a tendency to be delayed in its development and persistent in its duration. This delayed reaction may follow in cases in which the primary reaction was early. In the case of the cutaneous reaction it may persist at its maximum for as long as three or four weeks. We have not noted what we felt might be termed a delayed reaction after any of our eye or scarification tests; but in one instance we had a persistence of the ointment reaction at its maximum for about three weeks. An effort has been made to explain this type of reaction on the basis of the histologic study of the papule. Daels examined four such papules from cadavers and one from a living subject. Some of these showed nothing specific, but in two cases the papule accurately reproduced the structure of the tubercle.

This histologic picture, which was discovered in very circumscribed areas by the examination of serial sections, made him suspect the presence of dead bacteria in the tuberculin, which suspicion he confirmed by studying the centrifugated sediment of the same tuberculin that had produced the lesions.

He does not suggest the presence of dead bacilli in the tuberculin as an explanation of the occurrence and genesis of the von Pirquet reaction, but makes the rather interesting observation that the presence of the bodies or fragments of the bodies of dead bacilli might throw some light on the return reactions which follow the subcutaneous test, as well as account for the eye reactions which sometimes occur in apparently healthy individuals when the test is repeated with a sufficiently large dose.

II. CASES IN WHICH THERE WERE PHYSICAL SIGNS SUGGESTING TUBERCULOSIS.

Case.	Name.	Age.	Suspected Tuberculosis	Test Applied.	Dose. Per cent.	Pos. + Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reactions.	Remarks.
1	W. S....	4	Suspicious pulmonary tuberculosis (right apex).	Conj..... Scar..... Oint.....	0.5.....	+ + +	75 48 22	++..... + (9x8)..... +++ (100)..	None ..... " ..... Itching.....	Neg..... " ..... "	Phlyct. keratitis 10 days after test; inflammation continued from beginning of reaction.	.....	After complication set in it was discovered he had had a previous attack.
2	A. F.....	6	Palpable mesenteric glands.	Scar. { Human { Bovine Oint.....	....	+ + +	50 50 48	+++ (25x25) ++ (15x10).. +++ (250+)	None ..... " ..... Itching.....	Neg..... " ..... A few papules.	None. " "		
3	H. C.....	6	Palpable mesenteric glands.	Conj..... Scar..... Oint..... S. Cut.....	0.5.....	+ + + +	24 21 44	+..... ++ (15x10).. ++ (22)..... +.....	None ..... " ..... " ..... "	Neg..... " ..... " ..... "	None..... " ..... " ..... "	+ + ++	
4	N. McC..	4	Palpable mesenteric glands.	Conj..... Scar. { Human { Bovine Oint..... S. Cut.....	0.5.....	+ + + + +	28 49 49 41	+++..... ++ (25x20).. + (7x9)..... + (9)..... ++.....	Pain in eye ..... None ..... " ..... "	Neg..... ..... Neg..... "	None..... " ..... " ..... "	+ + +	
5	J. B.....	4	Suspicious pulmonary tuberculosis (right apex).	Conj..... Scar. { Human { Bovine Oint..... S. Cut.....	0.5.....	+ + + + +	24 48 48 96	+..... + (10x7)..... + (8x8)..... +++ (100).. +.....	None ..... " .... " ..... "	Neg..... " ..... " ..... " ..... "	None..... " ..... " ..... " ..... "	+ + +	
6	C. R. ...	5	Suspicious pulmonary tuberculosis (right apex).	Conj..... Scar..... Oint..... S. Cut.....	0.75.....	+ + + +	26 22 46	+++..... ++ (25x15).. + (10)..... ++.....	Photophobia Pain in eye ..... None ..... " ..... Pain locally.....	Neg..... " ..... " ..... "	None..... " ..... " ..... "	+ − −	
7	N. McF..	5	Suspicious pulmonary tuberculosis (right apex).	Conj..... Scar..... Oint ..... S. Cut.....	0.5.....	+ + + +	24 21 48	+++..... ++ (15x15).. + (5)..... +.....	None ..... " ..... " ..... "	Neg..... " ..... " ..... "	None..... " ..... " ..... "	+ − −	
8	K. W....	5	Suspicious pulmonary tuberculosis (left base).	Conj..... Scar. { Human { Bovine Oint..... S. Cut.....	0.5.....	+ + + + +	22 27 27 96	+..... + (4x4)..... + (5x5)..... ++ (25)..... +.....	None ..... " .... " ..... "	Neg..... " ..... " ..... " ..... "	None..... " ..... " ..... " ..... "	− − +	

9	S. K.....	4½	Palpable mesenteric glands.	Conj.....	0.75.....	—	....	—						
				Scar.....	.....	—	....	—						
				Oint.....	.....	—	....	—						
				S. Cut.....	.....	—	....	—	.....	.....	.....	.....	.....	
10	S. K.....	5	Suspicious pulmonary tuberculosis (right apex).	Conj.....	0.75.....	+	28	++.....	None.....	Neg.....	None.....	+	Positive local reaction.	
				Scar.....	.....	+	22	++ (15x10)..	"	"	"	—		
				Oint.....	.....	+	22	+ (6).....	"	"	"	—		
				S. Cut.....	.....	+	....	+.....	"	"				
11	K. K...	3	Doubtful pulmonary tuberculosis (right apex).	Conj.....	0.5.....	+	30	+.....	None.....	Neg.....	None.....	—		
				Scar.....	.....	+	24	+ (5x8).....	"	"	"	—		
				Oint.....	.....	+	24	+ (4).....	"	"	"	—		
				S. Cut.....	.....	+	....	+.....	"	.....				
12	H. D.....	3	Palpable mesenteric glands	Conj.....	0.5.....	—	....	—.....	....	....	.....	.....	5 days after test applied rt. eye "flared up" suggesting a reaction; 3 days later O. S. was affected. Boy had purulent conjunctivitis.	
				Scar.....	.....	—	....	—						
				Oint.....	.....	—	....	—						
				S. Cut.....	.....	—	....	—						
13	J. M.....	3	Palpable mesenteric glands.	Conj.....	0.5.....	—	....	—						
				Scar.....	.....	—	....	—						
				Oint.....	.....	—	....	—						
				S. Cut.....	.....	—	....	—						
14	J. K.....	6	Palpable mesenteric glands.	Conj.....	0.5.....	+	28	+.....	None.....	Neg.....	None.....	+		
				Scar.....	.....	+	24	+ (5x7).....	"	"	"			
				Oint.....	.....	+	24	++ (25).....	"	"	"	+		
				S. Cut.....	.....	+	....	+.....	"	.....				
15	M. G.....	3	Suspicious pulmonary tuberculosis (right base).	Conj.....	0.5.....	+	32	++.....	None.....	Neg.....	None.....	++		
				Scar.....	.....	+	24	++ (10x10)..	"	"	"	++		
				Oint.....	.....	+	24	+ (4).....	"	"	"	++		
				S. Cut.....	.....	+	....	+.....	"	.....				
16	C. C.....	6	Suspicious pulmonary tuberculosis (right apex).	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	None.....	Neg.....	None.....	+		
				Scar.....	.....	+	24	+ (10x10)....	"	"	"	+		
				Oint.....	.....	+	24	+.....	"	"	"	+		
				S. Cut.....	.....	+	....	+.....	"	.....				
17	J. C.....	3	Palpable mesenteric glands.	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	Photophobia....	Neg.....	None.....	•	*Child was taken home before return reaction could be observed.	
				Scar.....	.....	+	24	+ (8x10).....	None.....	"				
				Oint.....	.....	+	24	+ (1).....	"	"	"			
				S. Cut.....	.....	+	....	+.....	"					
18	G. M.....	4	Cervical adenitis (tuberculous?)	Conj.....	0.5.....	+	28	+++.....	None.....	Neg.....	None.....	+		
				Scar.....	.....	+	41	++ (15x15)..	"	"	"	+		
				Oint.....	.....	+	41	++ (50)...	"	3 papules.....	"	+		
				S. Cut.....	.....	+	....	+.....	"					
19	M. C.....	6	Palpable mesenteric glands.	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	None.....	Neg.....	None.....	—		
				Scar.....	.....	+	23	+.....	"	"	"	—		
				Oint.....	.....	+	76	+ (14).....	"	3 papules.....	"	+		
				S Cut.....	.....	+	....	+.....	"		"			

II (Concluded). CASES IN WHICH THERE WERE PHYSICAL SIGNS SUGGESTING TUBERCULOSIS.

Case.	Name.	Age.	Suspected Tuberculosis.	Test Applied.	Dose. Per cent.	Pos. + | Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction	Remarks.
20	M. C.....	4	Suspicious tuberculous pleurisy (l. base).	Conj.....	0.5.....	+	24	+.....	None.....	Neg.....	None.....	+	
				Scar.....	.....	+	72	+ (9x13).....	"	"	"	+	
				Oint.....	.....	+	70	+ (12).....	Itching.....	2 papules.....	"	+	
				S. Cut.....	.....	+	....	++					
21	A. L.....	4	Suspicious pulmonary tuberculosis (r. apex)	Conj.....	0.75.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
22	E. F.....	4½	Palpable mesenteric glands.	Conj.....	0.75.....	+	24	+++.....	None.....	Neg.....	None.....	+	
				Scar.....	.....	+	21	++ (20x15)..	"	"	"	+	
				Oint.	.....	+	24	+++ (250+)	"	"	"	−	
				S. Cut.....	.....	+	....	+.....	"				
23	M. M....	7	Tuberculous pleurisy?	Conj.....	0.75.	+	24	++.....	None.....	Slight redness in 48 hours.	None.....	+	
				Scar.....	. .....	+	24	+++ (25x30)	"	1 papule.....	"	+	
				Oint.....	.....	+	48	+ (17).....	"	.....	Much enlarged inguinal gland.	+	
				S. Cut..	....	+	....	+.....	"				
24	B. D.....	8	Suspicious pulmonary tuberculosis (r. apex)	Conj.....	0.5.....	+	24	+++.....	Photophobia....	Neg.....	Phlyct. conjunctivitis.	+	Note that Bovine Scar. was more marked than human.
				Scar. { Human	.....	+	48	++ (16x16)..	None.....	"	None.....	+	
				Scar. { Bovine	.....	+	72	+++ (20x20)	.....	.....	.....	+	
				Oint.....	....	+	72	++ (35) :...	"	"	"	+	
25	T. McF..	7	Suspicious pulmonary tuberculosis.	Conj.....	0.5.....	+	48	+++.....	Chimosis, photophobia.	Neg.....	None.....	+++	Most marked reaction of any case.
				Scar. { Human	.....	+	48	+++ (20x20)	.....	"	"	+++	
				Scar. { Bovine	.....	+	24	+ (9x9).....					
				Oint.....	.....	+	72	+++ (200+)	Itching.....	"	"	+++	
				S. Cut.....	.....	+	....	++.....					
26	G. D.....	6	Suspicious pulmonary tuberculosis (r. apex)	Conj.....	0.5.....	−	....	−.....	None.....	Neg.....	None.....	−	
				Scar. { Human	.....	+	96	+ (6x6).....	"	"	"	+	
				Scar. { Bovine	.....	−	....	−.....	"	"	"	−	
				Oint.....	.....	+	72	++ (25).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"			
27	M. J.....	3½	Lobar pneumonia and meningitis, probably tuberculous.	Conj.....	1....	−	....	−.....	.....	.....	.....	.....	Died 5 days after test; illness 3 wks.; fever 2 wks.; none last wk. of life.
28	H. G.....	8	Chorea and acute endocarditis; signs suggesting quiescent lesion of right apex.	Conj.....	1.....	+	48	+++.....	Photophobia, pain in eye.	Neg.....	None	.....	2 eye tests: 1st 1%, 2d 5%, other eye. First +++. Second ++. Return reaction in other eye.
				Scar.....	.....	+	24	++ (12x12)..	None.....	"	"		
				Oint.....	.....	−	....	−..					

The changes produced in the conjunctival sac by the first instillation are generally tuberculous tissue changes; hence the second and third instillations into the conjunctival sac produce a violent reaction, which is in accord with the fundamental discovery of Koch that tuberculin produces inflammation in tuberculous alterations. If the phenomena in the eye were due to a purely fluid poison, it would be hard to understand why the ability to react which is produced by the first instillation should persist for months, and also why this ability to react does not extend to the eye as a whole, in view of the rapidity with which fluid diffusible substances introduced into the conjunctiva make their way into the eye.

The theory of Wolff-Eisner that the efficacy of tuberculin injections and inoculations depends on the presence of the bodies of dead bacteria in the tuberculin—in other words, that it is a bacteriolytic reaction—is in accord with these views.

Bandler and Kreibisch also studied the late papules histologically and observed infiltration with mononuclear cells and some epithelioid cells and giant cells or what they termed the beginnings of giant cells, which, however, differed from the Langhans type. These findings are interesting and stimulated us to make histologic studies of the papules from the delayed abdominal reaction, above referred to. For the sake of comparison, we studied with this a papule from a normal reaction. The sections were kindly made and reported on by Dr. C. Y. White, and confirmed by Dr. M. B. Hartzell. They agreed that neither lesion differed in any way from the ordinary histologic picture of simple inflammation of the skin.

CONFIRMATION BY THE SUBCUTANEOUS TEST.

In eighty-five cases we applied the subcutaneous test in confirmation of the other tests. Sixty-three of these had been positive to the superficial tests and twenty-two negative. The subcutaneous test verified all the negative cases, by showing no evidence of reaction. In two of the positive cases, this confirmation was lacking, and in one case doubtful.

The injections were given in the lower right or left lumbar region. When it was necessary to repeat the dose, it was given on the opposite side.

In the first group of nine cases, including negative cases and mild reactions, the dosage was 0.1 mg. The only evidence of reaction occurred in the mild cases, and this was definite enough to leave no question as to the nature of the reaction.

In the second group we gave 0.1 mg. subcutaneously and, after forty-eight hours, repeated the test in the doubtful cases, giving 0.5 mg.

In the third group of somewhat older children we gave 0.5 mg., as the initial dose, in the doubtful cases, repeating with 1 mg.

In the last group we gave 0.75 mg. as an initial dose and found it unnecessary to repeat the injection in any. We observed no severe reactions. In one case there was vomiting about fourteen hours after the injection and in another enlargement of the inguinal glands associated with tenderness and some lymphangitis.

RETURN REACTIONS.

We observed very striking return reactions in all but 16 per cent. of the cases, 67 per cent. of the total number showing return conjunctival reactions, 65.5 per cent. return cutaneous reactions and 59 per cent. return ointment reactions. There were no evidences of inflammatory reaction in any of the tuberculin areas in the cases, which had been negative to the original tests. The most striking return reactions were those occurring on the abdomen over the area to which the ointment had been applied (Fig. 9). This so-called return reaction, as it appears after the cutaneous and ointment reactions, does not possess the characteristics of the original reaction. It is merely a mottled, pinkish blotching of the regions which had been occupied by the original reaction and shows neither elevation, papulation nor induration. The difference is very clearly shown by a comparison of the sketches showing the original and return abdominal reactions.

We observed no return reactions following the application of the superficial tests in the cases in which they were made at intervals. In several cases in which a second eye test was made in the original control eye there was a slight reaction in the opposite eye (original test eye). In this connection it may be pointed out that, in a few instances, we observed a bilateral conjunctival reaction after the instillation in one eye, a point which has been commented on quite frequently by other investigators and which has been explained most commonly on the basis of a transmission of the tuberculin from one eye to the other, by rubbing first the instilled and then the control eye.

POSTMORTEM CONFIRMATION.

In the few instances in which we were able to obtain autopsies the postmortem findings confirmed the results of the tests applied. Where the reactions were negative the autopsies failed to reveal any evidences of tuberculosis. In one case in which only the conjunctival test was applied with a positive reaction, some cervical glands removed surgically were proved tuberculous by the histologic examination, and in another

case reacting to the conjunctival test, miliary tuberculosis, tuberculous meningitis and enlarged tuberculous mesenteric glands were found at the autopsy.

There has been a considerable amount of postmortem study of cases in which the conjunctival and cutaneous tests have been applied. Von Pirquet made autopsies on one hundred children whom he had tested subcutaneously. Fifty-two of these, in whom the scarification test had been negative, showed no tuberculous changes macroscopically. Thirty-four of his patients died of tuberculosis, diagnosed clinically. Thirteen of these had been tested during the last ten days of life and none of them had reacted. Thirteen patients, dying of non-tuberculous conditions, had shown tuberculosis as an accessory finding. In this latter group nine had reacted positively, while in four, of whom three were not examined within the last ten days of life, the test was negative, and in one case, which had reacted, no macroscopic evidences of tuberculosis were found at autopsy.

Blum, Comby, Morelli, Wolff-Eisner, Letuelle, Prouff, A. Marie, Raviart, Otto Grunbaum, Hischler, Eyre, Wedd and Herz, Feer and Gaupp made autopsies in a large number of cases (more than sixty) in which either the conjunctival or scarification tests had been applied and, without exception, confirmed both their positive and negative findings. On the other hand, Bourget quotes two cases, one of hemiplegia and one of acute peritonitis; Massary and Weil a case of carcinoma; Bourget and Stilling a case of typhoid fever; Cohn and Simonin each a similar case, in which they obtained positive conjunctival reactions and failed to find evidences of tuberculosis at the autopsy.

It will be seen from the foregoing that the results of postmortem investigation have, in the main, confirmed the specificity of these reactions. The value of the negative results, as Soques has pointed out, may always be questioned, unless thorough macroscopic, microscopic and bacteriologic examinations, and animal injections of the tissues have been made.

When we realize that any of these tests will reveal the most minute foci of tuberculosis, it is very easy to understand how readily the lesions may be overlooked in the course of an ordinary autopsy.

When tuberculous lesions are found at the autopsy in cases which have not reacted, the relationship between the time of reaction and the date of death must be taken into consideration, because it is the rule that tuberculous cases fail to react during the last days of life, as well as under certain other conditions.

III. CASES WHICH WERE DEFINITELY TUBERCULOUS.

Case.	Name.	Age.	Tuberculous.	Test Applied.	Dose. Per cent.	Pos. + | Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
1	L. L.....	4	Advanced pul. tub. with cavity formation, pertussis.	Conj.....	0.5.....	+	24	+.....	None.....	Neg.....	None.		
				Scar.....	.....	+	24	+ (4x4).....	"	"	"		
				Oint.....	.....	+	48	+ (1).....	"	"	"		
2	A.S.(Col)	6	Lobar pneu. tub. (r. apex.)	Scar.....	.....	+	24	+ (10x10)....	None.....	Neg.....	None.		
				Oint.....	.....	−	....	−.....		"			
3	J. H.....	3	Tuberculous bronchopneumonia.	Conj.....	0.75.....	+	24	+.....	None.....	Neg.....	None.	.....	Tests applied 6 and 7 days before death. Fever fluctuating between 100° and 105°. All reactions very mild. Mother died of tuberculosis.
				Scar.....	.....	+	24	+.....	"	"	"		
				Oint.....	.....	+	24	+.....	.....	"			
4	E. S.....	4	Tub. dactylitis, tub. bronchial glands.	Conj.....	0.5.....	+	24	+.....	Photophobia....	Neg.....	None.	. ....	Father died of tuberculous.
				Scar.....	.....	+	48	+ (7x7).....	None.....	"	"		
				Oint..... ..	.....	+	48	++.....	"	"	"		
5	J.R.(Col)	6	Pulmonary tuberculosis..	Conj.....	0.5.....	+	24	++.....	None.....	Neg.....	None.		
				Scar.....	.....	+	24	++ (15x15)..	"	"	"		
				Oint.....	.....	−	....	−.....					
6	E. W....	8	Tub. cervical adenitis and pul. tuberculosis.	Conj	1.....	+	25	+.....	None.....	Neg.....	None.	.....	Glands removed surgically showed tuberculosis.
7	L. F.....	3	Tub. meningitis, miliary tubercles in spleen, tub. of mesenteric glands.	Conj..	0.5.....	+	11½	+...	None.....	Neg.....	None.	.....	Eye instilled 48 hrs. before death.
8	S. F.....	9	Tub. of tonsils and bronch. glands x-ray confirmation.	Conj.....	0.5.....	+	....	+.....	None.....	Neg.....	None.		
9	W. M....	5	Old Pott's disease.	Conj.....	0.5.....	+	24	++.....	None.....	Neg.....	None.		
				Scar.....	.....	+	48	+.....	"	"	"		
10	S. S.....	6	Tuberculous arthritis, knee.	Conj.....	0.5.....	+	24	+...	None.....	Neg.....	None.....	+	
				Scar.....	.....	+	48	++ (10x20)..	"	"	"	+	
				Oint.....	.....	+	24	+++ (250.)	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	Pain in knee and abdomen.	"	"		
11	A. B.....	10	Tuberculous peritonitis.	Conj.....	0.5...:	+	24	+.....	None.....	Neg.....	None.....	−	
				Scar.....	.....	−	....	−.....	"	"	"	−	
				Oint.....	.....	−	....	−.....	"	"	"	−	
				S. Cut.....	.....	−	....	−.....	"	.....	"	.....	Slight loc. reaction.
12	W. O'B..	9	Advanced pulmonary tuberculosis; entire r. lung and upper lobe l. lung.	Conj.....	0.5.....	−	....	−.....	.....	.....	.....	.....	Child died 9 days after tests were applied.
				Scar.....	.....	−	....	−..... .					
				Oint	.....	−	....	−.....					
				S. Cut.....	.....	−	....	−.....					

13	J. S.....	5	Pulmonary tub. chronic; r. upper lobe.	Conj.....	0.5.....	+	24	+.....	None.....	Neg.....	None.....	+	
				Scar.....	.....	+	24	+ (7x8).....	"	"	"	+	
				Oint..... ..	.....	+	72	+ (13).....	"	"	"	--	No fever, only local reaction.
				S. Cut.....	.....	+	....	+ ?.	"	"	.....	.....	Right eye tested .5% sol. negative, Left eye 6 days later 1% sol. positive.
14	A. D.....	7	Pulmonary tub. (r. apex), tub. mesenteric glands.	Conj.	1st dose 0.5 2nd " 0.75	+	30	+.....	None..	Neg.....	None.....	+	
				Scar.....	.....	+	24	++ (10x12)..	"	"	"	+	
				Oint.....	.....	+	24	+ (15).....	"	"	"	+	
				S. Cut	.....	+	..	+.....	"	"	"		
15	P. .C....	4	Glandular tuberculosis.	Conj.....	0.5.....	+	28	++.....	None	Neg	None.		
				Scar.....	.....	+	25	+ (10x10)....	"	"	"		
				Oint.....	.....	+	22	+ (5).....	"	1 papule.....	"		
16	G. B.....	4	Pulmonary tub. (r. apex.)	Conj..... . .	0.5.....	+	23	+.....	None.	Neg.....	None.		
				Scar.....	0.75.....	—	....	—.....	"	"	"		
				Oint.....	.....	+	52	++ (26). ...	"	"	"		
17	J. B.....	3	Glandular tuberculosis.	Conj.....	0.5.....	+	48	++.....	None.....	Neg.....	Phlyct. conjunc. 8 days after.		
				Scar.....	.....	+	24	++ (18x13)..	"	"	None.		
				Oint.....	.....	+	48	+++ (80)...	"	"	"		
18	K. L.....	4	Tub. adenitis (cervical).	Conj.....	0.5.....	+	48	+.....	None.....	Neg.....	Phlyct. conjunc. 8 days after test.	.....	Improvement and recurrence.
				Scar.....	.....	+	48	++ (25x12)..	"	"	None.		
				Oint.....	.....	+	48	+ (1).....	"	"	"		
19	A. C.....	4	Pulmonary tub. (r. apex.)	Conj.....	1st dose 0.5 2nd " 0.75	+	23	+.....	None.....	Neg.....	None.....	+++	
				Scar..	.....	+	48	++ (10x10)..	"	"	"	++	
				Oint.....	.....	+	48	+++ (60)...	Itching.....	Many papules.	"	++	
				S. Cut.....	.....	+	....	+.....			"		
20	D. D....	4	Pulmonary tub. (r. apex.)	Conj.....	1st dose 0 5 2nd " 0.75	+	17	++.....	Photophobia....	Neg.....	None.....	—	
				Scar.....	.....	+	30	+++ (25x20)	None.....	"	"	+	
				Oint.....	.....	+	39	++ (25).....	"	2 papules.....	"	+	
				S. Cut.....	.....	+	48	++.....	"				
21	T. M.....	3	Pulmonary tub. (r. apex.)	Conj.....	1st dose .05 2nd " 0.75	+	24	+.....	None	Neg.....	None.....	—	
			Adenitis.....	Scar.....	.....	+	24	+.....	"	"	"	—	
				Oint.....	.....	+	24	+.....	"	"	"	—	
				S. Cut.....	.....	+	46	+.....	"	"	"		
22	L. M....	7	Pulmonary tub. and tuberculous arthritis of r. elbow joint.	Conj.....	0.75.....	+	24	++.....	None	Neg.....	None	.....	Abdominal reaction continued at maximum for 3 weeks; had not disappeared entirely at end of 4 weeks.
				Scar	.....	+	48	++ (10x15)..	"	"	"		
				Oint.....	.. ..	+	48	+++ (100+)	"	"	"		

For instance, in one of our cases of advanced pulmonary tuberculosis, the patient being cachectic and emaciated, we obtained negative results to all three of the superficial tests, as well as to the subcutaneous. In the experience of those who have used these tests, negative results have been almost universal in cases of this type.

Dufour states that since 1899 he has had uniformly negative results to the subcutaneous test in cachectic cases, in individuals attacked with acute, fatal tuberculosis, and in practically all tuberculous cases during the last few days of life. With the newer tests, the results have been the same. This phenomenon is explained on the basis that the organism is so overwhelmed by the poisons of tuberculin, that it loses its power to react, or, as Baldwin expresses it, there occurs an exhaustion of the reactive mechanism by the excessive absorption of poison. Von Pirquet makes the suggestion, on the basis of some of his results, that the absence of reaction during the last days of life may be only relative and can be overcome by very large doses of the poison.

It not infrequently happens that individuals who fail to react to the first test will react when the test is repeated. This has been interpreted to mean that such individuals are the bearers of latent foci and, as their tissues have not been in contact with the poisons of the tubercle bacillus for a long time, the first application of the tuberculin merely stimulates immunization, thus paving the way for the occurrence of a reaction to the second test.

This question is closely related to the sensitizing of the tissues, in regard to which there must exist a great diversity of opinion until added knowledge makes it possible for us to arrive at more definite conclusions. Von Pirquet admits the possibility of inoculation producing immunity, but inclines, from his experiences in the inoculation of tuberculin, to believe that it is not followed by hypersensitiveness.

The latter view is maintained by Wolff-Eisner, Calmette and many others, and certainly the histologic findings of Daels previously referred to would seem to require some explanation in this connection.

This question of anaphylaxis will necessarily throw some doubt on the absolute specificity of the tuberculin test, if it is proved that it is entirely possible to produce a condition of hypersensitiveness in the use of tuberculin. On the other hand, the weight of experience, the enormous percentage of postmortem confirmations of the subcutaneous tests in animals, and of the superficial tests in human beings and the almost uniform confirmation of the superficial test by the subcutaneous method, would seem to suggest that the tests can be relied on to indicate the existence of tuberculosis in human beings, except in the type of cases

which has been previously referred to. Admitting this, the value of these tests, from the standpoint of diagnosis, would be absolute as to the existence of some form of tuberculosis, but the fact that they reveal the most minute and even the inactive and possibly healed forms of the disease, together with their failure to react in the presence of associated cachexia and in the advanced stages of the disease and especially in the most acute forms of tuberculosis, make them of much less value than we had hoped they might be in the differential diagnosis between the irregular types of tuberculosis and other conditions which simulate them.

Krause, Liesenberger and Russ, as well as Cohn, obtained a large percentage of positive results with the conjunctival test in cases of typhoid fever and also obtained positive results in tuberculous cases by the instillation of typhoid toxin, from which they argue that the test is not specific and that reactions are simply an expression of a hypersensitiveness of the organism to toxins in general. One of Cohn's cases came to autopsy and showed no evidences of tuberculosis. Bourget and Stilling also report a positive conjunctival test in a case of typhoid fever which showed no lesions of tuberculosis at the autopsy. These results have not, however, been confirmed by the observation of others. In our series, the test was applied to three cases of typhoid fever, both during the febrile period and in convalescence. In two cases, the result was negative, while in the other it was positive at both periods of the disease.

Austin and Grünbaum, Leroux, Trannoy, Hutchings, Lesne and Marré, Olmer and Terras, Levy and Wolff-Eisner report negative results in nineteen cases of typhoid fever. The negative results in cases of typhoid fever just quoted would seem to disprove the theory of the authors first mentioned and negative the value of their findings, as bearing on the specificity or diagnostic value of the tests.

It would seem to us that the negative results are probably of more value than the positive findings in differential diagnosis, except in serious febrile conditions. They definitely eliminate the possibility of tuberculosis.

We believe that the test will prove of value in its positive results in making it possible to separate the infected from the non-infected in institutions in the early recognition of infection and the consequent early adoption of treatment in the determination of the beginning of the infection, especially in tuberculous families, and possibly in connection with the determination of the origin of certain cases or groups of cases, as well as in stimulating us to a more careful study of the methods of transmission of the disease. The observations of Rosenberger regarding the frequency of tubercle bacilli in the stools, even in cases not clinically

tuberculous, as well as the recognition of the tubercle bacilli in the urine, suggest the possibility of a more frequent transmission of contagion through the medium of the discharges than we have been inclined to believe. This would seem to be an especially probable mode of transmission in the large overcrowded institutions, in which the soiled body and bed linens are washed either infrequently or inadequately. In an institution, for instance, such as that from which the majority of our cases have been drawn, it would seem unlikely that the number of actively tuberculous cases, especially of pulmonary cases, would be sufficient to account for the widespread dissemination of infection which exists there, and, unless we assume that these children are infected either prior to admission or that they are infected through the medium of the milk which is supplied them, we must conclude that there is some other manner of transmission of the disease.

There has been some effort made to place a prognostic significance on the type of reaction, especially on the type of the cutaneous reaction. It would seem possible that a gradual diminution of reaction in the advanced cases may indicate an unfavorable course.

COMPARISON OF HUMAN AND BOVINE SCARIFICATION TESTS.

Suggested by the differential tuberculin reaction of Detre, by which he attempts to differentiate between the bovine and human type of infection by the differences in reaction to filtrates of the human and bovine bacilli, we applied, by the scarification method, 10 per cent. solutions of tuberculin original—prepared, the one from bovine, the other from human cultures—in the same individual. The upper arm was chosen for the application and the tests were applied in twenty-four cases. The results showed the reaction to the human tuberculin the stronger in eleven cases, two of these which reacted strongly not reacting at all to the bovine. The degree of reaction was the same in eight cases and in two it was much stronger to the bovine than to the human, while in three there was no reaction to either. Generally speaking, the differences in degree of reaction where the one was stronger than the other were very striking. While these figures are of no value for purposes of deduction, they are nevertheless somewhat suggestive.

ANIMAL EXPERIMENTS.

In the hope that we might be able to throw some light on certain interesting features of this question, we undertook some experimental work on rabbits.

What we aimed to accomplish was to determine whether the type of the reaction bore any relationship to the stage of the disease or the nature or location of the lesion. Incidentally, we endeavored to create immunity in several normal rabbits by the intraperitoneal injection of tubercle toxin and to sensitize the conjunctival tissues in two normal rabbits and one tuberculous rabbit, which had shown no tendency to react, by the repeated instillation of tuberculin precipitate.

For some reason, which, up to the present, we have been unable to explain, our results were entirely negative. In the case of the attempts to induce immunity this may not be surprising, but our failure to obtain reactions in definitely tuberculous animals—proved by autopsy—the result is, to say the least, confusing.

We were at first inclined to believe that the inoculation with a bovine culture and the use of tuberculin of human origin might have some bearing on the result; but we note that Calmette, Breton and Petit obtained positive reactions in rabbits under similar conditions, from which we assume that this explanation is not satisfactory. We then incriminated the dosage, feeling that we might have overwhelmed the animals with so much toxin that immunity was not established. When we came to post our animals, we found that intravenous rabbit No. 4, killed on the fifty-first day, showed little beyond a lesion at the point of injection. We felt that this accusation would not hold for this case. When we found that one of our control rabbits which had had its eye instilled on the fifth of April (normal rabbit No. 1), and was killed on the sixth of May, showed a few tubercles in the left lung, we were still further convinced that the dose was not responsible for our negative results. We must, however, consider the possibility of infection in this case between the date of the last reaction (April 5) and the time of the autopsy (May 6).

In the light of the fact that the authors mentioned, together with Nobécourt and Montoux, Vallée, Lingnières, Naegeli, Akerblom and Venier and Gilliland (the last-named working with the same tuberculin which we used and in the same dosage), have obtained positive eye reactions after infecting their rabbits with both types of organisms, with varying doses, many of them larger than ours, and by the various methods, we feel that our negative findings, while failing to accomplish the purposes we had in view, have nevertheless presented a new problem which we hope to solve by further investigation.

The tuberculin which we used in testing these animals was of the same lot that we used successfully in human beings, both before and

after these experiments were done. The variability of the results of the authors referred to may bear some relationship to our uniform negative results.

LABORATORY REPORT ON THE ANIMAL EXPERIMENTS.

Culture Used for Inoculation.—Culture H of the laboratory of the State Live Stock Sanitary Board. It is a virulent bovine culture, and has been growing on artificial media since about 1902.

Preparation of Emulsion.—The emulsion was made from a six weeks old bouillon culture and in such strength that 1 c.c. of emulsion represented 0.001 gm. of dry tubercle bacilli.

Animals Used.—Seventeen rabbits were used in these experiments; twelve were inoculated with the above emulsion; four intraperitoneally with 0.5 c.c. (herein referred to as intraperitoneal rabbits 1, 2, 3 and 4); subcutaneously with 1 c.c. (subcutaneous rabbits 1, 2, 3 and 4); four intravenously with 0.25 c.c. (intravenous rabbits 1, 2, 3 and 4); two received subcutaneous injections of tuberculous toxin (filtrate from six weeks old culture) (toxin rabbits 1 and 2); three were not inoculated (normal rabbits 1, 2 and 3).

Tuberculin precipitate is indicated in the following tables by "T. P.":

CONJUNCTIVAL TUBERCULIN REACTION EXPERIMENTS ON KNOWN TUBERCULOUS RABBITS.

TABLE OF RESULTS.

Date.	Day.	No. of Rabbits, Instillation, etc.	18 hrs.	24 hrs.	48 hrs.
		Intraperitoneal Rabbit 1.			
Feb.					
26	1	Inoculated four rabbits intraperitoneally	....	....	....
28	3	Instilled left eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.
March.					
2	6	Instilled right eye 0.5 per cent. T. P.	Neg.	Neg.	*....
5	9	Autopsy; see below.			
		Intraperitoneal Rabbit 2.			
5	9	Instilled left eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.
10	14	Instilled right eye 0.5 per cent. T. P	†....	....	Neg.
12	16	Autopsy; see below.			
		Intraperitoneal Rabbit 3.			
17	21	Instilled left eye 0.5 per cent. T. P.	....	‡....	Neg.
18	22	Instilled right eye 0.5 per cent. T. P.	....	‡....	‡....
20	24	Autopsy; see below.			
		Intraperitoneal Rabbit 4.			
30	34	Instilled left eye 0.75 per cent. T. P.	....	‡....	Neg.
April.					
8	43	Instilled right eye 1 per cent. T. P.	Neg.	Neg.	Neg.
16	51	Died. Autopsy; see below.			
March.					
2	1	Inoculated four rabbits subcutaneously.			
		Subcutaneous Rabbit 1.			
9	7	Instilled left eye 0.5 per cent. T. P. Abscess at seat of inoculation at this date.	Neg.	Neg.	Neg.
23	21	Instilled right eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.

Date.	Day.	No. of Rabbits, Instillation, etc.	18 hrs.	24 hrs.	48 hrs.
		Subcutaneous Rabbit 2.			
April.					
2	31	Instilled left eye 1 per cent. T. P.	Neg.	Neg.	Neg.
		Abscess discharging at this date.			
14	43	Instilled right eye 1 per cent. T. P.	Neg.	Neg.	Neg.
		Subcutaneous Rabbit 3.			
30	59	Instilled left eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
		Subcutaneous Rabbit 4.			
30	59	Instilled left eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
May.					
5	64	Autopsies done on all subcutaneous rabbits; see below.			
March.					
13	1	Inoculated four rabbits intrathoracically.			
		Intrathoracic Rabbit 1.			
17	5	Instilled left eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.
23	11	Instilled right eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
25	13	Autopsy; see below.			
		Intrathoracic Rabbit 2.			
30	18	Instilled left eye 0.75 per cent. T. P.	....	‡....	Neg.
Apr.					
14	33	Instilled right eye 1 per cent. T. P.	Neg.	Neg.	Neg.
16	35	Autopsy; see below.			
		Intrathoracic Rabbit 3.			
8	27	Died. Autopsy; see below.			
		Intrathoracic Rabbit 4.			
May.					
1	50	Instilled left eye 0.3 per cent. T. P.	Neg.	Neg.	Neg.
5	54	Autopsy; see below.			
		Inoculated four rabbits intravenously, March 16.			
		Intravenous Rabbit 1.			
March.					
20	5	Instilled left eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
24	9	Instilled right eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
26	11	Autopsy; see below.			
		Intravenous Rabbit 2.			
30	15	Instilled left eye 1 per cent. T. P.	Neg.	Neg.	Neg.
April.					
16	16	Instilled right eye 0.3 per cent. T. P.	Neg.	Neg.	Neg.
12	28	Autopsy; see below.			
		Intravenous Rabbit 3.			
14	30	Died before test was applied. Autopsy; see below.			

Date.	Day.	No. of Rabbits, Instillation, etc.	18 hrs.	24 hrs.	48 hrs.
		Intravaneous Rabbit 4.			
30	46	Instilled left eye 0.3 per cent. T. P.	Neg.	Neg.	Neg.
May.					
5	51	Autopsy; see below.			

*A very faint injection of the vessels which we considered negative. It did not develop until 48 hours.

†An injection very slightly more marked than Note 1. Since this is the only rabbit in which we obtained this result, we considered it negative.

‡A milky discharge from the inner canthus. Not pus; unaccompanied by any injection of the vessels. Negative.

VON PIRQUET (SCARIFICATION) AND MORO (OINTMENT) TEST EXPERIMENTS.*

Date.	Day of		——Results——	
May	Disease.	No. of Rabbit, Test, etc.	24 hrs.	48 hrs.
		Normal Rabbit 2.		
2	..	Sacrification test.	Neg.	Neg.
April.				
2	..	Ointment test.	Neg.	Neg.
		Normal Rabbit 3.		
2	..	Scarification test.	Neg.	Neg.
2	..	Ointment test.	Neg.	Neg.
		Toxin Rabbit 1.		
2	24	Scarification test.	Neg.	Neg.
2	24	Ointment test.	Neg.	Neg.
		Toxin Rabbit 2.		
2	24	Scarification test.	Neg.	Neg.
2	24	Ointment test.	Neg.	Neg.
		Intrathoracic Rabbit 4.		
2	51	Scarification test.	Neg.	Neg.
2	51	Ointment test.	Neg.	Neg.
		Intravenous Rabbit 4.		
2	48	Scarification test.	Neg.	Neg.
2	48	Ointment test.	Neg.	Neg.
		Subcutaneous Rabbit 1.		
2	61	Scarification test.	Neg.	Neg.
2	61	Ointment test.	Neg.	Neg.
		Subcutaneous Rabbit 2.		
2	61	Scarification test.	Neg.	Neg.
2	61	Ointment test.	Neg.	Neg.

*Scarification test sol. 20 per cent. Koch's old tuberculin. Ointment test sol. equal parts tuberculin original and lanolin (anhydrous).

EXPERIMENTS

To Determine Whether the Conjunctival Tissues Can Be Sensitized by the Instillation of Tuberculin Precipitate; Whether This Results from Frequently Repeated Instillations or from Instillations Made at Longer Intervals; and the Time Required to Sensitize.

Three rabbits were used; two normal (Normal No. 1 and Normal No. 2) one tuberculous (subcutaneous No. 1).

Date.	Day.	Eye.	No. of Instillation.	Strength of Tuberculin Per Cent.	Result 24 hrs.
		Normal Rabbit 1.			
Feb.					
28	1	Left	1	0.5	Neg.
April.					
2	35	Left	2	1	Neg.
5	38	Right	1	1	Neg.
		See autopsy.			
		Normal Rabbit 2.			
April.					
2	1	Left	1	1	Neg.
3	2	Left	2	1	Neg.
5	4	Left	3	1	*....
6	5	Left	4	1	†....
7	6	Left	5	1	Neg.
8	7	Right	1	1	Neg.
May.					
1	30	Right	2	.3	Neg.
		Subcutaneous Rabbit 1.			
March.					
9	1	Left	1	0.5	Neg.
25	15	Right	1	.75	Neg.
April.					
2	24	Left	2	1	Neg.
3	25	Left	3	1	Neg.
5	27	Left	4	1	‡....
6	28	Left	5	1	Neg.
7	29	Left	6	1	Neg.
8	30	Right	2	1	Neg.
30	52	Left	7	.3	Neg.

*Very slight injection of vessels, a milky fluid from inner canthus and a sticky, granular appearance of conjunctiva.

†Some swelling of conjunctiva at inner canthus; injection of vessels equal in both eyes.

‡A very slight injection of vessels.

EXPERIMENTS

To Determine if the Subcutaneous Injection of Tuberculin will Sensitize the Tissues of the Eye to the Tuberculin Precipitate, and if Eyes Which Had Already Been Instilled Would Show Any Inflammatory Reaction.

Three rabbits were used; Normal rabbit 3, an animal on which no work had been done; Normal rabbit 2, whose eyes had been tested (see sensitizing experiment); Intraperitoneal rabbit 4, whose eyes also had been tested (see conjunctival tuberculin tables).

As shown in the accompanying tables, the temperatures of these rabbits were taken three times a day for three successive days; 0.1 c.c. of Koch's old tuberculin was injected subcutaneously into each rabbit on the fourth day at 8 a. m. and temperatures were taken at 12, noon, and every two hours thereafter until 6 p. m. and again at 8 a. m. of the next day.

Date.	Time.	Normal 3.	Normal 2.	Intraperitoneal.
April.				
9	2 p. m.	101.1	101.0	102.3
9	5 p. m.	100.4	101.2	102.4
10	8 a. m.	99.0	....	103.2
10	12 m.	101.1	101.1	101.3
10	5 p. m.	100.3	100.2	102.4
11	8 a. m.	99.4	100.0	102.3
11	12 m.	100.4	100.0	103.2
11	5 p. m.	102.0	101.0	104.0
12	8 a. m.	1/10 c.c. tuberculin subcutaneously.		
12	12 m.	101.3	100.0	103.4
12	2 p. m.	102.1	101.1	104.2
12	4 p. m.	102.2	100.1	103.4
13	8 a. m.	101.2	100.1	103.2

During the forty-eight hours following the subcutaneous injection of tuberculin in normal rabbit No. 2 and intraperitoneal rabbit No. 4 the conjunctival conditions were watched, but no change occurred. The following table will show, in the case of the first two animals, by how many days the various eye instillations preceded the subcutaneous injection and, in the case of the third animal, the number of days intervening between the subcutaneous injection and the various tests:

TABLE OF RESULTS.

Normal Rabbit 2.

Date.	Day.	Instillation, Etc.	24 hrs.	48 hrs.
April.				
2	11	Instilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
3	10	Reinstilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
5	8	Reinstilled left eye, 1 per cent. tuberculin precipitate.	See table.	Neg.
6	7	Reinstilled left eye, 1 per cent. tuberculin precipitate.	See table.	Neg.
7	6	Reinstilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
8	5	Instilled right eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
12	1	Subcutaneous tuberculin test. No eye changes occurred.		

Intraperitoneal Rabbit 4.

March.				
30	14	Instilled left 0.75 per cent. tuberculin precipitate.	Neg.	Neg.
April.				
8	5	Instilled right eye 1 per cent. tuberculin precipitate.	Neg.	Neg.
12	1	Subcutaneous tuberculin test. No eye changes occurred.		

Normal Rabbit 3.

12	1	Subcutaneous tuberculin test.		
18	7	Instilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
30	19	Instilled right eye, 3 per cent. tuberculin precipitate.	Neg.	Neg.
May.				
2	21	Scarification test.	Neg.	Neg.
2	21	Ointment test.	Neg.	Neg.

EXPERIMENTS

To Determine if Tubercle Bacillus Toxin Injected Into Non-tuberculous Rabbits Will Cause These Rabbits to React to the Conjunctival Scarification and Ointment Tests.

Two rabbits, called Toxin Rabbit 1 and 2, each inoculated with 0.1 c.c. of the tubercle toxin intraperitoneally.

Date.	Day.	No. of Rabbit, Instillation, Etc.	24 hrs.	48 hrs.
April.				
9	1	Inoculated 2 rabbits.		
		Toxin Rabbit 1.		
10	2	Instilled left eye, 1 per cent. tuberculin.	Neg.	Neg.
May.				
1	23	Instilled right eye, 0.5 per cent. tuberculin.	Neg.	Neg.
2	24	Scarification test (20 per cent. Koch's old tuberculin).	Neg.	Neg.
2	24	Ointment test (equal parts of tuberculin (T.O.) and anhydrous lanolin).	Neg.	Neg.
6	28	Autopsy; see below.		
		Toxin Rabbit 2.		
April.				
10	2	Instilled left eye, 1 per cent. tuberculin.	Neg.	Neg.
May.				
1	23	Instilled right eye, 0.3 per cent. tuberculin.	Neg.	Neg.
2	24	Scarification test (Koch's old tuberculin).	Neg.	Neg.
2	24	Ointment test.	Neg.	Neg.
6	28	Autopsy; see below.		

AUTOPSIES.

Intraperitoneal Rabbits.

Rabbit 1, March 5, Ninth Day.—Point of inoculation negative. Abdominal cavity: Five or six small tubercles on liver; staining shows tubercle bacilli. Two very small white masses on the mesentery also show tubercle bacilli; spleen, stomach, omentum, kidneys, postperitoneal and mesenteric glands normal. There is an adhesion between the liver and stomach which is not very recent and probably not connected with the tuberculous process. Thoracic cavity normal.

Rabbit 2, March 12, Sixteenth Day.—Point of inoculation shows a small tubercle, staining shows tubercle bacilli. Abdominal cavity: Extensive tuberculosis of the omentum and mesentery. Liver and spleen greatly enlarged and many tubercles scattered throughout the organs. Postperitoneal and mesenteric glands not enlarged; smears from liver, spleen, omentum and mesentery positive for tubercle bacilli. Thoracic cavity normal. An interesting anomaly in this rabbit is a transposition of the abdominal viscera.

Rabbit 3, March 20, Twenty-fourth Day.—Point of inoculation shows a small tubercle in both the skin and peritoneum. Smears positive for tubercle bacilli. Abdominal cavity: Intense injection of omentum and mesentery with small tubercles. Smears positive for tubercle bacilli. Mesenteric glands enlarged and show tubercle bacilli on staining. Spleen normal in size with a very few tubercles. Smears from both organs positive for tubercle bacilli. Thoracic cavity: A few slight pericardial adhesions; smears negative for tubercle bacilli. Lungs and pleura normal; smears negative for tubercle bacilli.

Rabbit 4, April 16, Fifty-first Day.—Rabbit died. Point of inoculation shows a large cheesy tubercle; smears positive for tubercle bacilli. Abdominal cavity: Omentum contracted and massed together by tuberculous adhesions, mesentery and parietal peritoneum contain enormous numbers of tubercles, mesenteric and postperitoneal glands enlarged, liver and spleen attached to stomach by adhesions and studded with tubercles; both are greatly enlarged. Kidneys swollen and congested. Smears from all these organs except the kidneys are positive for tubercle bacilli. Thoracic cavity: A few tubercles throughout the right lung and in the right pleura. Smears positive for tubercle bacilli. Left lung and pleura normal, heart normal, thoracic glands normal.

Subcutaneous Rabbits.

Rabbit 1, May 5, Sixty-fourth Day.—A large partially broken-down mass at the seat of inoculation. No appreciable enlargement of the subcutaneous glands. Abdominal cavity negative. Thoracic cavity: Both lungs and pleura and pericardium studded with tubercles, smears positive for tubercle bacilli; substernal glands swollen, smears from which show tubercle bacilli; extensive pericardial adhesions.

Rabbit 2.—Abscess which formed at the seat of inoculation discharged, leaving a partially healed ulcer. A chain of enlarged glands runs from this point (the left side midway between the front and rear legs) to the axilla. Axillary glands enlarged. These glands all show tubercle bacilli in smears. Abdominal cavity negative. Thoracic cavity shows a slightly more extensive involvement than in rabbit No. 1 of this series.

Rabbit 3.—A large partially broken-down tuberculous mass at seat of inoculation. No subcutaneous glandular involvement. Abdominal cavity negative. Thoracic cavity: A few tubercles in the lungs, pleura practically free. Pericardium normal; substernal glands enlarged and contain tubercle bacilli.

Rabbit 4.—Cutaneous appearance the same as No. 3 of this series. Abdominal cavity: A few white nodules not suggestive of tubercles on the right kidney; smears negative for tubercle bacilli. Thoracic cavity: A slightly more extensive involvement of the lungs than No. 3 of this series. Substernal glands slightly enlarged. Pericardium normal. Smears from lungs and substernal glands show tubercle bacilli.

Intrathoracic Rabbits.

Rabbit 1, March 25, Thirteenth Day.—The needle at inoculation passed through the lower point of the thoracic cavity, through the diaphragm into the abdominal cavity. There is a tubercle at the skin entrance, pleura and diaphragm all positive for tubercle bacilli. Abdominal cavity: The omentum and mesentery involved to about the same extent as intraperitoneal rabbit No. 2. The mesenteric glands enlarged and positive for tubercle bacilli. The postperitoneal glands normal. Liver shows many tubercles along anterior edge, the posterior and subsurface are comparatively free; smears positive for tubercle bacilli; spleen macroscopically normal. Smear negative for tubercle bacilli. Thoracic cavity normal. Sections of lung tissue negative. Smears from lungs negative for tubercle bacilli.

Rabbit 2, April 16, Thirty-fifth Day.—A cutaneous and pleural tubercle at point of inoculation. Smears positive for tubercle bacilli. Lungs in an advanced state of tuberculosis; cavities in both apices. Pleura and pericardium extensively involved, substernal glands only slightly enlarged, but show tubercle bacilli on staining. Smears from all mentioned organs positive for tubercle bacilli. Abdominal cavity negative.

Rabbit 3, April 8, Twenty-seventh Day.—The needle in this rabbit, at inoculation, did as in No. 1 rabbit, and there is extensive tuberculosis of the organs in both the thoracic and peritoneal cavities. As is shown in the accompanying table, this rabbit died without any conjunctival tests having been done.

Rabbit 4, May 5, Fifty-fourth Day.—A large tubercle at point of inoculation; smears positive for tubercle bacilli. Abdominal cavity negative. Thoracic cavity: Left lung shrunken and attached to pleura posteriorly, studded with tubercle. Same right lung; a large cavity in apex. Pleura and substernal glands extensively involved. Smears positive. Abdominal cavity negative.

Intravenous Rabbits.

Rabbit 1, March 26, Eleventh Day.—A small tubercle at point of inoculation in left ear. Smears positive for tubercle bacilli. Beginning tuberculosis of lungs, liver and spleen. No appreciable glandular involvement at any point.

Rabbit 2, April 10, Twenty-sixth Day.—A large tubercle at point of inoculation in left ear with a few glands at base of ear. General miliary tuberculosis involving the lungs, pleura, pericardium, substernal glands, liver, spleen, omentum, peritoneum, mesentery, postperitoneal and mesenteric glands.

Rabbit 3, April 14, Thirtieth Day.—Died. Autopsy picture practically the same as intravenous rabbit No. 2.

Rabbit 4, May 5, Fifty-first Day.—A large tubercle in left ear at point of inoculation, extending down to base and involving the glands in this region. Abdominal cavity negative. Thoracic cavity negative, except for an early tuberculosis of both lungs. We evidently did not enter the vein in this rabbit at the time of inoculation.

Normal Rabbits.

Rabbit 1, May 6.—Normal throughout, except for a few tubercles in left lung. Smears from lung positive for tubercle bacilli.

Rabbit 2, May 6.—Normal.

Rabbit 3, May 6.—Normal.

Toxin Rabbits.

Rabbit 1, May 6.—Normal.

Rabbit 2, May 6.—Normal.

1822 Spruce Street, 1805 Spruce Street, 6504 Germantown Avenue.

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American Medical Association, One Hundred and Three Dearborn Avenue.
CHICAGO.

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ACUTE LYMPHOPENIC LYMPHATIC LEUKEMIA.

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(From the William Pepper Laboratory of Clinical Medicine and the Pathological Department of the University of Pennsylvania.)

The case forming the substance of this report presented a group of interesting and unusual features. Some of them would be considered as quite out of harmony with the generally accepted view of the nature of leukemia. I think, however, that an analysis of the case will establish its identity as one of the more unusual forms of this disease.

The patient, A. D., was a dentist, aged forty years, who had been in practice for the past five years. Previous to this time he had lived on a ranch in the southern part of the United States. He was admitted to the University Hospital on January 1, 1907, under the care of Dr. Frazier, to whom I am indebted for permission to use these clinical notes.

Family History. Aside from the fact that several maternal uncles had died of tuberculosis, nothing in the patient's family history had any bearing upon his present condition.

Personal History. The patient had always been a man of good habits. He used neither alcohol nor tobacco to excess.

He had been married for ten years. His wife had had no children and no miscarriages. The patient denied venereal infection.

Previous Medical History. With the exception of the diseases of childhood, the patient had always enjoyed good health.

History of Present Illness. In the beginning of November, 1906, after having eaten rather liberally of pineapple, which he thought irritated his mouth, the patient developed an ulcer on the hard palate. This grew slowly but progressively worse, and about a month after its commencement he noted some ulceration of the gums of the lower jaw, localized to the lingual surface of the right side and the buccal surface of the left side. At about the same time the submaxillary lymphatic nodes became slightly enlarged and painful, first on the right side, and later on the left. The severity of these lesions steadily increased, but the patient was able to attend to his professional duties until a few days before his admission to the hospital.

Condition on Admission. On admission to the hospital the patient's temperature was 102°; pulse, 84; respirations, 24. His only complaint, aside from feeling slightly feverish, was soreness of the mouth and some difficulty in swallowing. He was found to be a man of good development and nourishment, and powerful physique. The physical examination, aside from that of the mouth and the adjacent lymph nodes, presents absolutely no features worthy of mention.

Mouth. The hard palate from the incisor teeth to within an inch of the uvula, the lingual surface of the right lower gingives, and the buccal surface of the left lower gingives are the seat of an extensive ulceration. The edges of the ulcerated areas are irregular but not ragged, nor have they a punched-out appearance. They do not bleed readily on being touched, and they present no evidences of granulations. The central portions of the ulcerations consist of a grayish-white slough, rather firmly adherent to the underlying tissues.

The bone is apparently not involved. The entire ulcerated area has an extremely offensive odor.

The tongue is covered with a heavy, shiny, grayish-yellow coating. The teeth are in good condition.

The submaxillary lymph nodes on the right side are slightly enlarged, firm, and tender; those on the left side are smaller and less tender.

Urine. Light amber; acid; specific gravity, 1022; no sugar or albumin; a moderate amount of mucus; numerous leukocytes, epithelial cells, and calcium oxalate crystals.

Sputum. Seropurulent; yellowish-white; offensive odor; numerous leukocytes and epithelial cells; a few erythrocytes.

Bacteriological Examination. Exhaustive bacteriological studies by Dr. D. H. Bergey revealed the following findings: In smears from the ulcerated areas there were found in great numbers streptococci, spirochetes, and an organism resembling the Bacterium fusiformum. Aërobic cutulres made from the same material showed practically a pure culture of streptococcus. Anaërobic cultures revealed streptococci and the Bacterium fusiformum. Sections taken from the diseased area and stained for organisms showed streptococci and a rod-shaped organism, apparently the Bacterium fusiformum. With specific stains no spirochetes or tubercle bacilli were found.

Blood Examination. Hemoglobin, 75 per cent.; erythrocytes, 3,400,000; leukocytes, 5400. Differential count: polymorphonuclear neutrophiles, 75 per cent.; lymphocytes, 19 per cent.; large mononuclear leukocytes, 4 per cent.; transitional cells, 2 per cent.; eosinophiles, none.

With these facts at hand, the etiology of the condition was extremely obscure, and a diagnosis was not made. Despite the patient's denial of venereal infection, antisyphilitic treatment was instituted on the possibility of the ulceration being specific.

The subsequent course of the disease will be given as

briefly as possible, consistent with a proper understanding of the case.

January 10.—Slight swelling and tenderness of the axillary lymph nodes on both sides was noted today. Temperature range has been between 100° and 103°. Patient has been uncomfortable and restless. Ulceration is slowly spreading. Leukocytes, 6800.

15*th.*—Blood culture reported sterile. Injections of diphtheria antitoxin instituted.

20*th.*—Patient has been receiving 9000 units of diphtheria antitoxin daily. Temperature has been showing a gradual downward tendency. The ulceration in the roof of the mouth is showing distinct signs of improvement; in the posterior portion granulations have appeared, and the odor has decidedly decreased.

25*th.*—Granulations on the hard palate progressing. The ulcerations on the lower gums increasing slightly. Temperature decreasing. Leukocytes, 6300. Diphtheria antitoxin discontinued.

February 2.—Injections of diphtheria antitoxin renewed. Leukocytes, 4500.

10*th.*—General condition considerably improved. Ulcerations continue to show slight improvement. Patient discharged to go to Atlantic City, where antitoxin injections will be continued under the supervision of Dr. Emery Marvel.

20*th.*—Patient readmitted. On frontal bone, just above right eye, is a tumor the size of a robin's egg. It is rather soft, but not fluctuating, and is not movable. General condition and condition of mouth about the same as on departure for Atlantic City.

Blood Examination. Hemoglobin, 72 per cent.; erythrocytes, 5,210,000; leukocytes, 8000. Differential count: polymorphonuclear neutrophiles, 64 per cent.; lymphocytes, 16 per cent.; large mononuclear leukocytes, 12 per cent.; transitional cells, 8 per cent.; eosinophiles, none.

25*th*.—Mass above right eye increasing in size. Right submaxillary lymph nodes slightly larger and more painful. Blood culture reported sterile. A dark red, umbilicated papule noted on the back of the neck. Lower down on the back are several red, shiny, non-umbilicated papules.

March 2.—A number of small, red papules similar to those above described have appeared on the chest. Those on the back have become larger, and some of them have become dark red and umbilicated.

Swelling over right eye increasing. Ulceration in mouth extending. Temperature steadily rising. Patient shows some mental hebetude.

Bacteriological examination of the mass over the right eye by Dr. Bergey showed micrococci similar to but *not* identical with streptococci; the examination of the umbilicated papules was reported sterile. Leukocytes, 4700.

5*th*.—Eruption has become much more marked over thorax, abdomen, and back. It appears first as small, dark red, glistening papules; within a day these become larger, and by the next day they have gone into the purplish, umbilicated stage.

The glandular masses on either side of the neck have become so large within the past few days that breathing is difficult.

9*th*.—Almost the entire trunk is covered with the eruption in various stages of development, and there are a few lesions on both arms and both legs. For the past week the temperature has remained between 102° and 105°.

Leukocytes, 5200. Differential count (500 cells): polymorphonuclear neutrophiles, 96 per cent.; lymphocytes, 1.6 per cent.; large mononuclear leukocytes, 1.4 per cent.; transitional cells, 1 per cent.

Died at 7 A.M., March 10.

Autopsy. The postmortem findings will be detailed as briefly as possible, only those tissues being described that presented pathological features.

External Appearance. The eruption described in the clinical notes presented the same characteristics after death as it had during life. The general distribution of the eruption and its multiform character, dependent upon the variations in age of the individual lesions, can be seen in the accompanying photographs. The remainder of the external examination confirmed the presence of the tumor over the right eye and the swelling of the submaxillary, cervical, and axillary lymphatic nodes described in the clinical records.

The spleen was greatly hypertrophied in all directions, and weighed 900 grams. It was pinkish gray, soft, and the follicles were prominent. The only noteworthy feature in the gastro-intestinal tract was a firm, non-ulcerated nodule presenting on the mucous surface of the ileum about two feet above the ileocecal valve. In the cortex of the right kidney was a moderately firm, well-marginated, grayish-red, structureless nodule about the size of a walnut. In the left kidney were three similar nodules about the size of peas. In the middle lobe of the right lung there was a firm, well-marginated, dark red nodule, and in the lower lobe of the same lung were two others of similar size and consistency. Within the mesentery, and not associated with the mesenteric lymph nodes, were a number of firm, well-marginated, pinkish-gray nodules, some of which showed slight surface umbilication. The retroperitoneal, mesenteric, mediastinal, and peribronchial lymph nodes were universally enlarged to the size of large beans. They were pinkish-gray in color, firm in consistency, and showed no central softening.

Microscopic Examination. The microscopic examination of the above described lesions showed one primary common feature—a lymphocytic infiltration. In the skin lesions this infiltration was in the subcutaneous tissue, and extended well into the corium. In some of the older lesions the overlying epidermis was necrotic; in others it was lifted from the corium, forming small bullæ, from which the fluid contents had apparently escaped. In the spleen there was marked

follicular hypertrophy, with extensive lymphocytic deposit in the pulp. The nodules in the kidney consisted of dense lymphocytic deposits, in the centre of the larger one of which necrosis had occurred. In addition to the lymphocytic deposits in the nodules of the lungs there was considerable hemorrhage. The nodules in the mesentery showed no variations from the lesions already described. The ulcerations in the mouth were the result of a dense lymphocytic deposit with necrosis of the overlying mucous membrane. The

FIG. 1.—Photograph showing the character of the nodules in the skin; some of them have become umbilicated.

nodule in the ileum was of a similar nature, without ulceration. The lymphatic nodes showed follicular hypertrophy with more or less extensive lymphocytic deposits in the sinuses, in some cases entirely obliterating the structure of the node. In some of the larger nodes there were numerous small areas of necrosis. There was no endothelial or connective tissue proliferation and no giant cells were found.

Bacteriological examinations made by Dr. Bergey resulted in the following findings: From one of the nodules in the

lungs the Sarcina lutea, Micrococcus aureus, and the Bacillus diphtheria were isolated. The diphtheria bacillus killed guinea-pigs in from forty-eight to seventy-two hours, with all of the typical lesions of experimental diphtheria. Cultures from one of the mesenteric lymph nodes showed a single colony of Bacillus diphtheria, conforming in all of its prop-

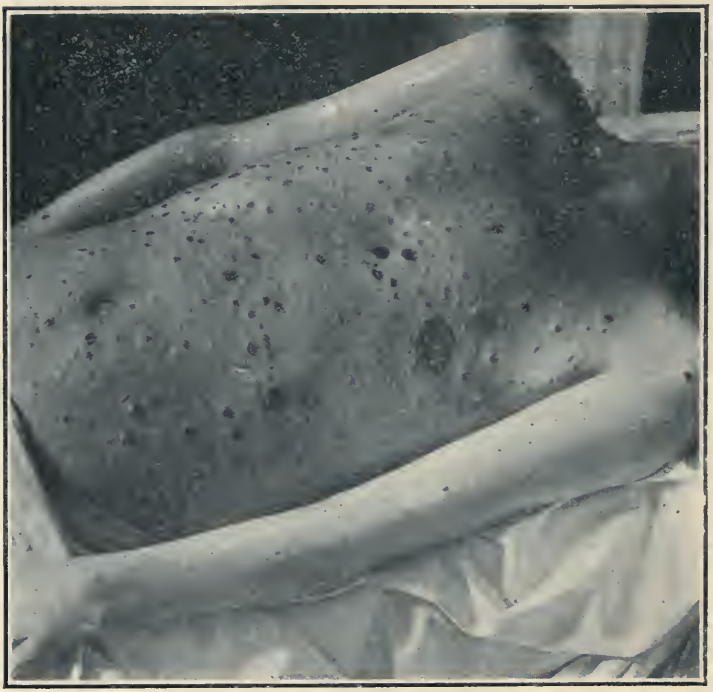

Fig. 2.—Photograph showing the distribution of the nodules in the skin.

erties to the one isolated from the lungs. Cultures from the liver and spleen remained sterile.

Remarks. In an analysis of this case a striking feature is at once appreciated in the lack of conformity between the blood picture it presented and the usual text-book interpretation of lymphatic leukemia. At no time during the disease

did the total number of leukocytes exceed the normal, and with the exception of a slight increase in the percentage of the large mononuclear and transitional cells on February 20, the percentage of the various cells usually classed as lymphocytes at no time exceeded the normal. However, it has long been recognized by hematologists that an increase in the

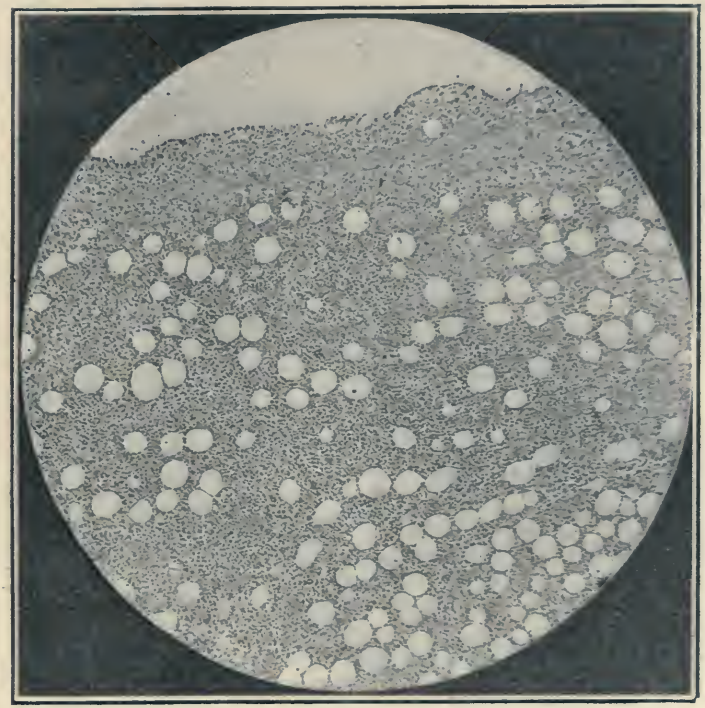

FIG. 3.—Photomicrograph of one of the nodules in the mesentery.

lymphocytes is not essential to a diagnosis of lymphatic leukemia. Türk,[1] in attempting to formulate a satisfactory classification of the lymphomatoses, divided lymphatic leukemia, both acute and chronic, into the following three varieties: (1) Lymphemic lymphatic leukemia, the common

[1] Wiener klinischen Wochenschrift, 1903, Nr. 39.

type, in which there is a high leukocytosis composed almost entirely of lymphocytes; (2) sublymphemic lymphatic leukemia, in which the total number of leukocytes is not materially increased, but in which the percentage of lymphocytes is increased; (3) alymphemic lymphatic leukemia, in which there is no alteration in the leukocytes as regards either their

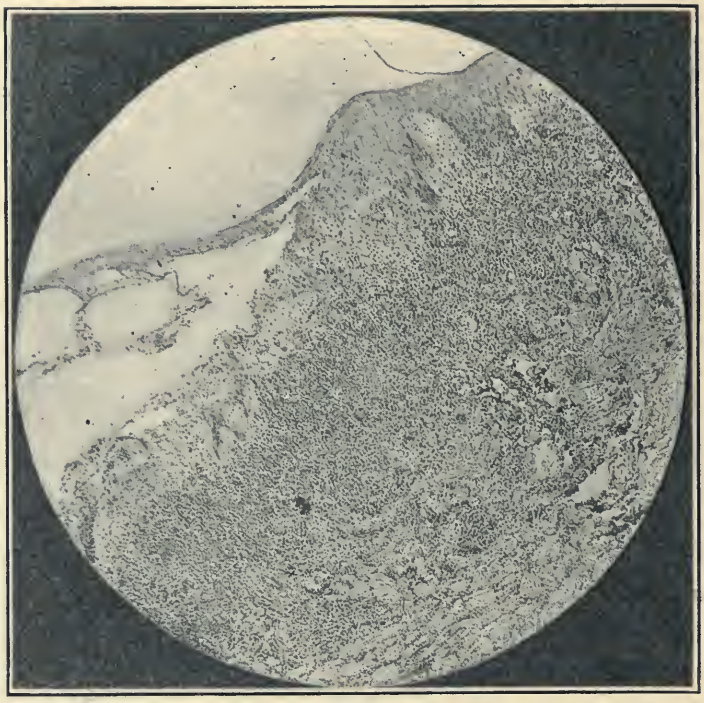

FIG. 4.—Photomicrograph of one of the nodules in the skin. Note the dense deposit of lymphocytes in the corium and the separation of the epidermis.

total number or the percentages of the individual varieties. This classification comprises all of the types of the disease ordinarily observed. When, however, we attempt to classify the case here reported according to Türk's scheme, it is seen that it does not conform to any one of the types. The total

number of leukocytes was never above the normal, and the lymphocytes showed a continuous diminution in number until on the day before death they were only 1.6 per cent. of a total of 5200 leukocytes. In other words, there was a marked

FIG. 5.—Photograph showing the swelling of the submaxillary lymph nodules and the large nodule over the right eye from which a piece of gauze packing protrudes.

lymphopenia, and it is to express this condition that I have used the term "lymphopenic" lymphatic leukemia.

An appreciation of the variations which the blood picture in lymphatic leukemia may undergo can be best obtained by an understanding of a theory of Türk's, which, artificial though

it be, is still very useful. He supposes that there is normally a definite ratio maintained between the production of lymphocytes and the rate of their extrusion into the blood channel. If, however, the tissues concerned in the production of lymphocytes become diseased, this ratio may become altered, so that the rate of extrusion of the lymphocytes becomes proportionally more rapid or less rapid than the rate of their production. Thus, for example, if there were some disease of the lymphatic tissues causing them to produce an abnormally large number of lymphocytes, and the rate of their extrusion were decreased, the lymphatic tissues would undergo great hypertrophy from the resulting retention of lymphocytes, but they would not be greatly increased in numbers in the circulating blood; if, on the other hand, the same increased production of lymphocytes occurred and the rate of their extrusion were increased, great numbers of them would appear in the circulating blood, but the hypertrophy of the lymphatic structures would be less marked than in the former case. Applying this theory to the case herein reported, we must assume that some influence incited the submucous lymphatic tissue of the mouth, the lymph nodes, the spleen, and possibly the bone marrow to an abnormally rapid production of lymphocytes, and at the same time the rate of their extrusion into the blood current was diminished, so that there resulted a rapid hypertrophy of the lymphatic structures but an unusually small number of lymphocytes in the blood.

The marked preponderance of ulcerative mouth lesions during the earlier course of the disease is possible of two interpretations. They may be looked upon as simple ulcerative lesions that acted as a portal of entrance for the infectious agent producing the leukemia, or as merely an early manifestation of the leukemia itself. I, personally, incline to the latter view, first, because the base of this ulceration was seen to consist microscopically of masses of lymphocytes, and secondly, because it is a well-known clinical fact that the

various portions of the gastro-intestinal tract are favorite seats for the deposit or proliferation of lymphatic tissue in the acute leukemias, the surface ulceration occurring as a result of this submucous proliferation. The history that the patient gave of the onset of symptoms shortly after having eaten heartily of pineapple, which he thought irritated his mouth, may have been simply the result of coincidence, though we are unable to exclude the possibility of this having instituted an ulcerative process that acted as a portal of entrance for the agent inducing the leukemia.

Concerning the etiology of the condition, no great amount of significance can be attached to the finding of spirochetes, fusiform bacteria, and streptococci in the ulcerated areas of the mouth, for these may be present in any severe inflammatory or ulcerative condition of the mouth. The finding of diphtheria bacilli in one of the nodules of the lungs and in one of the mesenteric lymph glands is somewhat more suggestive, but by no means conclusive, for their presence may have been entirely of the nature of a secondary invasion. The improvement that the patient manifested on injections of diphtheria antitoxin can scarcely be attributed to any specific action, and little significance from the etiological standpoint can be attached to its occurrence.

Of decidedly unusual interest during the later course of the disease were the skin manifestations. These, shown by microscopic examination to be true lymphocytic deposits, gave the case a picture very like that of the "lymphodermia perniciosa" of Kaposi, recognized by its describer as being closely allied to leukemia, and probably also to mycosis fungoides.

CONGENITAL OBLITERATION OF THE BILE DUCTS WITH CIRRHOSIS OF THE LIVER.*

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(From the Pepper Laboratory of Clinical Medicine and the Pathological Department of the University of Pennsylvania.)

My attention was first directed to the study of this condition by Dr. J. P. C. Griffith sending to me for examination the liver obtained from an infant dying at the age of six months. The necropsy was limited to the removal of the liver and it was received by me with only the slightly dilated hepatic portions of the bile ducts attached. However, the clinical course and the changes in the liver were of such a nature as to make it permissible to consider the case, on the basis of probabilities, one of congenital obliteration of the bile ducts with cirrhosis of the liver.

The infant when born was a normal twelve-pound baby. From birth it had been deeply jaundiced, the stools clay colored and the urine deeply pigmented. Shortly after birth the child lost in weight but later gained. The infant was brought to the University Hospital to the service of Dr. Griffith, to whom I am indebted for permission to publish these notes, when it was five months old. On admission it was a somewhat emaciated infant, deeply jaundiced, with a few small purpuric spots on the scalp. The liver extended from the fifth rib to three centimeters below the costal margin in the mid-clavicular line. The spleen extended two and one-half to three centimeters below the costal margin. The urine, aside from showing a large amount of bile, was normal. The examination of the blood showed three million nine hundred thousand red corpuscles, fourteen thousand leucocytes and sixty-eight per cent of hemoglobin. An examination of the feces for bile pigment was negative. The temperature varied between 98° and 100° F. until a few days before death when it varied between 98° and 103° F. About a week before death a large blood-filled cyst developed above the right ear. With progressive loss of weight and strength the child died at the sixth month of life.

At necropsy the liver was found to be dark green, large

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and firm and the surface irregular. On cross section, minute streaks and bands of gray were seen running in various directions throughout the substance. On microscopic section there was seen to be an extensive increase in the perilobular connective tissue with proportionally great multiplication of bile canaliculi. In a number of areas as many as twenty to thirty of these canaliculi could be counted in the connective tissue about the periphery of one lobule. Here and there the connective tissue invaded the lobules, but it was in general confined to the periphery. The connective tissue within the lobules was of a younger and more cellular type than that about the periphery. Many of the small intrahepatic bile ducts were distended and there was extensive deposit of bile pigment within the liver cells and connective tissue, somewhat more marked in the center of the lobules than on the periphery.

As far as I have been able to determine, the first record in the literature of this condition is by Cheyne, who, however, apparently slightly misinterpreted the findings. In his essays on "Diseases of Children," published in 1801, he speaks of "an original and incurable malconformation of the liver," which "malconformation is probably an impermeable thickening of the beginnings of the hepatic ducts or, as they are called, the Pori Biliarii." Since then a number of instances of the condition have been recorded and several more or less exhaustive treatises have been written upon the subject, the most notable being those of Thomson,[55] Giese,[19] and Skormin.[51] Though there have been variations in the degree of the cirrhosis found and variations in the localization of the biliary obstruction in the different cases, there is comparative uniformity of opinion as regards the clinical picture and the gross and microscopic pathological findings. The subjects are always deeply jaundiced either from birth or from a day or two later, the stools remain clay colored, and the urine deeply pigmented. Frequently the child remains well nourished for a considerable time and the bodily functions are performed in a manner strikingly out of harmony with the severity of the actual lesion. At times, and especially

has this been so in the cases reported in the early part of the past century, hemorrhages from the umbilical cord or from other portions of the body have been noted. Cheyne interpreted this association of jaundice and bleeding according to our present view as shown by his statement: "The bleeding proceeded from the unhealthy change produced in the blood by the reception of the bile into the mass of fluids." Frequently the large, hard liver can be felt as well as at times its uneven surface. The spleen is usually enlarged; at times ascites is present. The child dies usually before the eighth month; only three cases amongst the sixty-two that I have collected from the literature exceeded this limit, two living until the ninth month and one until the eleventh month. The pathological changes in the liver are those of a multilobular and monolobular cirrhosis with some intralobular involvement and a marked multiplication of bile canaliculi.

As regards, however, the actual cause of the condition, whether the primary lesion is that of the bile ducts or that of the liver, whether the changes in the ducts are due to a developmental anomaly or to the organization subsequent to an inflammatory process, great difference of opinion prevails. It is this phase of the subject that has especially appealed to me and is the one to which I shall devote the remainder of my remarks.

We shall consider firstly the question as to whether the condition is primary in the liver or in the bile ducts, and, if possible, come to some conclusion. Rolleston[80] is the most ardent supporter of the view that the cirrhosis is the primary condition induced by some poison being excreted by the liver and setting up in that organ a cholangitis that subsequently descends to the larger bile ducts and there sets up an inflammation that later leads to organization. In favor of his view he presents the following four arguments:

(1.) "The almost constant occurrence of cirrhosis in these cases of bile duct obstruction in infants as compared with the infrequency and irregularity with which cirrhosis follows obstruction of the larger bile ducts in later life." As to the alleged infrequency of the occurrence of cirrhosis

in adults consequent upon biliary obstruction, Mangelsdorf,[81] in 1882, collected one hundred and eighty-four cases of this condition, and in 1901 Ford[82] added twenty-four to this series. The obstruction in most of these cases was the result either of calculi or carcinoma of the pancreas or bile ducts. How many more cases have never been accorded the dignity of a report we cannot calculate, for so soon as a condition has been observed frequently enough for two hundred or more instances to have been reported, it is no longer of sufficient interest to warrant an individual report. Moreover, if the bile duct obliteration is secondary to the cirrhosis, why do we not find more frequently in adults obstruction of the ducts secondary to a Hanot's cirrhosis, a condition in adults essentially the same as that claimed by Rolleston to be the primary condition in children, namely, a descending cholangitis? A feature that impresses me as being of significant importance in this connection is the fact that in twenty-four (1, 10, 11, 13, 20, 23, 24, 25, 26, 29, 33, 34, 35, 38, 39, 42, 43, 44, 48, 50, 51, 54, 58, 59) of the sixty-two cases that I have collected, the obstruction was in the duodenal portion of the ducts and the hepatic portion was patulous, whereas, in only ten of the cases (3, 12, 17, 19, 22, 36, 45, 47, 56, 60) was the obstruction more marked in the hepatic end than in the duodenal end. If this obstruction were the result of an extension of inflammation from the liver it would be most natural for the involvement to be in those portions of the ducts nearest to the liver rather than in those portions farthest removed from it. Again, there have been cases of obliteration of the ducts in those dying very shortly after birth and in which, as far as the organ was described, only the earliest stages of cirrhosis of the liver have been found (1, 4, 8, 12, 23, 26). The only rational deduction that I think can be drawn from the association of these three facts, obstruction, early death, and little cirrhosis, is that the biliary stasis had not existed long enough to have produced more advanced changes. Rolleston admits in regard to Ross's[73] case that the evidence points in favor of the lesion in the duct being primary, but says that in the other cases as far as one

can judge fibrosis in the liver is quite as old as the lesion in the bile ducts. How one can judge of the relative ages of advanced fibroid change in two structures so totally different in function and morphology as the liver substance and the bile ducts is beyond my comprehension.

(2.) Rolleston's second point in favor of the cirrhosis being primary is the large size of the liver, resembling hypertrophic biliary cirrhosis. It is true that the livers of hypertrophic cirrhosis and obstructive cirrhosis resemble each other in size, but it is also true that the livers in cases of cirrhosis known to be due to biliary obstruction are large. Let me quote Ford's statement which is based on the one hundred and eighty-four cases reported by Mangelsdorf and the twenty-four cases collected by himself: "The livers in these cases of obstructive cirrhosis are greatly enlarged with a rough jaundiced surface and considerable perihepatitis." Very late in the process it is possible to have a decrease in the size of the organ in these cases of obstructive cirrhosis as in practically every other hypertrophic process in the liver, but the majority of cases of congenital obliteration do not live long enough for contraction to result.

(3.) Rolleston's third argument is "the large size of the spleen, a phenomenon not met with in uncomplicated biliary obstruction." This statement is undoubtedly correct but it can scarcely be construed as having any bearing on the subject under discussion, for these cases are practically all complicated by hepatic cirrhosis, and as Rolleston [103] himself says in discussing cirrhosis resulting from biliary obstruction in the adult, "the spleen is sometimes small or of normal size, but in cases where considerable fibrosis of the liver co-exists with obstruction of the larger ducts, as in Weber's cases, there may be very considerable enlargement, though not to the same degree as in hypertrophic biliary cirrhosis."

(4.) The fourth point Rolleston presents in favor of his view is "the fact that in some instances several cases of this rare disease have occurred in the same family." He does not mention the cases to which he refers. In a thorough

search through the literature I have been able to find but one instance in which more than one member of a family was shown by autopsy to have had an obliteration of the ducts. This was in a report by Binz[4] of two brothers, one dying when twenty-four hours old and the other on the second day. In both of them the cystic, hepatic, and common ducts were transformed into an irregular fibrous mass entirely without lumina. In the first case the liver was reported as being slightly enlarged and soft; the only note of the liver in the second case was that the capsule was thickened. The father was supposed to have had syphilis, and it is not improbable that both cases were instances of congenital syphilis. West[56] has reported one case dying of congenital obliteration of the bile ducts in which other children of the same mother were supposed to have died o the same condition, but there were no autopsies to support this supposition. A second case reported by West,[56] one of a number of sisters and brothers dying as claimed of congenital obliteration of the bile ducts, has insufficient data to warrant this diagnosis, and on the other members of the family no autopsies were performed. Thomas[54] reports a case of congenital obliteration in a child dying on the twelfth day; four other children of the same parents died before the ninth day of life, all jaundiced. Though Thomas assumes that they all died of the same condition, there were no autopsies to confirm his view. A few other instances, those of Arkwright,[83] Blomfield,[84] and Pearson,[85] have been reported in which several infants in one family have died with jaundice, but they had few, if any, of the symptoms of biliary obstruction and no autopsies were performed, so that when one considers the numerous causes of jaundice and subsequent death in childhood it is scarcely necessary to state that we cannot include these cases, however suggestive some of them may be, in the present consideration.

Furthermore, if we consider the cirrhosis to be primary and caused by he circulation through the liver of substances irritating to it, would it not be rational to look for

inflammatory lesions, the result of the same irritating substance in other organs? Such lesions have not been recorded in any of the autopsies on these cases. Moreover, as Rolleston himself admits, as speaking against his view, it would also be expected that the mother would give some evidence of the circulation of these toxic substances through her own organs.

With the presentation of the above facts, I think we are justified in considering that there is little or no support of the view that the obstruction is secondary to a cirrhosis. In support of the claim that the obstruction is the primary condition, and the cirrhosis a result of the ensuing biliary stasis, is the great weight of evidence that in both adults (Mangelsdorf[81]) and children (Ford[8]) biliary stasis has resulted in the same chain of events and the same pathological findings as are presented in these cases. Furthermore, the work of Steinhaus,[86] Pick,[87] Lannaeq,[88] Gerhardt,[89] Beloussow,[90] and Harley[91] showed in experimental obstruction in animals the same changes in the liver as are found in these cases of biliary stasis in human individuals.

Let us now see if we can determine the nature of these lesions in the ducts that give rise to the ensuing changes. The possibilities to be considered as causing the obliteration are primarily three: 1st, a developmental anomaly; 2d, the organization of a non-specific intrauterine inflammatory condition located in the ducts themselves, and 3d, a syphilitic induration of the ducts.

1. An anomaly of development. — A number of facts speak strongly for an anomaly of development being the causal factor in many of the cases. Firstly, the fact that the bile ducts are originally solid cords, Remak's fibers, as they are called, and that subsequently these have lumina formed within them suggests that obliteration may be the result of a simple failure of lumination in some portion of the biliary tract. According to Hertwig, quoted by Mohr,[41] the earliest fetal evidence of the liver and ducts is a solid cord that grows out from the gut tract about the third week. The

peripheral end of this branches to form the bile capillaries while the proximal end forms the hepatic duct. After a short time this entire mass detaches itself from the gut tract and lies free in the abdominal cavity. Some time later a second budding takes place from the gut tract to form the ductus choledochus which grows outward to join the ductus hepaticus already formed. This is a very suggestive fact, for in some of the cases (6, 16, 32, 46, 55) the obliteration was just at the point of junction of the hepatic and common ducts, the portions above and below this point being patulous. It seems plausible that the obliteration may have resulted from a faulty union of the two rudimentary portions of the ducts.

A feature lending even more weight to the view that an anomaly of development may be the cause of the condition under discussion is the occurrence of other undoubted anomalies of development in the liver and its appendages and the occasional occurrence of impervious ducts associated with striking congenital defects in other portions of the body. In the first group are such cases as those of Simpson [68] in which the gall bladder, the cystic duct, and the caudate and Spigelian lobes were all found absent. Simple congenital absence of the gall bladder as noted by Morgagni, Wahlbom and Büttner (quoted by Meckel [92]), Förster [93] and others is a not unusual occurrence. Eshner [94] collected a number of instances of this condition and reported one of his own.

In the second group are such cases as that of Feer [14] in which there was complete situs inversus associated with obliteration of the ducts; that of Witzel [95] in which there was obliteration of the ducts, situs inversus, cystic liver, cystic kidneys, absence of both eyeballs and other minor defects; and the case of Herbert [96] in which there was a persistent ductus Botalli and absence of the hand and ulna of the left arm associated with obliteration of the ducts. The association of these marked anomalies of development with impervious ducts is to my mind a feature of great significance and leads me to believe that a large percentage

of the cases of congenital obliteration are a result of a congenital defect of development.

2. The organization of a non-specific inflammation of the ducts. — In regard to this possibility it is difficult to say much on the basis of observation on account of the fact that these cases present themselves for study only long after the manifestations of an acute process would have been replaced by the fibroid changes which are not characteristic of any particular form of inflammation. Wronka [62] believes that the force and rapidity with which bile is expelled from the ducts in difficult labors may produce irritation and inflammation, and reported a case of an icteric infant dying on the eighth day in which the autopsy revealed a hemorrhagic-diphtheritic inflammation of the bile ducts. However, most of these cases undoubtedly have their origin a considerable time before birth. In Virchow's Archiv for 1867 four cases were reported in which simple catarrhal inflammation of the bile ducts was supposed to have caused a partial fibroid obliteration of them. Nevertheless, the relative infrequency of catarrhal jaundice in infants compels us to look upon inflammation of the ducts with subsequent organization as an improbable cause of the obliteration in the majority of cases, though it is possible that in intrauterine life the ducts are subject to some influences not present after birth.

3. Syphilis. — In a review of the cases appearing in the literature it will be observed that there are a number of syphilitic conditions affecting the liver and gall ducts simulating the one under discussion. Thus Lommer [35] reports a case of a macerated syphilitic fetus born dead in which the ductus choledochus was transformed into a fibrous cord and the right lobe of the liver was the seat of a syphilitic hepatitis. Schüppel's [69] third case was similar; the portal vein, hepatic artery, and hepatic duct of an infant dying on the ninth day were involved in a dense syphilitic infiltrating mass that extended into the liver. The cases of

Beck [97] and Chiari [98] showed a gummatous infiltration of the bile ducts with more or less constriction resulting, but no involvement of the liver. Again, there have been cases such as those of Hansemann,[99] Neumann,[100] d'Espine and Picot,[101] and Henoch [102] in which the livers have resembled biliary cirrhosis without obstruction, but have been thought by their observers to be due to an interstitial syphilitic hepatitis. In some of the cases (Neumann [63] and Ashby [3]) there has been a history of parental syphilis, but none of the stigmata of congenital syphilis in the infants. Two of the reporters of cases (Skormin [51] and Roth [50]) though presenting no basis for their view held syphilis accountable for the bile duct obliteration in their cases. I can see no rational basis for looking upon the condition as syphilitic, when the numerous, definite lesions of congenital syphilis are lacking.

Lastly, it is worthy of mention that a striking simulation of obliteration of the bile ducts can be conceived of in a condition such as was presented by Ford's [82] case: the patient was an infant with tuberculosis of the cervical lymph glands, developing at the age of one and one-half years deep jaundice, with clay-colored stools and pigmented urine. Later the liver became enlarged, and at autopsy a typical biliary cirrhosis was found as the result of an inflamed gland at the hilus of the liver pressing upon and completely obstructing the common duct. This case, furthermore, adds convincing evidence of the secondary nature of the cirrhosis in obstruction of the ducts, as the microscopic changes in the liver were identical with those found in congenital cases.

Let me add a word in regard to the use of the term "congenital obliteration of the ducts." Though I have used this term throughout my remarks, I believe that it does not most accurately express the existing condition. The word "obliteration" presupposes the existence of a lumen which subsequently becomes destroyed. As it is my belief as presented in the above analysis that the condition is in most cases the result of an anomaly in which there is a failure of formation of a lumen rather than a destruction of it, I believe

that the term "atresia of the bile ducts" would better express the existing condition.

Treatment. — As will be readily appreciated from an understanding of the condition of the bile ducts in these cases medical treatment is valueless. Surgical intervention may in suitable cases give some hope, for if the obstruction is low in the ducts a rational procedure would be to form an anastamosis between some portion of the small intestine and the upper, patulous portion of the ducts. Operation was unsuccessful in the cases of Putnam,[47] Giese,[19] and Morse and Murphy.[43] Nevertheless, since the outlook without operation is absolutely hopeless, and operation can be of service in suitable cases, one would be justified in resorting to this measure.

CONCLUSIONS.

1. In the congenital condition of which the two most prominent features are an obliteration of some portion of the bile ducts and a more or less extensive degree of cirrhosis of the liver, the obliteration of the bile ducts is the primary condition and the cirrhosis a result of the ensuing biliary stasis.

2. In the majority of instances the obliteration of the ducts is the result of an anomaly of development, a failure of the formation of a lumen.

3. The term "atresia of the bile ducts" better expresses the existing condition than "obliteration of the bile ducts."

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A NEW INSTRUMENT FOR MEASURING MARKED DIFFERENCES IN EXPANSION ON THE TWO SIDES OF THE CHEST.

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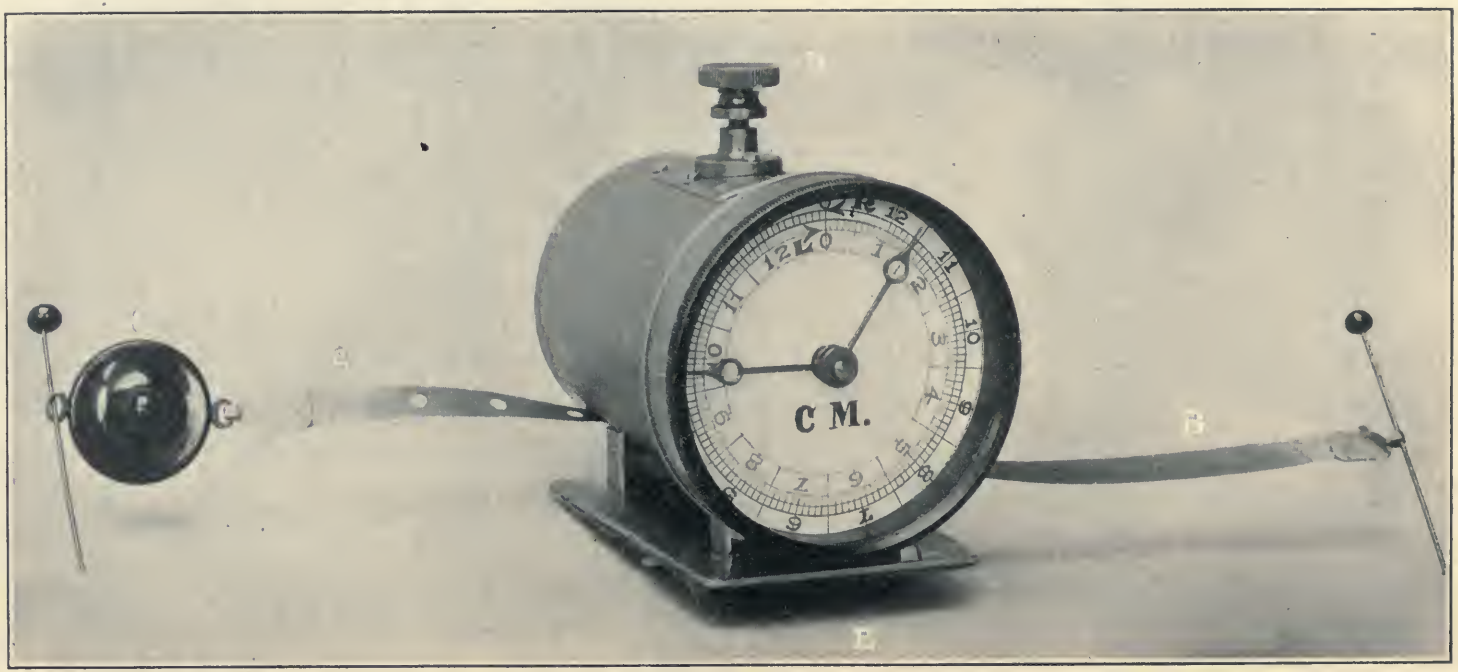
The instrument shown in the accompanying illustration was designed with the hope of its being of some diagnostic value in determining differences in the expansion of the two sides of the chest. This hope, however, had to be abandoned, as it proved to be of not sufficiently delicate accuracy, and its use is limited to that indicated in the title, the demonstration of marked differences of expansion on the two sides of the chest.

The instrument consists of a metal cylinder, on the top of which is a dial with centimeters marked in both directions from the zero point. Running from either side of the metal cylinder is a steel tape (*A B*), to the end of which a button (*C*) is attached. These two tapes work upon cylinders, the movements of which are independent of each other. Each of these cylinders is controlled by a spring, and is connected with the hands registering on the dial in such a way that the tapes may be withdrawn and allowed to return at will, the hands meantime remaining perfectly stationary. As soon, however, as the button *D* is pressed downward, the hands and cylinders are connected, so that movements of the tape


C M.

are registered in centimeters on the dial. The advantage of this arrangement will be seen in the manipulation of the instrument.

To use the instrument, the disk *E* is placed upon the sternum, a little below Ludwig's angle; the tapes are drawn horizontally about the chest and joined to the button *C*, which is placed directly upon the spinal column. With the instrument in this position, the patient inspires and expires at will without the respiratory movements having any influence upon the hands, both of which are resting at the zero point. At the beginning of any chosen inspiratory act, with usually the coincident request to the patient for a deep inspiratory effort, the button *D* is depressed, and the two hands move in accordance with the increase in circumference of the respective sides of the chest, the expansion of the right side registering on the outer line *R;* the left, on the inner line *L*. The two features which are apparently most potent in preventing the registration of small differences in expansion are the various degrees of compressibility of the soft tissues of the chest and the friction that at times exists between the skin surface and the steel tapes. These two conditions make possible the registration of only such degrees of difference as could be appreciated, though not so graphically, without the use of an instrument.

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TYPHOID MENINGITIS WITHOUT OTHER LESIONS.

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(From the William Pepper Laboratory of Clinical Medicine.)

The case forming the topic of these remarks presents an interesting and unique picture. Unfortunately, one of the links in the chain of clinical and pathological findings is missing, but the facts obtained are sufficiently striking to permit in the author's judgment of a rational deduction as to the nature of the case.

The patient was a woman, aged twenty-six years, admitted to the University Hospital on April 22, 1906, to the service of Dr. Stengel, to whose courtesy I am indebted for the use of the clinical data. The chief complaints were intense frontal headache, fever, vomiting, and photophobia.

Previous History. The patient had been healthy and vigorous excepting for an alleged attack of typhoid fever several years ago. For a number of weeks previous to the onset of the present illness she had assisted in nursing her brother through a severe attack of typhoid fever.

History of Present Illness. Four days before admission the patient was suddenly seized with agonizing frontal head-

ache associated with vomiting, photophobia, and great muscular soreness. These symptoms persisted until admission to the Hospital. There had been suppression of urine for thirty-six hours. Fever appeared two days before admission. On admission temperature was 103°; pulse, 80; respirations, 16. The patient was slightly stuporous, but not delirious, and she bore an expression of extreme suffering.

Physical Examination. The physical examination revealed absolutely no abnormalities excepting for pain over the forehead on pressure. There was no rigidity of the neck, no cranial palsies. Knee-jerks were normal. Kernig's sign was not present. There was no eruption. The spleen was not enlarged. There was no abdominal tenderness.

Urinalysis. Pale yellow; acid; specific gravity, 1024; thick, flocculent precipitate; triple phosphates and epithelial cells. Albumin and sugar negative.

Blood Examination. Hemoglobin, 72 per cent.; red blood corpuscles, 4,020,000; white blood corpuscles, 20,640.

April 25. Patient was mildly delirious. Kernig's sign was present.

27*th.* Tache cerebrale was noted.

30*th.* Rigidity of neck was observed.

May 3. Hematuria occurred.

4*th.* The patient developed edema of the lungs and died.

During the first two days' residence in the hospital the temperature varied between 101° and 103.3°. From then until death it remained between 99.3° and 102°, the fluctuations occurring without any regularity. The leukocytes remained in the neighborhood of 20,000 from the time of admission until death. Two Widal tests were made. The first was on April 23, approximately the fifth day of the disease, and was negative in dilutions of 1 to 10 and 1 to 50; the second was on April 26, the eighth day of the disease, and was positive in dilutions of 1 to 10 and 1 to 50.

On April 27 a lumbar puncture was performed, and from the fluid obtained cultures were made. The technique was

as follows: The original cultures were made on agar plates after the usual manner. About twelve colonies were obtained on the first plate, fewer on the others. They were all of the same type, conforming entirely to the characteristics of the typhoid bacillus. From these colonies inoculations were made on agar slants, potato, glucose agar, lactose agar, saccharose agar, bouillon, milk, gelatin tubes, gelatin plates, and agar plates. The results of all of these inoculations conformed absolutely to the cultural peculiarities of the typhoid bacillus.

A twenty-four-hour bouillon culture of this organism was then tested with the serum in dilutions of 1 to 10 and 1 to 50 of a stock rabbit immunized to the typhoid bacillus. The agglutination was complete.

The same culture was treated with the serum of rabbits immunized to the paratyphoid bacillus and to the colon bacillus, and the result was negative.

On April 27 blood cultures were made, all of the five flasks used remaining sterile.

Such stringent objections to the performance of an autopsy were made by the family that it could not be performed until twenty-four hours after death, by which time the body had been injected by the undertaker, a process which excluded the possibility of making cultures.

The autopsy presented absolutely negative findings excepting for the meninges. Especially to be noted are the facts that there were no intestinal lesions and that the spleen was not enlarged. Over the convexity of the right cerebral hemisphere, slightly anterior to the premarginal fissure, was a collection of thick pus in the pia-arachnoid. Slightly below and anterior to this area was a smaller area of similar character. The frontal portion of the left convexity showed one small focus of the same nature. No exudate was visible on the base. No tubercles could be determined in any portion of the meninges. The ventricles contained a moderate amount of light-yellow, slightly turbid fluid.

Smears from the purulent exudate showed a large number

of Gram-negative bacilli of the morphological characteristics of typhoid bacilli and a few larger, Gram-positive bacilli. Stains for tubercle bacilli were negative.

The particularly interesting features to be extracted from the above clinical and pathological data are: (1) The onset of symptoms of meningeal irritation at the end of a number of weeks' attendance on a case of typhoid fever; (2) the occurrence of a negative Widal five days after the onset of the symptoms and a positive Widal eight days after the onset; (3) the isolation of typhoid bacilli from the cerebrospinal fluid, and (4) the finding in the meningeal exudate of bacilli harmonizing with the morphological peculiarities of typhoid bacilli, associated though they were with bacilli of another type.

The onset of the symptoms after a number of weeks' attendance by the patient on a case of typhoid fever is a very suggestive occurrence. As to the probable mode of ingress of the bacillus we can but theorize. Some observers claim the possibility of the typhoid bacillus gaining entrance through the respiratory tract, while others contend that it is only through the gastro-intestinal tract that the bacillus enters the body. If we look upon the latter as the route of infection in our case, we must assume the possibility of the organism penetrating the mucous membrane of the gastro-intestinal tract, without the production of any lesions in the tract. Moreover, in this case we in all probability have no general infection such as occurs in the usual case of typhoid fever with intestinal lesions, as indicated by the negative blood cultures. This complete localization of the process is probably responsible for a number of features very unlike those of ordinary typhoid: the leukocytosis, the irregular temperature, the absence of rose spots, and splenic enlargement. The history of a possible attack of typhoid fever some years ago is very interesting in this connection. It suggests that a general infection with the typhoid bacillus does not protect against a subsequent local infection if the organism finds a suitable

habitat, though we cannot exclude the possibility of the organism having gained access to the body by passing through the mucous membrane of the intestines, leaving it apparently unharmed. It impresses the author as more rational to consider the infection as having occurred directly from the nasal cavities, where the organism may have been deposited directly from the air or by the patient's fingers.

The absence of a Widal reaction until the eighth day of the disease, the time of its usual occurrence in ordinary typhoid fever, is a very striking feature. Von Leube[1] says: "The occurrence of first a negative and, subsequently, a positive Widal reaction is the most reliable response to the test. In such cases typhoid can be positively diagnosticated." We can only assume that the local infection with the bacillus typhosus imparts to the blood serum the same agglutinative properties as does a general infection.

The isolation of the typhoid bacillus in pure culture from the cerebrospinal fluid is a fact needing no explanation, and one which, in conjunction with a clinical data, leaves little doubt as to the nature of the infection. The fact that in the smears from the meningeal exudate bacilli of different morphology were found in association with the typhoid bacillus has at most only the significance of a secondary infection. The deplorable inability to have made cultures from this exudate naturally makes the deductions as to the etiology of the case somewhat less positive, but, excepting to the most exacting critic, the typhoid bacillus must be looked upon as the cause of the purulent meningitis.

Cole,[2] in 1904, collected a number of more or less authentic cases of meningitis with serous or purulent exudate complicating ordinary typhoid fever with intestinal lesions.

Neumann and Schaffer[3] report a case of meningitis unassociated with other lesions, from the exudate of which they

[1] Münch. med. Woch., 1898, Nr. 8.
[2] Johns Hopkins Hospital Reports, 1904, vol. xii, p. 379.
[3] Virchow's Archiv, Band 109.

isolated an organism similar in most characteristics to the bacillus typhosus, but differing from it in others, so that they were not willing to identify the organism as typhoid.

I have been unable to find any case in the literature in which the typhoid bacillus was the apparent cause of a meningitis unassociated with intestinal lesions.[1]

I desire to take this opportunity of expressing my appreciation of Dr. Cope's work in the isolation and identification of the typhoid bacillus in this case.

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[1] Henry and Rosenberger reported before the Philadelphia Pathological Society a case, soon to appear in print, of typhoid meningitis without intestinal lesions.

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THE NATURE OF APLASTIC ANEMIA AND ITS RELATION TO OTHER ANEMIAS.[1]

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

Aplastic anemia was first described by Ehrlich[2] in 1888. Since that time isolated cases have been reported and recently the condition has received considerable attention. The following typical case occurred in the University Hospital in the service of Dr. Stengel, to whom I am indebted for the clinical data.

J. C., female, aged thirty-three years, white, married, was admitted to the University Hospital December 18, 1905, complaining chiefly of palpitation of the heart and vomiting after taking food.

Previous Medical History. The patient had measles, whooping-cough, and chicken-pox during childhood; diphtheria at twenty-two years; "congestion of the lungs" at twenty-five years. Menstruation began at eleven years, and has always been regular and at times painful. For the past eleven years, since her last child was born, the discharge has lasted about a week and has been profuse. The patient says that until the onset of the present illness she has always been robust.

Social History. The patient was married at the age of nineteen years, and is the mother of two healthy children, respectively twelve and eleven years of age. She had one miscarriage three years ago, apparently induced by severe exertion. Her work has been confined to household duties.

Family History. The patient's father died of "liver abscess" at the age of thirty-eight years. Her mother is living and well at fifty-seven years. Four sisters are living and well. There is in the family no history of tuberculosis, cardiac or renal disease, or neoplasm, and no condition similar to that of the patient.

History of Present Illness. The present trouble dates from about eight weeks ago, when the patient noticed that she was becoming

[1] Read at the meeting of the Association of American Physicians, Washington, D. C., May 15 and 16, 1906.

[2] Charité Annalen, 1888, xiii.

pale, objects appeared yellow to her, and she was constantly fatigued. Six weeks ago she began vomiting after taking food. This vomiting was inhibited by her lying down. Shortly after the vomiting commenced cardiac palpitation and dyspnœa on the slightest exertion made their appearance, and the patient noticed that she was becoming progressively paler and weaker. She judges that in the past eight weeks she has lost about twenty pounds. During the last week she has had six attacks of temporary unconsciousness lasting about five minutes each. They were induced by no apparent cause. She has not fallen in the attacks, has not bitten her tongue, and has had no convulsive movements during the attack. Her appetite is poor and the bowels constipated. She has sour eructations and vomits on the slightest exertion or excitement. She has noted no discharge of blood from the mucous membranes. The feet have not been swollen.

Physical Examination. The patient is a large-framed woman with subcutaneous fat well preserved. The contrast between the degree of nutrition and the degree of anemia is very striking. The skin is of a lemon-yellow color, the mucous membranes are universally pale.

There are no areas of hemorrhage in the skin or visible mucous membranes. There is no enlargement of the thyroid, or of the cervical, axillary, or epitrochlear glands. No jaundice. Pupils are equal and react sluggishly to light. The patient complains of some loss of vision in the left eye. Teeth are imperfect and carious. Thorax is well-formed. Pulmonary resonance extends anteriorly from one inch above the clavicle to the lower border of the sixth rib in the midclavicular line on the right; to the middle of the fourth rib on the left; posteriorly on the right, to the tenth dorsal vertebra; on the left, to the angle of the scapula. Below the angle of the scapula the resonance is somewhat impaired down to the tenth dorsal vertebra. In this area fremitus is diminished and breath sounds are feeble. No rales are heard. This area of diminished breath sounds extends anteriorly to the midaxillary line. In the remaining pulmonary area the breath sounds and fremitus are normal. The usual band of resonance over the shoulder is present on both sides. The physiological difference in breath sounds between right and left apex is less marked than usual.

The right border of the heart dulness is at the right border of the sternum; upper border, middle of fourth rib; left border, one inch outside of the left midclavicular line in the fifth interspace. The apex-beat is in the fifth interspace three-fourths of an inch inside of the midclavicular line. No thrills are present. There is a soft systolic murmur at the apex, heard also at the base, and most intense at the fourth interspace one inch to the right of the sternum. There is a slight accentuation of the pulmonic second sound. There is a continuous murmur heard over the innominate artery resembling

a venous hum in its rhythm. There is also a dull venous hum high in the neck, over the jugular vein.

The abdominal walls are thick, but the abdomen is neither distended nor retracted. The liver dulness extends from the lower border of the sixth rib to within one inch of the costal margin in the midclavicular line. It is not palpable. Neither kidney is palpable. No tumor is discovered in the abdomen. The spleen is not enlarged, extends from the eighth to the tenth rib. It is not palpable. Nervous examination reveals no irregularities of reaction or sensation.

Urine Analysis. Amber, clear, slightly acid; specific gravity, 1010; slight trace of albumin; no sugar.

Gastric Analysis. Free HCl, 36. Total acidity, 64. No lactic acid. No Oppler-Boas bacilli.

Feces Analysis. Stool is yellow, hard, and alkaline. Contains considerable vegetable detritus, a small amount of casein, triple phosphates, and a small amount of soap. Bile is present. There is no occult blood and no indication of the presence of parasites.

Blood Examination. Hemoglobin, 10 per cent.; red blood corpuscles, 800,000; white blood corpuscles, 2560; color index, 0.62. Differential count: lymphocytes, 67 per cent.; polymorphonuclear neutrophiles, 27 per cent.; polymorphonuclear eosinophiles, 0.4 per cent.; large mononuclear leukocytes, 3.5 per cent. No myelocytes were found. In counting over 1000 leukocytes, one normoblast was found. Despite repeated searches no megaloblasts were found. There were no microcytes. Very slight poikolocytosis, and no anisocytosis were found. Subsequent examination of the blood revealed but trivial variations from this count.

Ophthalmoscopic examination revealed a well-marked, low-grade neuroretinitis, with numerous hemorrhages of various size and shape lying in the nerve-fiber layer, and a few more deeply placed hemorrhages. The swelling of the left nerve head and obscuration of its edges was more marked than in the right eye.

Without the appearance of any new noteworthy symptoms, the patient grew progressively weaker and died with symptoms of œdema of the lungs eight days after admission, or approximately nine weeks after the onset. Permission for the autopsy, performed four days after death, was obtained through the efforts of Dr. F. H. MacFarland, to whom I am deeply indebted.

Autopsy. The macroscopic findings briefly stated were as follows: The body of a well-formed, well-nourished, adult female. Height approximately five feet three inches. Weight about one-hundred and thirty-five pounds. Subcutaneous fat moderately abundant, light yellow in color. Muscles of fair consistency and pale. The left pleural cavity contained 400 c.c. of serosanguineous fluid; the right pleural cavity approximately 200 c.c. of fluid of the same character. There was œdema of the

lungs and fatty degeneration of the heart muscle. There were no valvular defects. In the pelvic peritoneal cavity were 200 to 300 c.c. of dark-red, fluid blood containing one small clot. The liver was anemic and fatty; the spleen pale, firm, and not enlarged; the kidneys pale and fatty. Aside from pallor of the mucous membranes the gastrointestinal tract presented no abnormalities. There were no evidences of the presence of parasites. In the mesentery and retroperitoneal tissues a few hemolymph nodes were found, light reddish-brown in color, and of the size of small beans. The marrow of the ribs was light yellow in color; that of both the diaphysis and epiphysis of the tibia, fatty and extremely pale.

Histological Examination. There was fatty degeneration of the heart muscle in the form of extremely fine globules of fat, and a considerable hemosiderin deposit, mostly in the protoplasm of the cells at both poles of the nucleus. The section of liver showed a marked fatty change in the form of large globules confined almost exclusively to the central half of the individual lobules. There was an extensive deposit of hemosiderin occurring diffusely throughout the liver cells. In the section of spleen, there was noted a moderate proliferation of endothelium within the pulp. The follicles were prominent but apparently not hypertrophied. A few normoblasts were visible in the section. In the kidney the epithelium of the tubules of the cortex showed some disintegration and in many areas was detached from the basement membrane. Numerous small fat globules were present in the epithelium of the tubules, especially toward the free margins of the cells. The lumina were filled with a granular exudate including, here and there, shadows of red blood corpuscles. The hemolymph glands showed the peripheral sinuses to be small and there was some endothelial proliferation in the pulp. Smears and sections were made of the bone-marrow of the shaft of the tibia near the epiphysis. They both showed a large amount of fat, a very few normoblasts and normocytes, an absence of megaloblasts, a moderate number of lymphocytes, and a few myelocytes. No polymorphonuclear leukocytes could be identified.

I have succeeded in collecting from the literature ten cases in which the clinical phenomena and postmortem findings warrant their being considered cases of aplastic anemia. They are as follows:

Case I.—Bloch.[3] Female, aged sixty-three years; first symptoms noted, weakness and pallor; duration, six weeks. Blood: hemoglobin, 28 per cent.; red blood corpuscles, 1,970,000; leukocytes, 3250. Differential count: lymphocytes greatly preponderating; no nucleated red blood corpuscles; a few microcytes; no megalocytes; color index, 0.71. Postmortem findings: marrow of long bones

[3] Ziegler's Beiträge, 1903, xxiv, 331.

showed no lymphoid hyperplasia; in marrow of ribs there were no megaloblasts. Prominent clinical feature: four days before death hemorrhage from buccal mucous membrane.

Case II.—Bloch.[4] Female, aged fifty-three years; first symptom noted was weakness. Blood: severe anemia, marked reduction in leukocytes, those persisting being almost entirely lymphocytes. No megaloblasts; after prolonged search a few normoblasts were found. Postmortem findings: marrow of shafts of long bones pale and fatty. Marrow of epiphyses of normal red color. Prominent clinical feature: numerous gastric hemorrhages occurred during the course of the disease.

Case III.—Ehrlich.[5] Female, aged twenty-one years; metrorrhagia eighteen days before onset. Blood: hemoglobin, very low; red blood corpuscles, 213,360; white blood corpuscles, greatly reduced. Differential count: lymphocytes, 80 per cent.; polymorphonuclear neutrophiles, 14 per cent.; large mononuclear leukocytes, 3 per cent.; eosinophiles, 0; no nucleated red blood corpuscles. Postmortem findings: bone-marrow yellow in shafts of long bones, slightly pinkish in diaphyses. No megaloblasts. No normocytes. Very few normoblasts and myelocytes. No polynucleated granulated cells.

Case IV.—Engel.[6] Female, aged thirty-one years; shortly before onset blood noted in stools and hemorrhage from gums; duration, three weeks. Blood: hemoglobin, 18 per cent.; red blood corpuscles, 2,115,000; white blood corpuscles, greatly reduced. Differential count: small lymphocytes, 90 per cent.; polymorphonuclear neutrophiles, 7 per cent.; no microcytes; no macrocytes; no nucleated red blood corpuscles. Color index, 0.42. Postmortem findings: diaphyses and epiphyses of long bones yellow and fatty. Microscopically, nothing but fat. Marrow of ribs gray and watery. No cells present. Prominent clinical feature: there was a doubtful history of swallowing of corrosive shortly before the onset of symptoms. Chief complaint was weakness.

Case V.—Evans and Halton.[7] Male, aged thirty-six years; first symptoms noted shortly after bleeding from nose lasting two and one-half hours; duration, two months. Blood: hemoglobin, 10 per cent.; red blood corpuscles, 770,000; white blood corpuscles, 2300. Differential count: polymorphonuclear neutrophiles, 6 per cent.; small lymphocytes, 90 per cent.; large lymphocytes, 4 per cent.; eosinophiles, none; no nucleated red blood corpuscles. No marked poikilocytosis. Shortly before death two nucleated red blood corpuscles were found; color index, 0.65; actual number of lymphocytes, 2070. Postmortem findings: skull bones showed fatty marrow with very few cells. Prominent clinical features: chief complaint was weakness and faintness.

[4] Ziegler's Beiträge, 1903, xxiv, 331.
[5] Loc. cit.
[6] Ztschr. f. klin. Med., 1900, ii.
[7] Jour. Amer. Med. Assoc. 1905, i, 1195.

CASE VI.—Hirschfeld.[8] Female, aged twenty-eight years; onset shortly after delivery; duration, nine months. Blood: red blood corpuscles, 1,200,000; white blood corpuscles, 3600. Differential count: small lymphocytes, 72 per cent.; no eosinophiles; no nucleated red blood corpuscles; actual number of lymphocytes, 2592. Post-mortem findings: bone-marrow universally yellow; bone-marrow was composed chiefly of small lymphocytes, a very few granulated cells, and a few normoblasts. Prominent clinical features: numerous small hemorrhages into the skin, mucous membranes, and retina occurred during the course; menstruation was extremely profuse.

CASE VII.—Muir.[9] Male, aged fourteen years; the first symptoms noted were vomiting of blood, bleeding from nose, and hemorrhages into skin; duration, eleven weeks. Blood: hemoglobin, 12 per cent.; red blood corpuscles, 800,000; white blood corpuscles, 7000. Differential count: lymphocytes, 70 per cent.; polymorphonuclear neutrophiles, 25 per cent.; no nucleated red blood corpuscles; color index, 0.75; actual number of lymphocytes, 4900. Postmortem findings: bone-marrow fatty; very few nucleated red blood corpuscles or other normal cells of bone-marrow.

CASE VIII.—Pasteur.[10] Male, aged twenty-four years; first symptom was pain in epigastrium; duration, seven weeks. Blood: hemoglobin, 20 per cent.; red blood corpuscles, 1,090,000; white blood corpuscles, 2600. Differential count: lymphocytes, 74 per cent.; polymorphonuclear neutrophiles, 20 per cent.; hyaline and transitional cells, 6 per cent.; no megaloblasts; color index, 0.91; actual number of lymphocytes, 1924. Postmortem findings: bone-marrow, pale; no polymorphonuclear leukocytes.

CASE IX.—Zeri.[11] Female, aged fifty-seven years; first symptoms noted were hemorrhages into skin; duration, six months. Blood: hemoglobin, 20 per cent.; red blood corpuscles, 1,300,000; white blood corpuscles, 3580. Differential count: polymorphonuclear leukocytes were scarce in comparison to lymphocytes; no macrocytes; no megaloblasts; two normoblasts were found; color index, 0.76. Postmortem findings: marrow of long bones yellow in both diaphysis and epiphysis; the same in costal and vertebral bones. Prominent clinical features: during the course of the disease patient had prolonged epistaxis and numerous hemorrhages into skin.

CASE X.—Zeri.[12] Male, aged forty-six years; onset preceded by diarrhœa; duration, three months. Blood: hemoglobin, 38 per cent.; red blood corpuscles, 1,423,000; white blood corpuscles, 2700. Differential count: polymorphonuclear leukocytes and transitional cells, 57 per cent.; eosinophiles, 0; later moderate poikilocytosis; a few microcytes and macrocytes; no nucleated red blood corpuscles; color index, 1.33; actual number of lymphocytes, 1161. Postmortem

[8] Deut. med. Woch., 1904, xxii, 650.
[9] Brit. Med. Jour., September 29, 1900.
[10] Lancet, November 21, 1903.
[11] Il Policlinico, s. m. fasc. vii, 1905.
[12] Ibid.

findings: marrow of flat bones, orange yellow; of long bones, in both epiphysis and diaphysis, yellow and fatty; scarcity of polymorphonuclear leukocytes; normoblasts with multiform nuclei were present; in the marrow of the shafts of the long bones degeneration and proliferation of connective tissue.

Making a composite case from these ten cases and my own, we obtain one of the following characteristics: age, thirty-seven years; duration, three months. Blood: hemoglobin, 18 per cent.; erythrocytes, 1,116,600; leukocytes, 3574; lymphocytes, 73 per cent.; actual number of lymphocytes, 2393; color index, 0.77. It is readily seen that the more prominent features of such a case are sufficiently marked to furnish a very striking clinical picture, associated with unique postmortem findings.

The disease, as characterized by the cases quoted shows itself to be first manifested by symptoms common to any profound anemia: ready exhaustion, dyspnœa, disturbance of vision, tinnitus, nausea, and vomiting. In a strikingly large percentage of cases, considerable or numerous small hemorrhages occur shortly before, or coincident with, the onset of the symptoms of anemia, as noted by the patient. The patient usually remains fairly well nourished as far as the bulk of the fixed tissues, particularly the fat, is concerned, and there is a striking disharmony between the quality of the patient's blood and state of bodily nourishment. Usually without any prominent symptoms referable to any other system or function, the patient grows progressively weaker, and in from two to four months dies. Naturally the most noteworthy picture is afforded by the blood analysis, in which there is a profound reduction in the amount of hemoglobin and a somewhat less marked reduction in the number of red blood corpuscles, an absence or a remarkably small number of normoblasts, a total absence of megaloblasts, and a leukopenia associated with a relative lymphocytosis.

At autopsy, aside from the findings purely incidental to the grade of the anemia, there is the characteristic feature in the bone-marrow, which is intensely pale and fatty and lacks the evidences of blood regeneration.

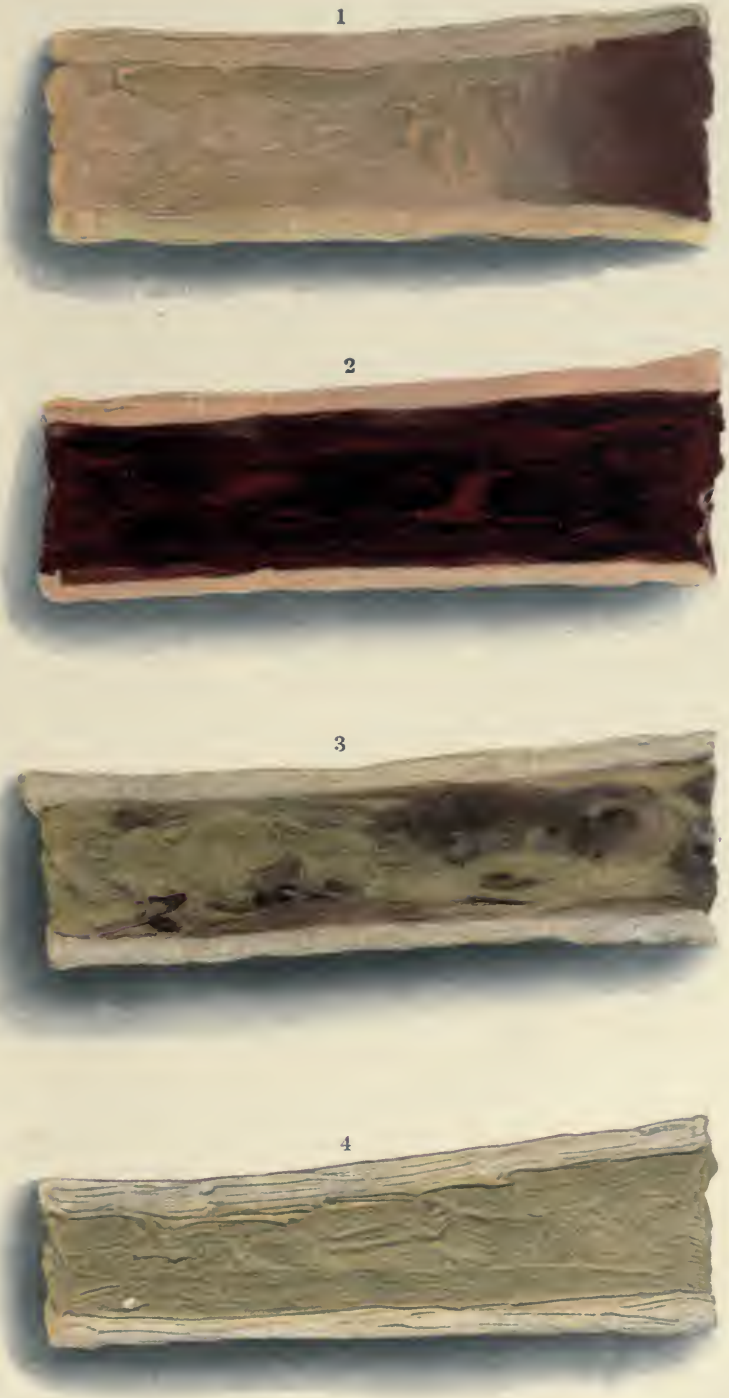
A critical review of these more prominent symptoms immediately suggests the question that has been the source of some argument in regard to aplastic anemia, namely, its relation to progressive pernicious anemia. The onset of the disease, its course, excepting as to the rapidity of a lethal termination, the absence of any marked loss of substance in the fixed tissues, and the great reduction in the amount of hemoglobin and the number of red corpuscles, are common to both conditions. In our attempt to determine the relation between aplastic anemia and progressive pernicious anemia, let us discuss individually the phenomena at variance in the two conditions. Probably the most striking of these, and surely the most important, is the blood picture in which we find an almost

complete absence in aplastic anemia of nucleated red blood corpuscles and the total absence of megaloblasts. Since the red corpuscles are a product of the bone-marrow, a consideration of them will necessarily involve a consideration of the bone-marrow. There is by no means a unity of opinion as to the primary effect of the etiological agent in pernicious anemia in its relation to the bone-marrow. Rindfleisch and Cohnheim[13] look upon the bone-marrow changes as primary, while others (Neumann, Litten, Orth) consider them as secondary, in the nature of an attempt on the part of the bone-marrow to compensate for the destruction of red blood corpuscles. Just as the character and number of the atypical red blood corpuscles vary in different cases of anemia, so does the character of the bone-marrow differ (see accompanying plate). In one case there is a red jelly-like marrow (megaloblastic degeneration) composed almost entirely of megaloblasts and associated with the presence of numerous megaloblasts in the circulating blood; in another case, but few megaloblasts and correspondingly little red marrow in the shafts of the long bones. In a case that I recently autopsied, there were a very moderate number of normoblasts and megaloblasts, and at the autopsy the shafts of the long bones were found to be fatty with islands of red scattered here and there through it. It is thus seen that deductions as to the condition of the bone-marrow can frequently be drawn from a consideration of the cells of the circulating blood.

What of these relations in aplastic anemia? I have said that the blood shows an extremely limited number of nucleated red blood corpuscles, and we would consequently expect to find, as we in fact do, a pale bone-marrow in which the evidences of new blood formation are entirely wanting. We see, then, that in aplastic anemia there is a blood picture which is but a reflection of the condition of the bone-marrow, in which evidences of regeneration are entirely lacking, but in which there is no indication that the determining factor in the causation of the disease acts in any way different from that of the usual type of progressive pernicious anemia. It is but a difference in response of the organism to the causative agent.

What of the color index which in typical progressive pernicious anemia is considered to be characteristically high, and in aplastic anemia has been in all cases, excepting one, considerably below 1, and averages in all the cases 0.77? In progressive pernicious anemia, aside from megaloblasts, there are non-nucleated red blood corpuscles of considerably more than normal size, megalocytes. Laache has offered the usually accepted explanation for the high color index in progressive pernicious anemia in the large number of these abnormal cells present, which containing more hemoglobin than

[13] Virchow's Archiv, lxvii, 291.



Bone Marrows.—1. Normal. 2. Typical progressive pernicious anemia. 3. Scattered areas of megaloblastic degeneration in progressive pernicious anemia. 4. Aplastic anemia.

the normal cell naturally raise the color value. As has been remarked, in aplastic anemia there is usually little anisocytosis, and with the absence of both megaloblasts and megalocytes, it is readily seen why, on the basis of Laache's theory, the color index should not be raised above the normal. An interesting theory for the high color index in progressive pernicious anemia is proposed by Schaumann.[14] He considers that some of the iron deposited as hemosiderin in the liver and spleen is taken up by the existing corpuscles, used as a nucleus for the formation of more hemoglobin, and thus each individual corpuscle bears more than the normal amount. Some weight is lent to this view by experiments of Tallqvist.[15] In experimental anemias in dogs he showed that the color index was higher in cases of slow growing anemia than in those of rapid growth, and in the former the siderosis was greater than in the latter. This theory would also explain the low color index in cases of aplastic anemia, as they have almost all been of extremely rapid course.

Let us consider for a moment this more rapid course and invariably fatal termination of aplastic anemia with the course and termination in progressive pernicious anemia. We have seen that in aplasic anemia destructive forces are at work as in progressive pernicious anemia, but the regenerative process present in the latter is wanting in the former. If a destructive process be active and there be no constructive process to counteract it, it is but a natural consequence that, other things being equal, exhaustion will more readily result than if there be constructive changes.

Another feature at variance in the two conditions is the number of leukocytes and the proportions to one another of the various forms of leukocytes. In uncomplicated cases of progressive pernicious anemia the leukocytes average from 5000 to 6000; in aplastic anemia they average 3574. What is even more striking than this difference is the difference in the percentage of lymphocytes. In progressive pernicious anemia the lymphocytes vary from 37 per cent. (Strauss and Rohnstein[16]) to 31 per cent. (McCrae), while in aplastic anemia they average 73 per cent. A discussion of the principles underlying this variance must be prefaced by a few words concerning the origin of leukocytes. It is generally conceded that the granulated leukocytes, *i. e.*, the polymorphonuclear leukocytes and their progenitors, the myelocytes, have their origin in the bone-marrow; but there has been a vigorous discussion existing for some time as to whether the lymphocytes be the product of the bone-marrow or of the other more distinctly lymphatic structures, lymph glands, spleen, and lymphatic tissue of the gastrointestinal tract. Ehrlich believes firmly in the origin of the lymphocytes from true lymphatic structures, while others claim them to be of common origin with the

[14] Berl. klin. Woch. 1899, Nos. 1 and 3.
[15] Ueber experimentelle Blutgiftanæmien, Berlin, 1900.
[16] Die Blutzusammensetzung bei den verschiedenen Anämien.

granulated cells. That lymphocytes are formed in the bone-marrow there can be little doubt, for wherever lymphoid tissue is present, lymphocytes are produced; and, as was shown by Arnold and Ribbert, there is an element of lymphatic tissue in almost every organ of the body. So although lymphocytes may be produced in the bone-marrow by reason of the participation of the bone-marrow in the general distribution of lymphatic tissue, I do not believe that the production of lymphocytes is a specific function of it. Let us observe what bearing the lymphocytes in aplastic anemia have upon the question. We have seen that the red blood corpuscles and the granulated leukocytes, both admittedly products of the bone-marrow, are enormously reduced. But what of the lymphocytes? We have seen that in the average case of aplastic anemia there are 2393 lymphocytes, and it will be observed that this differs but slightly from the average normal number of lymphocytes, about 2200. Does it not seem irrational that if the lymphocytes be an integral part of the bone-marrow they should be so slightly affected and the other bone-marrow elements so profoundly reduced? As to the relation between the percentage of lymphocytes in progressive pernicious anemia as compared with that of aplastic anemia, I look upon it that in neither condition are they actually materially affected. In progressive pernicious anemia they are, on the average, approximately 35 per cent. of the total number of leukocytes, 5000 to 6000, which is but little less than 73 per cent. of 3574, the total average number of leukocytes in aplastic anemia. The difference depends entirely upon the variations in the number of polymorphonuclear neutrophiles and in harmony with the generally more intense character of the lesions in aplastic anemia they are more markedly reduced than in the former.

In regard to the autopsy findings the essential differences in the two diseases lie in the bone-marrow, which, as we have attempted to show in the above analysis, manifests a complete failure of regeneration on its part.

Basing our deductions upon the above comparison, we thus see that progressive pernicious anemia is associated with regenerative processes which in aplastic anemia are lacking. As to the destructive processes, it has been shown by Hunter, Quincke, Pepper and Stengel that progressive pernicious anemia is primarily a hemolytic disease. That aplastic anemia is of the same nature, may be accepted by reason of the consistent occurrence of hemorrhages in practically all of the cases reported, and by reason of the hemosiderosis present in our case. It is unfortunate that in the previously reported cases no mention is made of this condition. We see, then, that the blood picture in aplastic anemia and the course of the disease are the result of two factors: the one the hemolysis, the other the failure of regenerative changes to compensate for this destruction. The failure of regeneration by the bone-marrow may be dependent upon one of the

following three factors: first, a simple deficiency of the regenerative powers; second, an inhibitive action on the bone-marrow by the factors producing the destruction of the blood elements; third, a true aplasia of the bone-marrow. If the latter be the case, the aplasia is probably of recent origin, for if it were of long duration there would, in all probability, have been manifestations of a deficiency in blood formation before the advent of the hemolytic agent.

It will be necessary to discuss but briefly the relation that aplastic anemia bears to simple anemia. Lazarus looks upon aplastic anemia as a variety of simple anemia, basing his view upon the fact that aplastic anemia is most like simple anemia in the blood picture. A review of the cases that we have collected reveals the fact that in practically none of the cases has there been the history of the various organic diseases so frequently associated in an etiological way with simple anemia. It is true that hemorrhages do appear to have been more frequent and probably more profound in aplastic anemia than in progressive pernicious anemia, but that they stand in an etiological relation to aplastic anemia can scarcely be entertained. They have occurred throughout the course of the disease rather than precedent to it, and as Birch-Hirschfeld[17] has emphasized, the severity of the anemia stands in marked contrast to the amount of hemorrhage, though it must be admitted that in some cases when hemorrhages are small and numerous, and especially when they occur in the gastrointestinal tract, a calculation of the amount of blood lost is difficult or impossible; but the most important elements differentiating aplastic anemia from simple anemia are furnished by a consideration of the clinical features of aplastic anemia. It is an essentially pernicious disease in course, duration, and termination, and serves well to illustrate the futility of attempting the diagnosis of most blood diseases on the blood picture alone.

The exclusion from our list of a number of cases that have been reported as cases of aplastic anemia, or present otherwise features suggestive of this disease, requires some words of justification.

Senator[18] reports the case of a girl, aged thirteen years, complaining, chiefly of weakness and vertigo. The disease was of three months' duration, and the blood findings were as follows: hemoglobin, 8 to 10 per cent.; erythrocytes, 1,040,000; leukocytes, 8000; poikilocytosis; no nucleated red blood corpuscles; no eosinophiles. The majority of the white blood corpuscles were lymphocytes. Blood from the heart, taken at autopsy, showed 728,000 red blood corpuscles and 11,200 white blood corpuscles, of which 83.6 per cent. were lymphocytes. At autopsy the bone-marrow was found to be universally red, showing microscopically large numbers of lymphocytes and a few normoblasts. Two elements

[17] Verhandl. d. Congress f. innere Medizin, Wiesbaden, 1892, xi.
[18] Ztschr. f. klin. Med. lix, 1.

in this case tend to exclude it from the aplastic anemias. The one is the metaplastic bone-marrow, containing numerous lymphocytes, the other the occurrence clinically of a considerable actual increase of the lymphocytes, as is shown by the fact that 83.6 per cent. of 11,200 leukocytes were lymphocytes. Senator himself says of the case, after a consideration of the clinical and postmortem features, "we are thus dealing with a case of myelogenous pseudoleukemia, and according to the present-day terminology one of a pure medullary form, since the lymphatic glands were not at all, and the spleen to a very moderate degree, swollen."

Blumer[19] reports a case of twenty-two months' duration, occurring after the loss of considerable blood from hemorrhoids. The blood showed 20 per cent. of hemoglobin, 1,516,000 red blood corpuscles, and 4000 white blood corpuscles, of which 88.3 per cent. were lymphocytes. An average of one normoblast to a field was found. At autopsy the bone-marrow of the upper part of the tibia was yellow, that of the ends of the other long bones partly red and partly fatty. On the basis of a duration of twenty-two months, which is more than seven times the average duration, and the presence of a considerable number of normoblasts, in harmony with which is the partly red and partly yellow bone-marrow of the diaphyses, we feel justified in looking upon this as a doubtful case of aplastic anemia. It has more of the features, excepting for the percentage of lymphocytes, of a low grade normoblastic progressive pernicious anemia.

Schaumann's[20] case, which he reports as aplastic anemia, is very suggestive, but the data furnished in the report of the case are insufficient to warrant the diagnosis.

The case of Pane,[21] quoted by Zeri as a case of aplastic anemia, is doubtful. The meager clinical data furnished, associated with the finding postmortem of a splenic tumor, and hyperplasia of Peyer's patches and the solitary follicles of the intestinal tract, do not justify us in considering the case one of aplastic anemia.

Wolff's[22] case presents, as he himself says, "more features of an aplastic leukemia than an aplastic anemia."

Escherich[23] reports a case of anemia in a child, aged four years, that strongly suggests aplastic anemia. The disease was of six months' duration. The red blood corpuscles varied between 575,000 and 737,500; the hemoglobin between 10 and 15 per cent.; the leukocytes between 3500 and 7000. The statement is made that the majority of white blood corpuscles were lymphocytes. There was considerable poikilocytosis and macrocytosis and no nucleated

[19] Bull. Johns Hopkins Hospital, April, 1905.
[20] Volkmann's Sammlung klinischer Vorträge, n. f. No. 287.
[21] Riforma Medica, 1900, xvi, No. 4.
[22] Berl. med. Woch., 1905, xlii, No. 2.
[23] Wien. klin. Woch., 1892, Nos. 13 and 14.

red blood corpuscles. There was at first some swelling of the lymphatic glands in the region of the mastoid and in the left axilla. It is to be regretted that there was no postmortem examination to confirm the strong suggestion of its having been a case of aplastic anemia.

Kurpjeweit[24] has recently reported two cases of anemia in the aged, which present some features suggestive of aplastic anemia, especially the first case. However, the greatly enlarged spleen, measuring 18.5 cm. x 12.5 cm. x 6 cm., and the but moderately severe course of the disease, together with the lack of leukocytic examination in the case, will not permit of a diagnosis of aplastic anemia. The second case also had a remarkably large spleen, 800 grams. Lymphocytes did not preponderate, and the bone-marrow showed normoblastic regeneration.

Conclusions. 1. Aplastic anemia is a variety of progressive pernicious anemia.

2. The essential features of aplastic anemia are: a rapidly fatal course; a marked reduction in the number of red blood corpuscles; a greater proportionate reduction in the amount of hemoglobin, resulting in a low color index; a leukopenia with a relative lymphocytosis; an absence of megaloblasts, and usually normoblasts. Postmortem: the characteristic finding is a pale bone-marrow in which the signs of erythrocytic and granulated leukocytic formation are wanting.

3. The differences between aplastic anemia and the usual form of progressive pernicious anemia result entirely from the absence of regenerative processes in the former.

4. The blood picture in aplastic anemia is the result of two factors, one the hemocytolysis, and the other the failure of regeneration on the part of the bone-marrow.

5. The failure of regeneration of the blood elements of the bone-marrow represents the result of one of the three following conditions: (*a*) A simple deficiency of the regenerative powers; (*b*) an inhibitive action on the bone-marrow by the factors producing the destruction of the blood elements; and (*c*) a true aplasia of the bone-marrow. If there be a true aplasia it is probably of recent origin, for if it were of long duration there would in all probability have been manifestations of a deficiency in blood formation before the advent of the hemolytic agent.

6. The relations of lymphocytes to leukocytes and red blood corpuscles in aplastic anemia lend evidence to the view that lymphocytes are not a specific product of the bone-marrow.

[24] Deut. Archiv. f. klin. Med., lxxxii, Nos. 5 and 6.

A CASE OF CHRONIC OSTEO-ATROPHIC ARTHRITIS.*

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PHILADELPHIA.

The extraordinary features presented by the bones and joints of the patient forming the subject of this communication justify, in my opinion, the publication of the case as an almost unique one.

Patient.—K. I., a woman aged 54, white, single, and a native of Ireland, is an inmate of the Philadelphia Home for Incurables.

Family History.—Her family history presents no features bearing any relation to her own condition. There is no history of rheumatism.

Previous Medical Condition.—The patient's previous history shows her to have been strong and healthy excepting for some undeterminable infection when she was about 10 years old. Her work was confined to household duties. At the time of the onset of the present trouble she was a woman of about 5 feet 3 inches in height, weighing in the neighborhood of 135 pounds.

Present Illness.—About twenty-seven years ago the patient noted some pain and stiffness in the right hip, coming on after a severe wetting. This disappeared within a few weeks, and for a year she was entirely well. At this time pain and stiffness occurred in the third toe of the right foot. Very shortly after, the right knee was similarly involved, and then successively, the right hand and wrist and the left wrist. Later, most of the remaining joints of the body were involved, and within a few months from the onset of symptoms in the toe, practically all the joints of the body were affected. There was some

* From the William Pepper Laboratory of Clinical Medicine. Phoebe A. Hearst Foundation.

swelling, but pain on movement and stiffness were the most prominent features. The patient does not recall having had any fever at this time. About twenty years ago, approximately six years after the onset, the patient noted that the thumb of the right hand was becoming shorter, and soon after observed a similar process in all fingers of both hands. There

Fig. 1.—A radiograph of the right hand.

was a gradual progression of this shortening until a few years ago, since which time she believes there has been no increase in the process.

Physical Examination.—The patient is an extremely small woman, sitting continuously in a chair with the trunk flexed at about a right angle to the thighs and the head slightly

flexed. She is able to execute only the slightest movements of arms or head. The examination of the thoracic and abdominal viscera reveals no unusual features. On account of the inability of the patient to extend the body, the measurement of her height is impossible, but estimation places it at not more than 4 feet 10 inches. The examination of the bony

Fig. 2.—A radiograph of the left hand.

framework and joints reveals the following: In the neck there is a lateral motion of approximately 5 degrees. Flexion and extension are limited to 10 degrees. There is very limited motion in the spine. Over the sternum, commencing an inch below the suprasternal notch, is a bony prominence, one inch in length and two inches in breadth, which shades gradually

to the level of the surrounding tissue. The measurement from one acromial process to the other is ten and one-half inches. From the right sterno-clavicular articulation to the right acromion is five and one-half inches. From the left sterno-clavicular articulation to the left acromion is four inches. Both shoulders are completely ankylosed. The right elbow is ankylosed at an angle of 90 degrees. The left elbow permits of a motion from almost complete flexion to almost complete extension. There is marked relaxation of the bones entering into the left elbow so that a deep groove is visible both in the line of the articulation and extending from this downward between the radius and the ulna. The measurement from the acromion to the external condyle is ten inches on both sides. From the external condyle to the wrists is seven inches on

Fig. 3.—Photograph of a wax cast made from the right hand.

both sides. Both hips are completely ankylosed, the right at an angle of about 110 degrees with the trunk, the left at an angle of about 140 degrees. Both knees are completely ankylosed, the right at an angle of 130 degrees and the left at an angle of 160 degrees. The ankle permits of approximately 25 degrees of motion in the direction of flexion and extension. There is no lateral motion. In the left ankle the flexion and extension are limited to 10 degrees. The toes on the left foot are moderately free. In the toes of the right foot motion is extremely limited. The right wrist admits of 10 degrees of flexion and extension. The left wrist is completely ankylosed in a slightly flexed position. In none of the larger joints can any bony outgrowths be determined by palpation.

The most interesting features in the case are presented in the fingers and hands. The fingers have, without an exception, become greatly shortened. Since this shortening is due apparently to bony change in which the soft tissues have not kept pace, the latter are thrown into folds, giving the phalanges an appearance of being telescoped into each other. Associated with this shortening of the fingers there is relaxation of most of the joints, so that the hands present, especially on manipulation, a most grotesque appearance. Some of the fingers can be extended to a right angle with the metacarpal bones, so that they give the impression of being nothing more than tags of soft tissue. The right hand measures from the wrist to the tip of the middle finger four and one-half inches; from

Fig. 4.—Photograph of a wax cast made from the left hand.

the wrist to the distal end of the middle metacarpal bone two and three-quarter inches. The right hand measures from the wrist to the distal end of the middle metacarpal bone two and one-half inches. In the little finger of the right hand there is almost complete ankylosis at the second phalangeal joint. In the fourth finger there is partial ankylosis in the first phalangeal joint. In the index finger there is partial ankylosis in the metacarpo-phalangeal joint. In all of the other joints of the right hand there is more than the normal amount of motion, due to the relaxation spoken of above. In the left hand there is slight limitation of motion in the distal joint of the little finger. In the third and fourth fingers there is considerable limitation of motion in the distal joints,

and in the thumb there is almost complete ankylosis at the metacarpal articulation. In all the other joints of the left hand the relaxation is marked.

Urinalysis.—Clear, amber, slight flocculent sediment. Sp. G. 1024. No albumin. No sugar. A small amount of epithelium. Some W. B. C.'s. Some cylindroids.

Blood.—Hemoglobin, 84; R. B. C., 4,400,000; leucocytes, 10,560. Differential count: Polymorphonuclear neutrophiles, 74 per cent.; eosinophiles, 1.8 per cent.; basophiles, 0.3 per cent.; lymphocytes, 15.2 per cent.; large mononuclear leucocytes, 7.9 per cent.

The accompanying skiagraphs made by Dr. G. E. Pfahler, show the changes in size and form of the bony parts responsible for this remarkable clinical picture of the hands. The soft parts show the folds caused by the accommodation of the flesh to the changes in the bony parts. The joints, inclusive of the wrist joint, are all obliterated. The distal joints of the middle and ring fingers of the right hand, the distal joints of the middle, ring and little fingers of the left hand and the wrist joint are obliterated by fibrous or bony union, the remaining joints by reason of the absorption of bony tissue. Luxations are frequent. There are a few exostoses, notably at the proximal ends of the phalanges of the thumb of the right hand and at the proximal ends of the proximal phalanges of the ring and little fingers of the left hand. In the bones the most prominent features are a general rarefaction of the phalanges, apparently a result of lacunar atrophy. Many of the phalanges are atrophic and shortened and, as it were, pegged at one end. This is especially noticeable in the distal end of the proximal phalanx of the thumb, and the proximal ends of the middle phalanges of the ring and middle fingers of the right hand, and in the distal ends of the proximal phalanges of the middle, ring and little fingers of the left hand. The most profound changes are where entire phalanges have apparently been absorbed, giving radiographically no indication of the preservation of bony tissue. This is the case with the middle phalanx of the little finger and the middle phalanx of the index finger of the right hand and the proximal phalanx of the thumb and the middle phalanx of the index finger of the left hand. That the same process of absorption has occurred in other bones, of which, unfortunately, no skiagraphs could be made, there can be little doubt, as indicated by the measurements of the extremities, as given above, and by the undoubted decrease in height of the woman since the commencement of the disease.

A review of the literature presents but one case bearing any resemblance to the one here reported. In that case Watson[1] presented photographs and skiagraphs of

1. Brit. Med. Jour., March 10, 1906.

the hands which show a resemblance to my case that is really striking. A brief summary of the case is as follows:

The patient was a man 47 years of age, who had enjoyed good health until he was 39 years old, when he had an attack of what was diagnosed as acute articular rheumatism. Soon after multiple tumors developed over the entire surface of the body. These were described by Crocker as of myeloid structure. Later these tumors gradually disappeared and at the end of two years the patient was entirely free from them. At about this time he was suddenly seized with violent pain in the shoulders and hips. It was then that he noted the fact that his hands were growing smaller, since which time this process has been steadily progressing. The hands now show a marked atrophy of the phalanges, as in my case, and the consequent wrinkling of the skin, well described as "telescoping." The knees are almost completely fixed in a semiflexed position. The shape of the joints is not altered and there are no osteophytes. No other joints are affected, but the patient thinks that there has been some shortening of the face. The only other noteworthy feature of the case is the fact that the patient's blood contained 15 per cent. of eosinophiles in a normal leucocyte count.

The case reported by Schultze,[2] although scarcely similar to mine, presents some features suggestive of the same type of case:

The patient was a woman, aged 39, who, when she was 27 years of age, first showed signs of a spondylose rhizomelique which became progressively worse. Associated with this was an atrophic condition of the bones, especially of the arms and fingers. The circumference of the wrist joint was 13 cm. and the width of the hand, exclusive of the thumb, 7 cm. The patient had a younger brother with pseudohypertrophic muscular atrophy, also showing some bony atrophy.

Without more exhaustive details it is impossible to assume any great resemblance between this case and the one here reported.

In practically all of the various types of cases included under the term rheumatoid arthritis, two pathologic processes are at work: a destructive process and a proliferative process. In one type of cases the proliferative changes predominate, resulting in fibrous ankylosis, or, if this fibrous tissue become ossified, a true bony ankylosis results, arthritis ankylopœtica (Ziegler). In another type the destructive and proliferative changes oc-

2. Deut. Zeitschr. für Nervenheilkunde, vol. xxiv, 1899.

cur in a more equal distribution. We find first the central portions of the articular cartilages undergoing degeneration, at the same time proliferation occurring about its margins; later the ends of the bones coming into apposition by reason of the degeneration of the cartilage, undergo atrophy, partly from pressure, and later the opposed surfaces become compact and eburnated. At the same time a moderate amount of lacunar atrophy of the bone usually occurs. In this association of destructive and proliferative changes, however, no such degree of atrophy has been described as is found in my case. Moreover, this atrophy has occurred in many of the bones practically independent of proliferative changes. This extraordinary degree of atrophy suggests some influence other than those due to the local joint disease as playing some part in the process. The most rational consideration is naturally of some trophic disturbance, either primary or reflexly, induced by the joint disease. The determination of these factors must await further observation of similar cases and, above all, postmortem findings.

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ACUTE INSUFFICIENCY OF THE SUPRARENALS.*

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It is interesting that a condition looked on as one of considerable importance by the French clinicians is accorded but the most indifferent consideration by those of other countries. Hemorrhage of the adrenals has been generally recognized as a common pathologic finding in still-born infants or those dying shortly after birth, and the literature of Italy, Germany and England contains occasional references to hemorrhage or other acute destructive lesions of the adrenals in adults. In none of the countries outside of France, however, has acute insufficiency of the adrenals become a factor in medical diagnosis in advanced life as well as in infants. It might be suggested that this state of affairs is but the result of the conservatism of the American, German, English and Italian clinicians contrasted with the somewhat more unstable, fanciful attitude of their French brethren. That a symptom-complex dependent on acute insufficiency of the adrenals does occur, however, in such a striking form as to demand clinical recognition is well exemplified by the case which I have to bring before you.

Patient.—A woman, admitted to the University Hospital, where in the capacity of clinical assistant to Dr. Stengel, I had the opportunity of observing her during her illness and of subsequently performing the postmortem examination. She was a widow, 44 years of age, white, and a native of Ireland. The few elements of her family history that were obtainable had no bearing on her present condition. Her previous history revealed the fact that during the past seven years she had had infrequent attacks of asthma, and that during the past two years she had been subject to occasional attacks of abdominal pain with vomiting. During the past two years she had lost slightly in weight.

History of Illness.—On November 30, shortly after eating breakfast, and while in comparatively good health, the patient had an attack of vomiting, with some pain in the epigastrium, at the same time she felt weak and prostrated. A half hour later she drank a glass of water, when she again vomited. The pain in the epigastrium became more severe and the attacks of vomiting more frequent. During the afternoon there were frequent attacks of vomiting, and toward the evening the patient became slightly delirious. She was then seen by Dr. H. Kennedy Hill, who immediately sent her to the University Hospital. On admission to the hospital, temperature was 95, respiration 48, and no pulse could be felt. Vomiting had ceased by this time. The patient complained of pain in the epigastrium, and there was tenderness in this region and in the loins. The predominating symptoms were those of shock; the patient was extremely apa-

*Read in the Section on Practice of Medicine of the American Medical Association, at the Fifty-ninth Annual Session, held at Chicago, June, 1908.

thetic; her extremities were cold, the skin leaky and absolutely no radial pulse could be felt. During the earlier part of the next day the breathing became of the Cheyne-Stokes type.

Physical Examination.—The lungs were slightly emphysematous, and on respiration numerous dry râles could be heard. The upper border of the heart was on a level with the fourth rib; the right border at the right border of the sternum; the left border about a quarter of an inch outside of the left midclavicular line; the apex-beat was in the fifth interspace in the midclavicular; the cardiac sounds were weak and somewhat obscured by the respiratory râles; no murmurs could be detected. The tenderness in the epigastrium and in the loins persisted. There was slight rigidity of the abdominal wall, but no distention. The extremities were cold and slightly cyanosed.

Urinalysis.—Straw colored; slight brownish sediment; acid; specific gravity, 1002; no sugar or albumin; a small amount of mucus; a few leucocytes.

Blood Examination.—Hemoglobin, 61 per cent.; erythrocytes, 4,930,000; leucocytes, 52,800.

Clinical Course.—With vigorous stimulation during the day after admission, the patient reacted slightly, her temperature becoming 100 at noon on the day following admission. This reaction lasted for but a short time, the patient dying at 8 o'clock in the evening following her admission, or about thirty-six hours after the onset of the illness. Respiration had remained in the neighborhood of 48; the radial pulse had at no time become palpable. As counted by auscultation, the heart beat from 120 to 140 times per minute.

It is almost needless to emphasize how impressive a clinical picture the patient presented—the suddenness of onset, the vomiting, the epigastric pain, the lumbar tenderness, and, above all, the profound shock formed a most striking group of symptoms. In the light of our knowledge at the time, it resembled most acute hemorrhagic pancreatitis, though the shock was more profound and the vomiting and epigastric tenderness less marked than would have been expected in this condition.

The autopsy revealed the interesting and unexpected nature of the affection. The following brief notes are abstracted:

Pathologic Report.—The lungs showed, macroscopically and microscopically, a moderate degree of emphysema with slight hypostatic congestion. The heart was of normal size; both ventricles were relaxed; the cavities and walls were of normal proportions; the valves were soft and competent; the coronary arteries were slightly sclerotic; the muscle was somewhat grayer than normal. Microscopically, the heart muscle presented the picture of a slight, chronic fibrous myocarditis. The peritoneum was smooth and glistening. The uterus and appendages, aside from slight atrophy, presented no pathologic features. The kidneys were of normal size; their consistency considerably increased; the capsule stripped with some difficulty, but did not tear the kidney substance; the surface was slightly granular and showed a number of dark-based depressions and a few small cysts containing clear fluid. The microscopic features were characteristic of an arteriosclerotic, chronic interstitial nephritis of moderate degree. The stomach showed itself to be the seat of a chronic catarrhal gastritis. The intestines were without noteworthy characteristics, except for considerable venous congestion. The spleen was slightly enlarged and softer than normal. The liver was of normal size, its consistency slightly reduced; the organ was paler than normal, its structure somewhat obscured. The microscopic examination revealed fatty degeneration with early periportal fibrosis. The bile ducts were patulous; there

were no gallstones. The pancreas was of normal size, the consistency increased, the structure somewhat obscured; on squeezing the organ, a few droplets of turbid, yellowish fluid were expressed from the smaller ducts; several pinhead-sized areas of fat necrosis were found in the peri-pancreatic fat. Microscopically, a distinct interlobular and intralobular fibrosis was seen, with some atrophy of the secreting cells; there was no necrosis; in the interlobular tissue, especially in the neighborhood of the ducts, there was a diffuse, polynuclear leucocytic infiltration of moderate degree. Both suprarenals were enlarged and soft, and presented on section a dark-red, homogeneous appearance; both suprarenal veins were thrombosed. Microscopically, there was almost complete destruction of the gland substance; with the exception of small, scatttered islands, the parenchyma of the cortex stained a homogeneous pink with hematoxylin and eosin. Nuclei of the connective tissue cells of the stroma were preserved here and there, but scarcely any epithelial nuclei were visible. Scattered throughout this necrotic tissue were hemorrhagic extravasations of various size. There was considerable hemorrhage into the medulla, but less cellular and nuclear destruction than in the cortex. Cultures from the pancreas showed staphylococci, colon bacilli, and a non-identified Gram-positive bacillus. Cultures from the suprarenals were negative.

Pathologic Diagnosis.—Emphysema and hypostatic congestion of the lungs; chronic fibrous myocarditis, chronic interstitial nephritis; chronic catarrhal gastritis; acute splenic tumor; fatty degeneration of the liver, with beginning periportal cirrhosis; chronic pancreatitis, with acute interlobular suppurative pancreatitis; thrombosis of the suprarenal veins and acute hemorrhagic necrosis of the suprarenals.

My interpretation of these pathologic findings in their relation to the clinical phenomena is that the woman had a chronic pancreatitis of probably some years duration. Recently an acute suppurative inflammation was engrafted on this, the suprarenal veins became thrombosed as a result of this neighboring inflammation, and the hemorrhagic necrosis of the suprarenals resulted. The remaining pathologic features were for the most part the result of the existing arteriosclerosis.

Almost the only two conditions characterized by insufficiency of the suprarenals are hemorrhage and so-called adrenalitis. These two can be neither clinically or pathologically well differentiated in most cases. Adrenalitis is in the vast majority of cases not a true inflammation, as the term would imply, but a necrotic process, with which more or less hemorrhagic extravasation is always associated. When both necrosis and hemorrhage are present the two are generally the common results of the same condition, a vascular thrombosis. On the other hand, a number of the cases do present the clinical and pathologic features characteristic of simple hemorrhage. Many of these cases, by reason of the suddenness of the insult and the frankness of the hemorrhage, are appropriately termed adrenal apoplexies. The relation of suprarenal hemorrhage to acute hemorrhagic adrenalitis may be perhaps better understood by calling attention to the analogy that at least pathologically exists

between them and pancreatic hemorrhage and acute hemorrhagic pancreatitis.

I have been able to find but two cases in which insufficiency of the adrenals was dependent on other pathologic lesions than hemorrhage or necrosis. One is the case of Janowski,[1] in which the two adrenals formed small abscesses above the two kidneys. The other is the case of Stursberg,[2] in which suppuration was found in both suprarenals of a woman suffering from Pott's disease. It is not improbable that the glands in this case were tuberculous.

Confining our attention then to necrosis and hemorrhage, let us determine what the factors are bearing on these two conditions. The extraordinarily rich vascularization of the organs naturally impresses itself as standing in some relation to the frequency of hemorrhage. The gland receives its blood supply from three sources, the aorta, the renal artery, and the arteries of the diaphragm. The arterioles and the capillaries from these sources form a dense network about the cells of the cortex, and the capillaries and venules finally unite in the inner cortical layers and medulla to form a single vein, which emerges at the hilus of the organ. The facts that such a large amount of blood unites to enter one vessel in the medulla, and that extensive hemorrhages usually seem to occur into the medulla, suggest that simple alterations in the blood supply or blood pressure of the organ may be the determining factors in the production of the hemorrhage. This hypothesis has been put forth as especially applicable to hemorrhage of the adrenals so frequently found in the new-born. The great increase in intra-abdominal pressure in the child, incident to the uterine contractions, and especially the pressure of the liver on the vena cava just above the suprarenals, have both been thought to be the direct cause of increasing the adrenal blood pressure sufficiently to induce hemorrhage. This view receives some support from the fact that when hemorrhage has occurred into only one of the suprarenals, it has been more frequently on the right than on the left (according to Hamill,[3] fifteen times in twenty-four cases), and the right vein enters the vena cava directly, while the left enters it through the renal vein. These relations would naturally subject the vessels of the right gland to greater pressure than the left in the presence of any cause obstructing the return of venous blood.

Chronic heart disease associated with passive congestion has been observed in a number of cases, and has thus been looked on as a causal factor.

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1. Janowski: Gaz. lek., 1898, liv, 354.
2. Stursberg: Deutsch. med. Wchnschr., 1904, xxx, 1406.
3. Hamill: Arch. Pediat., 1901, xviii, 161.

Similarly, chronic pulmonary disease has been not infrequently found in these cases, and it is possible that the chronic passive congestion resulting therefrom has been an active factor in the production of hemorrhage.

A certain number of cases have been observed in which death has resulted after the occurrence of phenomena tending to a great increase in blood pressure, and in which, at autopsy, hemorrhage of the suprarenals was found. A striking example of this is a case reported by Ogle[4] of an epileptic dying after two weeks of almost continuous convulsions. At the autopsy hemorrhage into both suprarenals was discovered. I believe that it is not improbable that in some of the cases said to have manifested themselves clinically by convulsions these were the cause rather than the result of the hemorrhage, induced by the great increase in blood pressure incident to the convulsions. Duckworth[5] refers to a case in which the paroxysms of coughing in a child with pertussis apparently induced hemorrhages into both adrenals.

The great tendency to hemorrhage throughout the body in asphyxia, in all probability as the result of venous engorgement, has caused it to be looked on as one of the possible factors in the production of suprarenal hemorrhages, especially in the new-born. A factor emphasized by Spencer[6] as responsible for the greater frequency of suprarenal hemorrhages in infancy is the normal delicacy of the blood-vessel walls in this period of life.

Thus far we have dealt with only passive congestions. It has been asserted that active congestion also plays a rôle in the production of adrenal hemorrhage. One of the functions attributed to the suprarenal capsule is that of neutralizing toxins, and it is said that the functional activity of the gland in the presence of a toxic agent in the body so increases its blood supply as to lead to hemorrhage.

It is doubtful, however, if it is alone by increasing the blood supply to the gland that infections and intoxications act in inducing insufficiency of the suprarenals. In a number of cases organisms have been isolated directly from the adrenal glands, the seat of hemorrhage and necrosis. Klebs and Eppinger[7] isolated an organism in several cases of suprarenal hemorrhage in the new-born, which they called *Mona hemorrhagica*. Gaertner[8] isolated a bacillus resembling the colon bacillus, and

4. Ogle: Tr. Path. Soc., London, 1863, xiv, 127.
5. Duckworth: Twentieth Century Practice of Medicine, ii.
6. Spencer: Tr. Obst. Soc., Lond., 1891, xxxiii, 203.
7. Klebs and Eppinger: Boston Med. and Surg. Jour., 1891.
8. Gaertner: Arch. f. Kinderh., 1895.

Riesman[9] the *Staphylococcus albus* and *aureus* from four out of six cases occurring within a short space of time.

Experimentally, hemorrhage and acute destructive lesions of the glands have been produced by Roux and Yersin[10] by inoculating rabbits and guinea-pigs with diphtheria bacilli; by Charrin and Langlois[11] with the *Bacillus pyocyaneus;* and by Roger[12] with the bacillus of Friedlander. Pettit,[13] Pilliet[14] and Wibaud[15] have confirmed these results. Oppenheim and Loeper[16] have produced similar results by injecting the toxins of Friedlander's bacillus, of the diphtheria bacillus and the tetanus bacillus, as well as by arsenic, phosphorus and mercury. Practically the same results were obtained by Bernard and Bigart[17] in injecting various metallic poisons.

Adrenal hemorrhage associated with a general purpuric eruption can be looked on only as a visceral manifestation of a general hemorrhage tendency. As the purpuras of childhood are practically always infectious, the functional activity of the gland as the result of the infection, according to the above-mentioned hypothesis, probably increases its predisposition as a seat of hemorrhage.

Trauma does not seem to play a very important rôle in the production of acute destructive suprarenal lesions. In but two cases, those of Canton[18] and Mattei,[19] does trauma seem to have been the cause of the adrenal hemorrhage found subsequently at autopsy. The secluded, well-protected position of the adrenals is probably the cause of its being so infrequently affected by trauma.

In the cases of Arnaud,[20] Churton[21] and Dudgeon[22] adrenal hemorrhage was apparently induced by severe surface burns. In Dudgeon's and Arnaud's cases there were symptoms of adrenal insufficiency before death. This association suggests that which exists between surface burns

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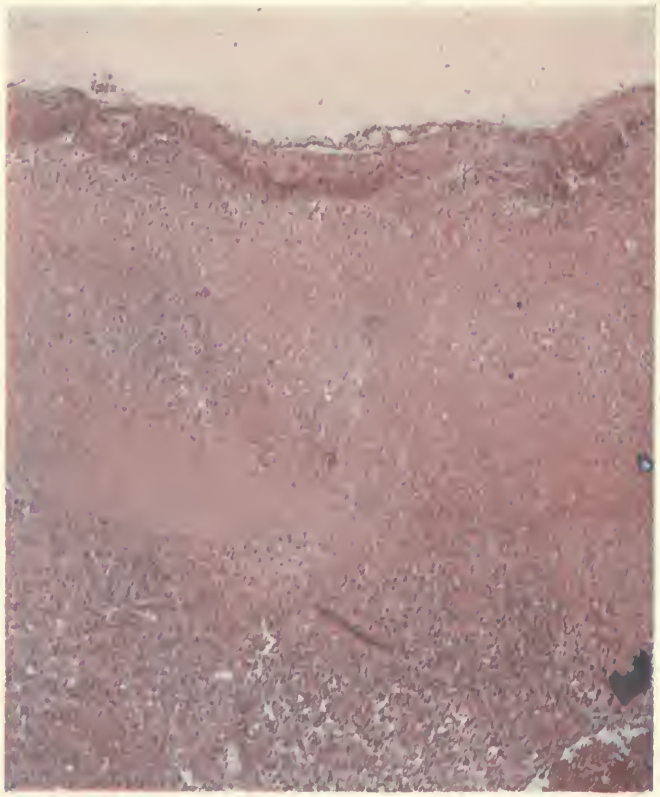
9. Riesman, quoted by Hamill: Arch. Pediat., 1901, xviii, 161.
10. Roux and Yersin: Ann. de l'Inst. Pasteur, 1889.
11. Charrin and Langlois: Compt. rend. Soc. biol., 1896, Series 10, iii.
12. Roger: Presse méd., 1894, i, 35.
13. Pettit: Thèse de Paris, 1896.
14. Pilliet: Arch. de physiol. norm. et path., Series 5, F. 7.
15. Wibaud: Etude des capsules surrénales dans les maladies infectieuses expérimentales, Brussels, 1897.
16. Oppenheim and Loeper: Arch. de méd. expér., 1901, xiii, 332.
17. Bernard and Bigart: Jour. de physiol. et de path. gén., 1902, iv, 1014.
18. Canton: Tr. Path. Soc. Lond., 1863, xiv, 257.
19. Mattei: (Case 2) Sperimentale, 1883, li, 386.
20. Arnaud: (Case 1) Arch. gén. de méd., 1900, clxxxvi.
21. Churton: Lancet, London, 1886, i, 245.
22. Dudgeon: (Case 2) Am. Jour. Med. Sc., 1904, cxxvii, 134.



Lumière photomicrograph of necrotic suprarenal. Section stained with hematoxylin and eosin.

Lumière photomicrograph of normal suprenal. Section stained with hematoxylin and eosin.

Archives of Internal Medicine.
Illustrating Article by R. S. Lavenson, M.D.

and duodenal ulcer. Whether the adrenal lesion results from internal congestion, toxic products or embolism is quite as much open to question as the pathogenesis of duodenal ulcer.

Suppurative inflammations of adjacent organs has apparently been the cause of necrosis and hemorrhage of the suprarenals, with the clinical signs of insufficiency in three cases—my own and two of Arnaud's.[23] In one of Arnaud's cases the neighboring lesion was an abscess of the liver, in the other a suppurating hydatid cyst of the liver. In all three cases thrombosis of the adrenal veins was apparently the immediate cause of the changes in the glands. It is possible that pneumonia acts in the same way in producing acute insufficiency of the adrenals as to these lesions of neighboring abdominal viscera.

The appearance of the gland varies with the nature and extent of the lesion. Simple hemorrhages usually occur into the medulla of the organ. If of small size the hemorrhage merely distends the cortex slightly, producing but little destruction of its cellular elements. If of larger size it may so distend the organ that the cortex forms but a thin shell enclosing a large blood cyst. Rayer[24] records a case in which hemorrhage into a suprarenal gland resulted in a blood cyst weighing two kilos. Carrington[25] reports a case in which the suprarenals were transformed into cysts the size of large oranges, and in Routier's[26] case 1,600 cubic centimeters of a blackish-brown fluid were evacuated from a suprarenal, the seat of hemorrhage. At times the capsule of the gland ruptures, permitting the escape of blood either into the surrounding retroperitoneal tissues or into the peritoneal cavity itself.

When hemorrhages are multiple and small they are usually found in the cortex rather than in the medulla. In such cases more or less necrosis of the epithelial elements of the cortex is usually present. The necrosis and hemorrhage may be the common result of the same cause, thrombosis, or the necrosis may be either the cause or the result of the hemorrhage. Judging from the pathologic features of my case, venous thrombosis results in extensive necrosis with but slight hemorrhage. In such cases the gland presents macroscopically a homogeneous, reddish-brown appearance and a microscopic picture similar to that described in the above pathologic notes of my case.

The fact that the lesions are at times limited more or less to either cortex or medulla has led to an attempt to classify the symptomatology

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23. Arnaud: (Cases 2 and 3) Arch. gén. de méd., 1900, clxxxvi, 5.
24. Rayer: (Case 1) Journal de l'expérience, 1837.
25. Carrington: Tr. Path. Soc., London, 1885, xxxvi, 454.
26. Routier: Bull. Soc. d'anat. de Paris, 1895, 73.

according to the involvement of one or the other of these parts. Experimental evidence indicates that the functions of the cortex and medulla are different. The medulla seems to supply the elements having to do especially with the preservation of vascular tone, while the function of the cortex, aside probably from acting to an extent in a compensatory way for the medulla, appears to be the furnishing of an antitoxic agent to the body. In the majority of the cases of sudden death in adrenal insufficiency the hemorrhage does seem to have occurred into the medulla, but we are hardly justified in deducing from this fact the conclusion that this result attends destruction of only this portion of the gland. The functions of the adrenals are as yet too little understood and the limitations of the pathologic lesions involving them too poorly defined to warrant more than the statement that insults to the glands, regardless of their location or extent, may call forth certain profound symptoms such as will be described in the clinical discussion.

A study of the literature reveals a number of apparently incongruous relations requiring discussion. Numerous cases have been observed presenting the symptoms of acute suprarenal insufficiency in which only one of the glands was involved, the other being apparently normal. Why the compensatory action of the normal gland should not be capable of abolishing these symptoms is beyond the limitations of our pathologic knowledge to say. It is not improbable that our means of study are incapable of discovering lesions which, without destroying the morphologic integrity of the apparently normal organ, yet seriously interfere with its functions. A number of cases (those of Addison,[27] Goolden,[28] Carrington,[25] Greenhow,[29] and Mattei[30]) have been reported in which the symptoms of Addison's disease were presented and in which at autopsy acute adrenal lesions were found. In all of them the diagnosis of Addison's disease, as judged by the reported symptoms, is open to doubt, but even were it authentic it is rational to consider that a chronic degenerative process would only predispose the gland to hemorrhage or other acute process which by its prominence could obscure the recognition of the chronic changes. An interesting group of cases is that in which the signs of acute suprarenal insufficiency occur, followed shortly by death, and at autopsy the destructive lesions of a chronic process are found in the suprarenals.

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27. Addison: On the Constitutional and Local Effects of Disease of the Suprarenal Bodies (Case 10), London, 1855.
28. Goolden: Lancet, London, 1857, ii, 266.
29. Greenhow: Lancet, London, 1877, i, 349.
30. Mattei: (Case 3) Sperimentale, 1883, li, 386.

In regard to such cases it must be emphasized that the degree of tissue destruction is not always a measure of functional incapacity, and it is very possible that only when the destructive process has reached a certain degree, or involved certain elements, does it manifest itself clinically.

Since, as above stated, hemorrhage of the suprarenals and acute hemorrhagic adrenalitis can not be strictly differentiated either clinically or pathologically in the majority of cases, I shall not employ these two conditions as a basis for classification. The symptoms presented result from interference with the function of the adrenals, regardless of the agent inducing it. Even on the basis of the clinical phenomena I hesitate to attempt a classification for fear of confusing the reader in a maze of artificial grouping, for few of the cases conform to one type entirely distinct from the others. However, on the basis of the preponderance of one or another group of symptoms, I think that the following classification will serve as a basis for clinical consideration.

1. Cases of sudden onset with epigastric pain and tenderness, vomiting, profound prostration, feebleness and rapidity of pulse, coldness of extremities, lumbar tenderness, and at times diarrhea, and abdominal distention, followed within a few days by death. This is the symptom-complex that at times is called the peritoneal type of acute insufficiency of the adrenals, of which my case is a striking example. The literature of the subject contains a number of similar instances, among the most impressive of which are those of Stursberg,[2] Pritchard,[31] Mattei,[32] Arnaud,[33] Janowski[1] and Sotti.[34] The occurrence of the same group of symptoms in children is well exemplified by such cases as those of Batten,[35] Dudgeon,[22] and the two cases of Talbot.[36] There is a striking resemblance between the cases of this type and many cases of acute hemorrhagic pancreatitis. Judging from the one case that I have observed, the shock is more profound, the lumbar tenderness more acute, and the epigastric pain and vomiting less pronounced in adrenalitis than is usually the case in acute hemorrhagic pancreatitis.

2. The asthenic type, in which the predominant feature is a profound asthenia ending within a few days in death. Instances of this

31. Pritchard: Lancet, London, 1890, i, 750.
32. Mattei: Sperimentale, 1863, ii, 3.
33. Arnaud: (Case 1) Arch. gén. de méd., 1900, clxxxvi, 5.
34. Sotti: Policlinico, 1908, xv; Sem. méd., 1.
35. Batten: Tr. Path. Soc., London, 1893, xliv.
36. Talbot: St. Barth. Hosp. Rep., 1900, xxxvi, 207.

type have been reported by Greenhow,[20] Murray,[37] Sicard[38] and Voisin and Norero,[39] all occurring in adults. In Sicard's case the asthenia was so pronounced as to give the case the appearance of an acute bulbo-spinal myasthenia. Interesting cases resembling those included in this group, except for their duration, are those reported by Marchand,[40] and Bernard and Heitz.[41] In Marchand's case the duration was three months, in Bernard and Heitz's case five months. In both of them there was an extreme degree of asthenia, and at autopsy simple atrophy of the adrenals was found in both cases. Bernard and Heitz employ their case to justify them in originating a condition which they term subacute insufficiency of the suprarenals.

3. The nervous type, in which the predominant symptoms have been either convulsions, as in the cases of Portal,[42] Valleix,[43] Parrot[44] and Droubaix;[45] or coma, as in the cases of Arnaud,[46] and Laignel-Lavastine;[47] or delirium, as in the cases of Mattei[48] and Ribadeau-Dumas and Bing;[49] or a typhoid state, as in the cases of Virchow[50] and Kohler.[51] These varied symptoms have been noted in children, as well as in adults. In some of the cases in which convulsions have been a predominant feature I think it not improbable, as mentioned above, that they were the cause rather than the result of the injury to the adrenals.

4. Cases of sudden death. In this group I include the cases of sudden death in which at autopsy nothing except a destructive lesion of the adrenals, usually hemorrhage, has been found. It may be thought presumptuous in such cases to conclude that the sudden death was due to the adrenal lesion, but realizing from experimental evidence and from the clinical evidence of the more protracted cases how profound an influence destruction or injury of the suprarenals has on life, I think that it

37. Murray: Tr. Path. Soc., London, 1870, xxi, 395.
38. Sicard: Bull. Soc. méd. d'hôp. de Paris, 1904, xxi, 848.
39. Voisin and Norero: Bull. Soc. d'anat. de Paris, 1906, lxxxi, 320.
40. Marchand: Deutsch med. Wchnschr., 1903, xxix.
41. Bernard and Heitz: Tribune méd., 1904, New Series ii, 325.
42. Portal, quoted by Lieutaud: Historia anatomica, 1769, i, 285.
43. Valleix: Clinique des maladies des enfants nouveau-nés (Case 22), Paris, 1838.
44. Parrot: (Cases 10 and 11) Arch. gén. de méd., 1872, xix, 257.
45. Droubaix: Thèse de Paris (Case 1), 1887.
46. Arnaud: (Case 4) Arch. gén. de méd., 1900, clxxxvi, 5.
47. Laignel-Lavastine: Bull. Soc. anat. de Paris, 1902, lxxvii.
48. Mattei: (Case 1) Sperimentale, 1883, li, 386.
49. Ribadeau-Dumas and Bing: (Case 2) Bull. Soc. anat. de Paris, 1904, lxxix, 477.
50. Virchow, quoted by Lancereaux: Dict. encycl. d. sc. méd., 1875, iii, 155.
51. Kohler: Dict. encycl. d. sc. méd., 1875, iii, 155.

is a justifiable inference. This I believe to be true of still-born infants in whom this lesion is found, as well as in cases of advanced life. Instances of this type have been reported by Rayer[52] and Goodhart,[53] and Hamill[3] has collected the cases occurring in still-born infants and children reported up to the year 1900.

5. Cases occurring in association with a purpuric eruption or hemorrhages into the abdominal viscera. Numerous cases of this type occurring in children are reported in the literature. I have been able to find none occurring in adults. Undoubtedly the hemorrhage into the suprarenals in these cases is but a manifestation of the general hemorrhage tendency as a result either of infection, or, in some cases, possibly of asphyxia. The English clinicians have been inclined to look on these cases as possible instances of hemorrhagic smallpox, especially by reason of the fact that many of the affected children have been unvaccinated. As there is little else than this one fact in support of their view, I think it can not be looked on as a probable one.

Though the majority of cases permit themselves to be classified in one or another of the above groups, many are characterized by symptoms common to more than one group. The cases in which purpura is a prominent feature may present symptoms characteristic of the peritoneal or nervous type, and cases of the asthenic or nervous type may in addition present some symptoms belonging to the peritoneal type. Of all the symptoms the most constant and one of the most characteristic is a greater or less degree of asthenia. The occasional occurrence of two other symptoms is worthy of mention. They are tumor and the *ligne blanche* of Sergent.[54] A tumor, the result of suprarenal hemorrhage, is mentioned as having been determined during life in three instances. In one of Rayer's[24] cases it involved the right suprarenal and presented itself in the epigastrium. In Routier's[26] case a hemorrhage into the left suprarenal formed a palpable tumor in the left hypochondrium. In Leconte's[55] case there was a fluctuating tumor on each side of the mid-line extending from the hypochondrium to the iliac fossa. The *ligne blanche,* or white lines produced by stroking the skin with the finger, are looked on by Sergent as being of great diagnostic value in suprarenal insufficiency. They result from the temporary constriction of the relaxed vessels. As the majority of observers agree that they can be produced in various conditions attended by vasomotor relaxation, I can not agree with Ser-

52. Rayer, quoted by Roger: Jour. de l'expérience, 1837.
53. Goodhart: New Sydenham Society's Atlas of Pathology, 1879, ii, 50.
54. Sergent: Bull. Soc. méd. d'hôp. de Paris, 1904, xxi, 380.
55. Leconte: Thèse de Paris (Case 48), 1897.

gent in looking on them as diagnostic of adrenal insufficiency. As clinical investigation has as yet advanced no pathognomonic signs of the condition, it is only when the symptoms observe a sufficiently characteristic grouping that the possibility of diagnosis during life can be entertained. Attention should be paid to the relative frequency of the condition in the purpuras of childhood and during or shortly after the acute infections. An interesting case occurring subsequent to an acute infection is that reported by Sicard of a woman 33 years of age, who shortly after the crisis in Friedlander's pneumonia suddenly manifested a most profound asthenia; death occurred within a few days, and at autopsy hemorrhage and necrosis of both adrenals was found. Bousset[56] asserts that he has recognized acute insufficiency of the suprarenals as indicated by asthenia, arterial hypotension, nausea, vomiting and diarrhea eight times in the course of various acute infections and that he has caused their subsidence by hypodermic injections of adrenalin. Due consideration must be paid to the apparent etiologic relationship that exists between acute suprarenal insufficiency and inflammations in the neighborhood of the suprarenals, surface burns, chronic heart or pulmonary disease, and any phenomenon tending to a great increase in internal blood pressure.

Such cases as those of Laignel-Lavastine and Arnaud claim for acute suprarenal insufficiency a rôle of some importance as a possible factor in apoplectiform deaths. Both of the patients were men, respectively 36 and 47 years of age, apparently previously in good health, who suddenly fell unconscious and died in coma, one twelve hours, the other forty-eight hours after the onset. At autopsy the only finding of note was hemorrhage into the suprarenals. When physiology has taught us more of the functions of the suprarenals, and when they are subjected to a more rigid routine postmortem examination, and when clinicians pay more attention to the facts already determined, I have no doubt that acute suprarenal insufficiency will assume a position of greater clinical importance than it has maintained in the past.

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56. Bossuet: Gaz. hebd. de méd. de Bordeaux, 1904, xix.

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PSEUDODIPHTHERITIC SEPTICEMIA, WITH REPORT OF A CASE DIAGNOSTICATED BY BLOOD CULTURE.

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The exact relationship of the Bacillus diphtheriæ and the so-called "pseudodiphtheria" bacillus has been a subject of discussion ever since the discovery of the latter by Hoffman in 1887. The question as to whether the two organisms are to be looked on as members of the same group, the differences in their morphology and other properties being due to changes in their environment, or whether they represent two separate and distinct but probably allied groups, is still unsettled. The present tendency is toward the latter view. If this be accepted, the main practical difference between the two groups must rest on the ability of the true diphtheria bacillus and the inability of the pseudodiphtheria bacillus to produce a specific toxin.

The more extended studies of recent years have demonstrated that while there is but a single species of the true

diphtheria bacillus which may, however, show slight variations in virulence, there are several species making up the group of "pseudodiphtheria" bacilli. Of these, some can be easily distinguished from the true bacillus by differences in morphology, staining and cultural characteristics as well as by their inability to produce toxin. Others again resemble the true Klebs-Loeffler organism so closely that the production of toxin is the only reliable distinguishing characteristic. The case we are about to report represents an infection with an organism of this latter group—an organism which can be very easily confused with the true bacillus.

The patient was under the care of Dr. MacLeod, and was seen on several occasions by Dr. Alfred Stengel.

A male, aged twenty-seven years, married, civil engineer, a temperate liver and of good habits.

His family history is unimportant and without bearing on the case.

He had had an attack of scarlet fever when seven years of age, followed in a few months by an attack of acute articular rheumatism of some severity. His heart was known to have been affected from this time, but it is uncertain whether the cardiac involvement followed directly upon the scarlet fever or developed in the course of the rheumatism.

He had never had any severe illness since those mentioned above, but had never considered himself as particularly robust, having always to observe considerable caution as to prolonged exertion. In the last two or three years he played a good deal of tennis, but was always forced to stop after the second set on account of general fatigue but not of dyspnea. From time to time he had suffered from rheumatic twinges, and had been treated frequently in the last few years for a pharyngitis diagnosticated as rheumatic. During the fall and winter of 1907 and 1908 he had three of these attacks. In none of them was there any fever or other constitutional symptoms; the throat at each time remained quite free from lacunar or follicular exudate or membrane, presenting merely

a severely congested appearance of pharynx and half arches. The last of these anginoid attacks occurred on February 16, and yielded so promptly to aspirin that he went to his office at the usual time the next morning apparently quite recovered.

On March 19 the patient arose feeling rather badly, but was able to go on a short business trip. His malaise, headache, and general condition of aching of the joints grew progressively worse, and upon his arrival home at 7.30 that night he had a severe rigor. When seen at 8.30 P.M., his temperature was 104.2; pulse, 108; respirations, 24; his face was intensely flushed, the pupils dilated, and the lips rather cyanosed; his principal complaint was of pain of an influenzal character in the back and legs, together with the sensation of warmth to be expected from his rise of temperature. Questioned as to the presence of his accustomed sore throat, he replied that it did not bother him this time in the slightest. Examination of the throat was absolutely negative.

The next morning his temperature had fallen to 100°, his pains under aspirin and camphor were greatly diminished, and his other symptoms were materially improved. Examinations of the lungs and abdomen were negative. Auscultation of the heart revealed no change in the mitral systolic murmur which he had had for many years.

For three days his temperature fluctuated between 99° in the morning and 101° at night; his pulse between 90 and 116. His constitutional symptoms seemed to be improved, but he complained of intense lassitude and almost complete anorexia.

On March 24 his temperature was normal, and he expressed himself as feeling better than at any time during his illness, even going so far as getting up to shave himself. Following the exertion, his temperature at 6 P.M. rose to 103.2°, his pulse to 122, and he was generally prostrated. The heart sounds for the first time were not to be easily separated, and a slight pericardial friction rub was present. The following morning, March 25, his temperature was 101°;

pulse, 128; respiration, 38. Examination of the lungs was negative. Urinalysis showed a slight trace of albumin. The leukocytes were 17,800 and the Widal reaction was negative. The patient was in a weaker condition than at any time previous, his mentality apathetic, tongue heavily coated, and general condition typhoidal in character. His condition showed little change for the next week. On April 3 the blood examination showed 58 per cent. of hemoglobin, 4,530,000 erythrocytes, and 20,800 leukocytes. The differential count showed 79 per cent. polymorphonuclear leukocytes, 12 per cent. lymphocytes, 7 per cent. large mononuclears, and 2 per cent. transitionals in the 100 cells counted. The Widal reaction was again negative in dilutions of 1 to 50 and 1 to 100 in an hour. The urine was very high colored, a brownish red, with specific gravity of 1020, acid reaction, a heavy cloud of albumin, no sugar, cylindroids and hyaline casts, a few epithelial cells and leukocytes. The test for bile was negative, while the test for urobilin was distinctly positive. Ehrlich's diazo-reaction was positive, and there was only a very faint trace of indican.

A blood culture was taken at this time in the usual manner from the vein at the bend of the elbow, about 15 c.c. of blood being withdrawn and distributed in bouillon and in agar plates, in all of which a fairly luxuriant growth occurred which in subcultures proved to be an organism similar to the Bacillus diphtheriæ. In view of the presence in the blood of what was thought to be the true Klebs-Loeffler organism, injections of diphtheritic antitoxin were given, but without the slightest change in the symptoms. On April 7 a second examination of the blood showed 34,320 leukocytes, of which there were 68.5 per cent. polymorphonuclears, 10.5 per cent. lymphocytes, 11 per cent. large mononuclears, and 11 per cent. transitionals in the 200 cells counted. A blood culture taken at the same time showed in five of the six flasks of bouillon, and in all six plates an organism similar to the one isolated in the first blood culture. A smear taken from the throat

showed a mixed growth in which cocci seemed to predominate. A careful search failed to reveal any organisms resembling those found in the blood. From this time on to the day of his death, April 16, his condition became gradually but progressively worse. His temperature never rose to the height which it attained on the night of the onset, but fluctuated between 101° and 103°. His mental condition changed from hebetude to a low muttering delirium with carphologia. His abdomen was scaphoid, emaciation was marked, and his tongue board-like and protruded with great difficulty. His pulse remained between 120 and 145 except on exertion, as after sponging, when it could not be counted at the radial. The heart sounds became one confused murmur, roughened in character, and transmitted almost all over the chest and back. The apex beat was diffuse and the heart somewhat dilated, more, however, to the left than to the right. A petechial eruption appeared especially on the legs and arms. Intense anemia and general wasting were present and the patient became semiconscious, finally passing into coma, in which condition he died after being sick twenty-eight days. There was no autopsy. The clinical diagnosis was pseudo-diphtheritic septicemia, with endocarditis following a chronic valvulitis.

In the case reported above, the great number of organisms in the blood was very striking. The agar plates, to which about 1 c.c. of blood had been added, each showed from 900 to 1200 colonies. This is considerably more than we have ever noticed in a long series of blood cultures in other diseases. On the agar plates the growth occurred as small whitish colonies, varying in size from a pin point to a pin head, moist, showing little tendency to adhere to the media. On Loeffler's blood serum the organism grew well as discrete pale yellow colonies. Smears from these showed a Gram-positive rod of irregular size and shape, with enlargements either at the end or at the middle, and the rods for the most part arranged parallel in small groups. The organism

varied in length and width, the shorter forms being straight, the longer forms curved at one or both ends. With Loeffler's methylene blue the organisms showed rather marked differences in size and shape, and each organism took the stain irregularly. Neisser's stain demonstrated the polar granules to better advantage. The growth on agar was a thin uniform film fairly abundant, and smears here showed the organism to be larger, thicker, and more uniformly barred than when grown on serum; club-shaped forms were also common.

The growth in bouillon was quite characteristic. After twenty-four hours there was very slight general clouding; at the end of forty-eight hours, or, better, after seventy-two hours, a granular surface growth appeared with some sediment collecting along the sides and bottom of the flask, the fluid remaining fairly clear and of acid reaction. The surface growth on the slightest disturbance was precipitated through the liquid as a cloud and settled to the bottom. Milk showed a very slight acidity. No gas was produced in glucose, lactose, or saccharose agar, nor was there a visible growth on potato. As soon as suspicion had been aroused as to the organism being the Bacillus diphtheriæ, about thirty surface colonies were picked up from the agar plates, emulsified in bouillon, and injected subcutaneously into a small-sized guinea-pig. The pig showed no signs of infection and was killed at the end of a week. Aside from a slight subcutaneous infiltration at the site of inoculation, no signs of disease were present. The same result followed the injection of even larger amounts of the culture from Loeffler's blood serum and bouillon when given subcutaneously or intraperitoneally. In one instance death did result in thirty-six hours, following an intraperitoneal injection of 4 c.c. of a forty-eight-hour bouillon culture in which had been emulsified the growth from a good-sized serum slant. At the autopsy there was an acute peritonitis with effusion from which the organism was cultured; cultures from the blood of

the heart, however, were sterile. An effort was now made to increase the virulence of the organism by injecting very large doses of the culture subcutaneously into guinea-pigs, killing them the next day, culturing the organism from the site of inoculation, and injecting into a second pig. Several attempts to carry this out were unsuccessful, as we were not always able to recover the organism. In one set the organism was passed through three guinea-pigs without apparent increase in virulence. This, to be at all conclusive, should have been carried through a larger number of animals, but in the short series there seemed to be no change in virulence. The fact that bouillon cultures of this organism remained acid suggested a study of its fermentative ability as compared with that of a member of the pseudodiphtheria group, and of the true Bacillus diphtheriæ. Flasks of glucose bouillon, 1 per cent., were inoculated with each organism, and one flask was kept as a control, all being incubated at 37°. On successive days 10 c.c. were removed from each flask and titrated with $\frac{n}{10}$ sodium hydroxide solution, using phenolphthalein as an indicator. The amounts of the solutions used were too small for accurate results, but it was quite evident that the organism under discussion resembled more closely the true Bacillus diphtheria in the production of acid than it did the pseudobacillus. Loss of the culture by an accident prevented carrying out more accurate observations.

The organism found in this case then resembles the true Klebs-Loeffler bacillus so closely that practically it cannot be differentiated from it except on the basis of its not producing a specific toxin.

A search of the literature reveals few similar cases.

Roosen-Runge[1] reported a case of empyema developing after pneumonia in which nine days after resection of a rib, blood cultures showed an organism in pure culture similar to the diphtheria bacillus. Cultures from the pus of both pleural cavities before death and from the ulcerations on the tricuspid and aortic valves after death all showed an organism

identical with that found in the blood. The growth in bouillon produced a marked acidity. Six guinea-pigs inoculated subcutaneously with the organism showed nothing more than slight signs of illness, while two inoculated intraperitoneally with 10 c.c. of a twenty-four-hour culture of the organism died in five or six weeks in cachexia and showed no signs of infection at death.

Mahler[2] reported a case of septicemia caused by the streptococcus and an organism similar to the diphtheria bacillus. After a mild angina the disease began with irregular fever, swelling of the cervical lymphatic glands, enlargement of the spleen and 19 days after the onset by a petechial eruption over the lateral aspects of the body in the axilla and on the elbows. Blood for blood cultures were taken on the 19th, 29th, 33d, and 40th days of the disease in the usual manner and placed in bouillon. The first culture after a week's growth showed an organism resembling the diphtheria bacillus. The last three cultures showed the same organism together with a streptococcus. It is interesting to note that no improvement followed the repeated injection of diphtheria antitoxin, while convalescence seemed to date from the injection of streptococcic antiserum. The bacillus isolated was not pathogenic for guinea-pigs when injected subcutaneously in doses of 0.5 c.c. and 1 c.c. of a twenty-four and thirty-six-hour bouillon culture, and caused only slight subcutaneous infiltration at the site of inoculation.

Ucke[3] reported a case of septicemia caused by the diphtheria bacillus following a mild angina and complicated by an abscess in the gluteal muscles, from both of which, as well as from blood cultures, organisms similar to the diphtheria bacillus were obtained. The blood was taken from the vein in the arm and added to several tubes of bouillon and slanted agar. From only one of these tubes (agar) did he obtain a growth of diphtheria bacilli. Before the gluteal abscess was opened, 3000 units of diphtheria antitoxin had been administered with no change in the condition of the

patient. Recovery, however, occurred after opening and draining the abscess. One c.c. of a bouillon culture of the organism was injected subcutaneously into a guinea-pig of 200 grams weight. An infiltration developed at the site of injection, but did not kill the animal.

Von Niessen[4] found an organism similar to the diphtheria bacillus in the circulating blood in a case of combined scarlet fever and diphtheria. No mention is made of its pathogenicity.

Besides these four cases (if von Niessen's case be included) diagnosticated by blood culture during life, there are a number of instances where this same organism, so far as can be determined from the meagre description given, has been found postmortem.

Howard[5] reported an interesting case of ulcerative endocarditis in which at the autopsy, eight hours after death, an extensive thrombosis was found on the superior surface of the mitral valve and the evidences of septicemia in the other organs. Coverslip preparations from the mitral valve, the spleen, and kidneys showed in pure culture and in great numbers an organism which could not be differentiated from the Klebs-Loeffler bacillus except that it was non-pathogenic for guinea-pigs. The organism was studied by Welch, Abbott, and others, and by all was thought to be the true diphtheria bacillus.

Wright[6] reported a case of acute endocarditis in which the aortic and tricuspid valves were affected and in which cultures postmortem showed the pneumococcus, staphylococcus, and an organism corresponding to the Klebs-Loeffler bacillus except that it was non-pathogenic for guinea-pigs.

In the cases so far reported the infection has not had any direct connection or relation with the disease ordinarily known as diphtheria, and in every instance except possibly in von Niessen's case the organism was non-pathogenic for guinea-pigs.

We have been unable to find the record of any case of

true diphtheria in which diphtheria bacilli pathogenic for guinea-pigs have been found in the blood during life. Many instances, however, are recorded where the organism either alone or with the streptococcus or staphylococcus has been found in the blood and internal organs after death. Such cases are reported by von Babes,[7] Kolisko and Paltauf,[8] Johnson,[9] Nowak,[10] Frosch,[11] Kutscher,[12] Booker,[13] Flexner,[14] Cannon,[15] Wright,[6] Wright and Stokes,[16] Stokes,[17] Kanthack and Stephens,[18] and Pearce.[19] In many of these cases the distribution of the bacilli was so general that it must have occurred before death, so that we feel that the bacilli could be isolated from the blood in these same cases had they been cultured during life. Unfortunately many of these reporters do not state whether the organisms found by them were pathogenic for guinea-pigs. Wright, however, in his work found that all the organisms isolated by him from fatal cases of true diphtheria were pathogenic for guinea-pigs, except one to which reference has already been made.

Pearce[19] says "the clinical significance of this general infection with the Klebs-Loeffler bacillus is not apparent. It occurs generally, but not always, in the gravest cases, or those known as 'septic' cases. It is probable that it may be due to a diminished resistance of the tissue cells, or of the germicidal power of the blood. Whether the Klebs-Loeffler does or does not continue to produce its toxic products, wherever it may be, in the blood or internal organs it is impossible to say, but from the number of fatal cases with such an infection, it would seem very probable that it does."

In the cases reported we seem to have two groups of organisms which resemble each other more or less closely in morphology, staining properties, and cultural characteristics, but differ from each other in the ability to form toxin when injected into guinea-pigs. The one group seems to have been definitely identified as the true Klebs-Loeffler bacillus and the question arises as to whether the other group is to be

looked on as an entirely distinct but allied group or whether it is a true diphtheria bacillus which has under peculiar conditions lost its power of producing toxin.

A study of the conditions under which this interchange of pathogenicity could take place has been made by a number of observers. Of the results of this work, Graham-Smith, in his exhaustive treatise on diphtheria published in 1908, states that "experimental attempts to artificially decrease the virulence of diphtheria bacilli produce somewhat conflicting evidence, but show that under any conditions their attenuation is a matter of difficulty and uncertainty. Attempts to give virulence to totally non-pathogenic diphtheria bacilli have been almost uniformly unsuccessful and even attempts to raise the virulence of lowly virulent bacilli have frequently failed."

Again, "it has been asserted that Hoffman's bacillus (the form usually referred to as the pseudodiphtheria bacillus) may be pathogenic to man but no bacteriological proof has been produced, and except by one or two observers Hoffman's bacilli derived from all sources have been found to be non-virulent to guinea-pigs in fairly large doses."

The opinion seems to be gradually gaining ground that the diphtheria bacillus and the pseudobacillus represent two allied but separate groups of organisms. Hamilton[20] in a thorough critical review of the literature shows that the various methods proposed in the past for differentiating these two groups have not been satisfactory and decisive. She quotes the opinion of Beck, Loeffler and Spronck that "it is impossible to distinguish the true from the pseudobacillus by means of cultural pecularities, morphology, presence of Neisser granules, chemical activity or virulence for animals, and the only hope for a sure method of differentiation lies in the application of specific sera to neutralize specific toxins."

After a careful study of 29 organisms which were, with the exception perhaps of three, pseudodiphtheria bacilli, she concludes that this indefinite group "may be divided into at

least three separate groups. First, there is the group of those which are non-pathogenic to guinea-pigs—a group which probably should be further subdivided, for some are apparently pathogenic to man and there are certainly decided differences as far as cultural characteristics go. Yet a basis of subclassification would be hard to find. Second, there is the well-defined group of organisms pathogenic to guinea-pigs, producing a general bacteriemia, and neutralized by the serum of a rabbit immunized against one member of the group; third, the organisms which form gas in glucose media produce bacteriemia in guinea-pigs and are neutralized neither by diphtheria antitoxin nor by the pseudodiphtheria serum."

Graham-Smith comes to much the same conclusion when he says that "evidence is rapidly accumulating to show that many other species of diphtheria-like organisms besides Hoffman's bacillus are to be found in the throat, nose, eye, genital tract, and on the skin of healthy and diseased persons, some of which more closely resemble the diphtheria bacillus and others Hoffman's bacillus in character."

H. M. Goodman,[21] after a careful study of the three types of the diphtheria group, the Bacillus diphtheriæ, the Bacillus pseudodiphthericus, and the Bacillus xerosis, concludes that "separation of the members of the diphtheria group into two or more species on the basis of morphology, staining properties, character of growth or pathogenicity is not justifiable because of inconstancy. The same applies to immunity reactions which have the additional objection that their significance as species reactions is as yet unknown. The only character which experience has not shown to be untrustworthy is that of difference in behavior toward carbohydrates," and this he does not consider a species characteristic because "it can be readily and markedly altered at will by artificial selection." We feel that his conclusions are sound in regard to the interchangeability of different characteristics with the exception of pathogenicity. He proved quite conclusively

that by natural selection an *increase* in toxicity for guinea-pigs could be brought about in the diphtheria bacillus, but we are not convinced that he has shown that this can be depressed entirely nor that it can be added to those forms which usually do not possess virulence.

Zinsser[22] has recently confirmed the opinion of Knapp that these groups may be differentiated by their fermentative action on certain sugars, the true diphtheria bacillus fermenting dextrin but not saccharose, the xerosis bacillus fermenting saccharose but not dextrin, and the pseudodiphtheria bacillus not fermenting either. We did not apply this test to our organism. This may prove to be a satisfactory method of differentiation, but as yet the difficulties of carrying it out prevent its use as a practical method.

From these opinions and quotations it seems reasonable to look on pathogenicity for guinea-pigs as the only reliable difference between the true and the pseudodiphtheria bacilli. In the cases reported above (except those diagnosticated as true diphtheria) the organisms have been considered diphtheria bacilli, in some cases being specially called Klebs-Loeffler bacilli. With our present knowledge we fail to see the grounds for this opinion.

We feel, therefore, that we are justified in looking on the organism found in our case, and also probably those found antemortem in the cases reported by Roosen-Runge, Mahler and Ucke, as well as those reported as found postmortem by Howard and Wright, as belonging to the group of pseudodiphtheria bacilli, and for them would suggest the term diphtherioid bacilli to differentiate them from Hoffman's bacillus on the one hand, from which they can be distinguished by morphological and cultural characteristics, and especially by the production of acid in bouillon culture and from the diphtheria bacilli on the other, from which they can be distinguished only by their inability to produce toxin when injected into guinea-pigs.

Further work is necessary on the pseudodiphtheria group

before a proper classification can be arrived at. This may also bring to light a method for differentiating the members of this group from the true Klebs-Loeffler bacillus, which will be shorter than the one we have now which depends on guinea-pig inoculation. We would repeat the suggestion made by others that pathogenicity for guinea-pigs, which can be neutralized by diphtheritic antitoxin, is the only crucial test for the true Klebs-Loeffler bacillus.

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THE INHIBITION OF PANCREATIC ACTIVITY BY EXTRACTS OF SUPRARENAL AND PITUITARY BODIES.*

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In a recent publication[1] we had the privilege of considering at some length the question of the activation of the pancreas by secretin, with especial reference to malnutrition and diabetes.

In it we pointed out, among other things, that in some animals, especially those which are carnivorous and are not provided with grinding molar teeth, in which animals there must, therefore, be either a large amount of acid gastric secretion or a high degree of acidity within the stomach, there was evidence that pro-secretin is present in the intestines in quantities larger than are found in human beings. We also reached the conclusion that the evidence to date for the absence or deficiency of pro-secretin as the cause of some cases of diabetes and malnutrition was insufficient.

These were our main findings as far as the present communication is concerned, but the experience gained in these connections led us to experiment further. The question of the relation of the pancreas and its evident activity, when excited by secretin, to digestion in general and to other organs in particular, is a very wide one, and, as we ventured to point out, offers a most promising and relatively unexplored field for research. It occurred to us that with a definite and sure method of activating at least the "external" secretion of that gland, and with an experience equal to measuring and interpreting its response, we had at hand a means whereby its correlation with other organs might be studied.

In his Harvey address[2] Starling says: "Secretin may be taken as a type of a whole group of chemical messengers, which, formed in one organ, travel in the blood stream to other organs of the body and effect

*From the Pepper Laboratory of Clinical Medicine, and the Laboratory of Experimental Surgery, University of Pennsylvania; reported before the Society of Normal and Pathological Physiology, University of Pennsylvania, March 30, 1908.

1. Sweet, J. E. and Pemberton, R.: The Archives Int. Med., 1908, i, 231.
2. Starling, E. H.: Jour. Am. Med. Assn., March 14, 1908, l, 835.

correlation between the activities of the organs of origin and the organs in which they exert their specific effect." This effect, he says, as a deduction from many observations in this connection, is not due necessarily to the formation of a special substance which shall exert a specific influence on some distant organ, but possibly to the development in that distant organ of a specific sensibility to the common product of the first organ. The chemical adaptations which Starling considers and of which we know most, have resulted almost exclusively in increasing the activity of the responding organ. "We can not, however, draw sharp lines between the reactions involving increased activity or dissimilation and those which involve increased assimilation or growth, since, under physiologic circumstances, the latter is always an immediate consequence or accompaniment of the former."

Some unknown function of the pancreas by virtue of which it seems to have a close relation with diabetes has long been recognized, chiefly from von Mering and Minkowski's well-known observation, that extirpation of the pancreas causes glycosuria. As is well known, many agents may cause glycosuria when injected intravenously or otherwise given; for example, isotonic salt solution injected intravenously in large amounts; interference with the supply of oxygen; etherization; and, lastly and more specifically, adrenalin injected subcutaneously. Whatever the mechanism by which these agents act the last one named does so by producing a true hyperglycemia. Now the fact, on the one hand, that a small excess of suprarenal substance in the circulation of an animal, its own suprarenal glands being intact, produces glycosuria, and, on the other hand, that extirpation of the pancreas produces a like result, suggests an antagonism or balance of action between these two organs in particular which might profitably bear investigation. A relation of this kind has been suspected, though full experimental evidence has been lacking to establish it. Thus, Herter has shown that painting the pancreas with adrenalin causes glycosuria, but whether this is merely a feature of its action when injected subcutaneously or intravenously is not yet known. G. Zuelser[3] has advanced some ideas as to the interrelation of the adrenals and the pancreas. To quote his own words, he makes "the assumption that the secretion of the suprarenals is normally neutralized by the pancreas and that, therefore, the 'pancreatic diabetes' of Minkowski, which follows extirpation of the pancreas, is really a suprarenal diabetes." He also claims that by injecting simultaneously

3. Zuelser, G.: Berl. klin. Wchnschr., 1907, xliv, 474.

suprarenal extract and pancreatic juice, no glycosuria results. Pflüger[4] has shown that extirpation of the duodenum in frogs causes glycosuria. (It is from the duodenum, of course, that the pancreas normally obtains the stimulus for the discharge of its external secretion at least.) Ehrman[5] has found that this extirpation does not cause glycosuria in dogs; but Pflüger criticizes Ehrman's work on the ground that the separation of the pancreas from the intestines was not complete and that the animals did not survive the operation for a period long enough to make the experiments conclusive.

It was, therefore, with the basal thoughts just suggested that we sought to investigate the influence of various factors on the one gland of the body whose excitation by "hormones" can be induced at will, as a basis for inquiring into that further interdependence of organs which we know exists. Our first thought was to look within the body for factors which might have some effect, though the question of outside influences, such as "drugs," is an important one of itself.

We attempted, therefore, at the start, to influence in dogs the flow of pancreatic juice when excited by secretin, with intravenous injections of adrenalin chlorid, taking 3 c.c. at a dose.[6] Three c.c. of adrenalin was sufficient instantly and markedly to increase the blood pressure, without evidently injuring the animal during the period of observation and in a few minutes the blood pressure fell again to normal, so that the dose could be several times repeated.

We found on injecting adrenalin chlorid that the flow of pancreatic juice was almost at once inhibited and in most cases absolutely so. With injection of fair amounts it was at all times slowed, proportionately to the size of the dog and the activity of his pancreas. Moreover, the simultaneous injection of secretin and adrenalin resulted in a total absence of flow; and, furthermore, the injection of adrenalin a few moments prior to the injection of secretin prevented a flow. Occasionally, if the gland were very active and the dose of adrenalin moderate, a slight response to

4. Pflüger: Arch. f. d. ges. Physiol., 1907, cxix, 227.

5. Ehrman: Arch. f. d. ges. Physiol., 1907, cxix, 295.

6. The secretin we used was prepared from normal dog intestines. The animals on which we experimented were all dogs. They were kept under profound ether anesthesia, and, at the end of the experiment, were killed. The amounts of secretin injected were 10 c.c. of solutions made from 300 to 400 c.c. 0.4 per cent. HCl. This quantity of acid was found well adapted to the extraction of mucosa from the upper four feet of dog intestines, and served for numerous observations, making a total of about 150 to 200 c.c. of secretin solution. The details of preparation are otherwise as given in our previous article (The Archives Int. Med., 1908, i, 231).

flow would occur late, as though, in the end, the action of the secretory factor had preponderated.

In considering the matter, one of our first thoughts was, of course, that the inhibitory power of adrenalin was due to its blood-pressure-raising principle, notwithstanding the fact that changes in blood pressure are well known to have little influence in the output of most glands, and that the pressure in the secretory duct of such glands may, without much effect, be higher or lower than that in the vessels supplying it. This is well illustrated by numerous long-established experiments on the salivary glands. As a matter of fact, however, the injection of secretin is followed by an immediate and pronounced fall in the blood pressure. The blood-pressure-lowering element of secretin is probably purely incidental, as shown by Bayliss and Starling, and, as can be seen from our records, is a feature of many extracts of tissue because of various elements present. Further, under some circumstances, after the injection of adrenalin of known vasomotor activity, the blood pressure has for various reasons failed to rise very much, and again, after adrenalin injections, secretin has greatly reduced the blood pressure to a point much below normal, and yet no flow has resulted in either event, showing conclusively that this action is not the result of high blood pressure. Further, the simultaneous injection of both agents frequently results in such an antagonism of the elements which affect the blood pressure that no change in its level occurs and still no flow appears. We shall later refer fully, after considering further experiments, to some results obtained with old solutions of adrenalin which had undergone changes whereby they lost their property of preventing pancreatic flow, but yet powerfully raised the blood pressure. A flow, therefore, took place with the blood pressure raised almost to a maximum by adrenalin. More direct experiments to this end can be conducted with difficulty, as no other known substance raises the blood pressure to a degree at all comparable with adrenalin.

That this inhibition of secretion is not a feature of any general action of adrenalin is shown by a number of observations, the results of which are summarized as follows by Cushny:[7] "The secretion of the salivary gland and of the mucous glands of the mouth and throat is increased, apparently through stimulation of the nerve terminations, as under pilocarpin. The secretion is arrested by atropin, but can be reinstated by larger amounts of suprarenal extract, which is a more powerful antagonist to atropin than pilocarpin. The lacrimal gland and the bile

7. Cushing, Arthur R.: Pharmacology and Therapeutics, Lea Brothers & Co., Philadelphia.

are also increased." Speaking of the blood pressure, he says: "This active principle exists only in the medulla of the gland and, therefore, does not represent the whole function of the organ, in all probability."

It may be well here to mention the methods by which we recorded the observations which appear later. In our previous work we measured pancreatic activity by registering with a watch the exact moment at which the flow of juice through the canula in the duct of Wirsung passed definite graduations marked along the canula. This method was accurate enough, but not at all graphic and was, as well, voluminous in reproduction, so we had recourse to the following method:

The blood pressure was recorded on a kymographic drum by means of a manometer in the femoral or carotid artery, and the respiration by a manometer introduced into the trachea. By means of the electric push-button connected with the pen drawing the base line on the drum, it was possible, by watching the flow of juice through a graduated canula placed in the duct as usual, to record in vertical and momentary elevations of the base line the exact moments at which the juice flowed past any given division.

In order that the record of an experiment, which often covered a period of several hours, might be made continuous, we made use of a modification of the well-known "endless roll," a method which had for our purpose the advantages of recording the blood pressure in all its variations from the normal established at the beginning of the experiment.[8]

The experiments above recorded of the action of adrenalin were repeated a great many times and, as our tracings show, with almost invariably the same results. The amount generally used was 3 c.c. of the "adrenalin chlorid" of Parke, Davis & Co., which is said to contain two and one-quarter grains of chloretone to the ounce. In order to obviate the possibility of the latter preservative being a factor we prepared several chloretone solutions of different strengths, one of over twice the strength in which it occurs in adrenalin, but no inhibitory effect could be observed from it. We next made up a solution of pure adrenalin from the dried active extract of the suprarenal glands also on the market. This is said to contain no preservative of any sort, but a solution made from it of the same strength as that containing chloretone again gave the same results. Finally, we made a suprarenal extract of our own, from the suprarenal glands of thirteen dogs on which various surgical

8. We are under great obligations to Prof. E. T. Reichert for his kindness in devising the simple and effective kymograph which proved so perfect for the use of the endless paper roll. We are further indebted to him for assistance in many technical points.

operations had been performed some weeks previously in the course of experimental surgery at the University of Pennsylvania. These animals were in good health and were all killed by gas at the same time for autopsy study; advantage was taken of this fact to obtain the suprarenals. The glands were run through a hash machine and the resulting mass ground up with sand and about 30 c.c. of normal salt solution in a mortar for about fifteen minutes till the whole was reduced to a uniform pulp. Salt solution was then added to a total of 78 c.c. and the mortar contents strained through unbleached muslin. This preparation was opaque, white and cloudy in appearance, and our observations show that to all intents and purposes it had all the properties of that put on the market in regard to both blood pressure and inhibition of pancreatic flow. On an earlier occasion we made a normal salt solution extract from the two suprarenals of one dog and added to it 1 c.c. of a saturated solution of chloretone. This preparation was also active in all respects.

In order to establish any peculiarity or specificity of action in this connection, however, it was then necessary to utilize other glandular extracts and other substances in the same connection.

To this end we experimented with as many animal extracts of known activity as could be obtained. There are, of course, but few such, and there is only one of any definite therapeutic value, viz., the thyroid. A tablet of dried thyroid extract (the therapeutic dose for an adult human being) was ground up in a mortar and the powder rubbed up with 10 c.c. of water. The liquid assumed a brownish color, indicating some solubility of the substance, but for the greater part this injection consisted of a fine suspension. A solution of thyroid extract was also made by treating the mashed and ground pulp of two sheep thyroids with slightly more glycerin than was sufficient to cover them. This was allowed to extract all night and then diluted one-half with water, strained and used in various amounts for injection. There can be no question that this preparation contained much of the peculiar colloid thyroid elaboration, because the slightest amount gave the characteristic viscid reaction which occurs when the latter is treated with alkali. The glands used in this instance were taken from fresh material obtained from the abattoir and used at the University Hospital in the treatment of a case of myxedema which was improving rapidly. We also tried a liquid preparation of thyroid extract distributed by the manufacturers. All of the above thyroid extracts, however, were without influence on the flow of juice.

It has been shown by Schäffer and Oliver and others that the pituitary gland contains a substance which acts somewhat analogously to the active principle of the suprarenals, in that it raises blood pressure. It does this to a degree less than the latter, though the effect is said to be

continued somewhat longer. We attempted next, therefore, to obtain an extract of the pituitary body, and used first a liquid preparation said to be of the infundibular portion, distributed by Parke, Davis & Co. for experimental clinical observation. In answer to some questions addressed to them by letter, the manufacturers of this solution state that it contains 0.5 per cent. of chloretone. Taking the same dose of this that we used of adrenalin chlorid, we injected it after exciting the flow by secretin and obtained almost the same consequences as followed the use of adrenalin. In other words, the pancreatic flow was at once cut short and generally completely inhibited. In nearly every instance the rise in blood pressure was considerably less than is witnessed after the same dose of adrenalin, and, moreover, it was less abrupt, though the longer continuance noted by somé observers was not so apparent. Notwithstanding its evidently inferior activity in respect to blood pressure, its inhibitory action on pancreatic juice seemed to be more marked. The cessation was in most cases more prompt, and on several occasions a second injection of secretin failed to excite a response after an interval of time following the injection of pituitary extract such as would probably have insured a flow, even though slight, had adrenalin been used, showing apparently that this preventive action sometimes lasts longer in the case of the pituitary gland. That this feature in no way depends on an increase in blood pressure is better illustrated by the pituitary than by the fresh adrenal extracts, since the former on many occasions fails to raise the blood pressure and more frequently the rise is so slight and so temporary as to be of evidently little consequence. In this respect of raising the blood pressure, the pituitary extracts used by us were by no means as constant or reliable as those made from the suprarenals.

On varying the time of injection, as we had done with adrenalin, and giving the extract after excitation of the pancreas by secretin, then before its excitation, and, finally, with the injection of secretin, we met with nearly identical results. In both of the latter instances the flow is prevented by the dose mentioned (3 c.c.), and in the former it is greatly slowed and generally promptly stopped. In regard to both the adrenal and pituitary extracts it is noticeable that their action is apparently more marked when the injections precede or are coincident with the injection of secretin than when they follow it. Sometimes, with a very active pancreas, the initial dose of adrenal or pituitary would be insufficient to retard very much a violent response to secretin, but we found that if given before the injection of secretin the flow was always inhibited.

The commercial extract of pituitary gland which we first tried (the exact nature of which was, of course, entirely unknown to us) was open

to the same theoretical objection as adrenalin, and it was possible that methods of preparation or the preservatives used in its manufacture might conceivably produce these effects or modify in some way its own properties; indeed, they might actually disguise those with which we were concerned. We, therefore, determined to prepare our own extract, which we did as follows:

On the occasion mentioned above, when thirteen dogs were killed, we removed separately both portions of the pituitary gland, nervous and glandular. This procedure is relatively simple in the dog, as the organ is easy of access and is exposed to view as soon as the frontal lobes of the brain are raised. The nervous part in the dog is a small white globule about the size of a grape-seed, and on being crushed extrudes a slightly viscid juice which can be rubbed into a paste. To the thirteen infundibular portions so treated we added 30 c.c. of normal salt solution, agitating the whole for some time to insure as complete extraction or solution as possible. The resulting fluid contained very little residue of any sort and was transferred directly to a small sterile Erlenmeyer flask. The glandular portion of the pituitary was then treated in the same way with an equal amount of salt solution and transferred to another flask. It might be mentioned here that, while histologically the glandular portion of the pituitary body is epithelial tissue, it in no way resembled a gland macroscopically, and by the uninitiated eye would be taken for the nervous element. On being crushed it resembles so much fairly dense tissue and gives a solution more tinged with blood than the nervous extract, which is almost white in color.

The extract from the nervous portion of the pituitary was active in regard both to blood pressure and to the suppression of the pancreatic flow, agreeing in all respects with the other preparations tried. The dose used was 10 c.c. of extract, which was equivalent to the nervous fraction of about four and one-third whole glands. The blood pressure was raised to a degree somewhat less than was seen after most of the other pituitary injections, but this may well be accounted for by the strength of the preparation, which must have been considerably lower in actual extractive content than the commercial article, which is made from the organs of larger animals.

The extract from the epithelial portion of the pituitary was injected without any evident effect on either the blood pressure or the flow of juice, which is quite remarkable, considering the immediate contiguity of the structures, and argues much for a specificity of action. We shall have more to say on this subject later.

Having satisfied ourselves that the pituitary and the suprarenal both contain something whose action on the pancreatic flow is marked, it remained now to investigate other tissues. The one of known physiologic interest as regards its therapeutic action we had already tried with a negative result, but it could not be postulated that other organs or other tissues might not contain some principle which would act analogously. Consequently we made extracts of the parenchyma of other glands and of other nervous tissue. Of the former the epithelial portion of the pituitary already served as a striking instance. About one-fourth of the liver of a freshly killed dog was put through a hash machine and then ground with sand and a small amount of normal salt solution in a mortar until a fairly uniform mass resulted. More normal salt solution was then added, making a total of 150 c.c. used, and the whole agitated and ground in a mortar as well as possible for about twenty minutes. It was then passed through unbleached muslin to free it from sand and tissue residue and then transferred to a sterile Erlenmeyer flask.

In addition to the above, on another occasion, a glycerin extract of liver was made by adding about 150 c.c. of glycerin to the mass passed through the hash machine as recorded, and after agitation and pressure in a mortar the whole was allowed to extract for twenty-four hours. A small amount of water was then added and the mass strained. Another watery extract had been previously prepared and this procedure was repeated only because it was thought that an unavoidable delay of some hours might in some way have impaired the activity of the first. With the exception just noted, the glandular extracts of our own preparation on which we based conclusions were all made within a few hours of the death of the dogs and injected within a few hours at latest after their preparation.[9] None of the liver preparations seemed, however, to have the slightest effect on the flow of juice, though the blood pressure was sometimes considerably lowered, as has been shown by Halliburton, Dixon and others to be the case with several organ extracts.

We next experimented with nervous tissue, for which purpose we obtained the brain of a freshly-killed dog, passed it entire through a hash machine and then ground the pulp in a mortar with sand and a total of about 130 c.c. aqua distillata. Distilled water was used inadvertently instead of normal salt solution, as in the other experiments.

While the subject of the depressing effect of extracts of nervous tissue has already been pretty thoroughly studied by Halliburton and others, it

9. The animals were killed between 6 and 7 a. m. The suprarenal and pituitary glands removed between 8 and 10 a. m., and extracts made by noon. They were injected during the afternoon and evening of the same day.

is interesting, apart from their relation to pancreatic activity, to compare the systemic effects produced by injections of this last preparation with those of other extracts. The amount of fresh liver substance taken for extractive purposes was about one-quarter of the organ, to which was added 150 c.c. of extracting fluid. The brain of a medium-sized dog compares closely with this in bulk as well as in percentage of water. We macerated the brain with 110 c.c. of extracting fluid, so that bulk for bulk the solutions were approximately equal, putting aside the question of their respective yields on attempts at extraction. The first dose of brain extract used was 10 c.c. and with a slight fluttering and preliminary rise of blood pressure the dog almost instantly died. The doses of liver and other tissue extracts were 10 c.c. and more. The next dose of brain extract was 5 c.c., and with a marked fall of blood pressure this animal died at once, though nothing had been previously injected into him. The next dose administered was 1 c.c. of extract in 10 c.c. H_2O, and again a fresh animal at once died; and finally we injected 0.25 c.c. diluted with 10 c.c. of water, and though the blood pressure fell alarmingly and it seemed by the cardiac inhibition and small excursion of pulse that this animal would also succumb, the blood pressure rose again and the animal seemed to recover. However, after one or two injections of secretin and adrenalin, which had been well borne in nearly every other instance, this dog also suddenly died, apparently from injury due to the first injection.

It is interesting to note that, notwithstanding the powerful and almost lethal effect of even a small dose of the watery extract of brain tissue, absolutely no effect could be detected on the flow of pancreatic juice, which continued, as we had frequently observed before, when the animal was moribund.

That the inhibitory action of the pituitary is therefore not a function of nervous tissue in general is clearly seen, because the mass of the brain as compared with that of the diminutive pituitary bodies is very great, and the effect of its extract, if potent, should be both actually and relatively greater. Moreover, the pituitary gland and brain substance are, of course, in the most intimate contact, and were this activity of the hypophysis common to other higher nervous tissue it is almost inconceivable that it should be so sharply differentiated in our work. Whether every part of the brain would act similarly in extract, or whether in such a gross method of extraction we have diluted, beyond evident potency, tissues from other active regions, is problematic.

In view of the relation which the pituitary is supposed to bear to the testes, as evidenced by those cases of acromegaly in which a lesion is dem-

onstrable in the hypophysis, and testicles also, it seemed advisable to try the effect of extracts from testicular tissues, although the immediate physiologic effect of these on the circulation and economy in general has been extensively studied by Dixon. We macerated two dog testes freed of their epididymes and then ground them up as before, with sand and mortar, finally adding a total of 78 c.c. of normal salt solution. The whole was then meshed through linen and injected in the usual manner, but no effect on the flow of juice was noticeable, whatever the time of the injections.

Our purpose in making glandular extracts of our own was two-fold. In the first place, such a procedure was necessary to give us the material we needed to widen the scope of our work; and, in the second place, it seemed advisable to test whether, by the methods we used, we could extract the features of certain glands which are known to be present in them. Failing in that, it could hardly be assumed that we were capable of extracting the active features of other parts; but if, on the other hand, we were successful, it could be reasonably believed that in the tissues under consideration no active substance was present, or that, if present, it was not susceptible of extraction by these methods. We desire to be understood, therefore, as claiming, not that this observed antagonism of action is one positively peculiar to two organs alone, but that it is one manifested by them under certain conditions of treatment and a property which we have been unable to extend as yet to other tissues. That a certain degree of specificity is probable from the evidence now at hand must be granted. Whether further observation will corroborate or disprove this it remains for the future to show.

We also experimented with atropin. According to the physiologists, atropin depresses or suppresses practically every secretory activity in the body except that of the kidney, and possibly the pancreas. On the flow of pancreatic juice, however, we were unable to perceive the slightest effect from it. The amounts administered were nearer the physiologic limit for a dog than were the doses of adrenalin, which can be repeatedly given in quantities of 10 c.c. at a time, in the form of the commercial adrenalin chlorid, without much evident injury. Our records show that one of our dogs received 1/300 gr. atropin sulphate, followed in a few minutes by another dose of 1/300 gr., without evident result on the flow, whereas another fresh dog died from what resembled paralysis of the respiratory center, apparently as the immediate result of an injection of 1/150 gr. Atropin neither prevented nor stopped the flow of juice.

Efforts were also made to simulate with digitalis the rise in blood pressure produced by adrenalin and pituitary extract, but no effect of any value could be obtained in this connection.

Now it is true that to speak of making an extract of so highly organized and differentiated a structure as the liver, not to mention the brain, seems crude; but it is also true that in considering such a problem as we have here we must first begin with the lowest terms and with such methods as are compatible with our knowledge of the subject. Having found in two organs some active substance which can be extracted by their treatment with salt solution, we are driven to applying the same methods to other parts of the economy if we would learn more of its extent and distribution. It can well be urged that in different sites the same property or different properties require different methods of extraction, and that treatment with water or glycerin in one instance will not effect the same result in another. Nevertheless, we have indubitable proof that both water and glycerin can extract certain of their activities from several organs, as, for example, the suprarenal and thyroid glands respectively, and we also have equal proof that from other regions of the body can be derived substances of such toxicity that an animal subjected to their action immediately succumbs. Just which of their numerous ingredients are responsible for these properties we are often unable accurately to say, and it is even a disputed point as to what factor in the extraction of nervous tissue produces the profound depression of the vascular system which is followed by death. That the same methods of attack, under such circumstances, should therefore necessarily appear superficial and crude follows perforce. When we consider how easy of extraction by almost identical means is that principle of the adrenals with which we are most familiar, namely, the blood-pressure-raising element, it seems astounding that its discovery should date from a period so recent as 1894; and if it be borne in mind that such methods in that instance furnished striking knowledge and that we have progressed little since then in our knowledge of the functions of the suprarenals themselves, the methods necessary in dealing with such an unknown subject appear less general and more definitely specific.

We hope to be able to investigate this antagonism of action, after separating the pancreas from its nerve supply, as thoroughly as possible, since it may well be that the effects noted result from the mediation of the sympathetic system. It is of some interest to consider here briefly a few points in the morphology of the suprarenals and the pituitary in their relation to our observations. It has been shown[2, 7, 10] that the

10. Dixon: Jour. Physiol., Cambridge, 1900-1901, xxvi.

classic effects of adrenalin are produced in large part by its action on the sympathetics, and wherever we test its action, in respects other than those under consideration, we find the results identical with those obtained by stimulation of this system of nerves and ganglia. The suprarenals are derived morphologically from two sources, the cortex coming from the mesoblastic tissue and the medulla from a direct outgrowth of the sympathetic system. As evidence of the latter we find in many of the lower orders distinct nervous tissues consisting of neurogliar cells, which are, however, harder to differentiate in man; indeed, in certain forms, viz., teleostean fishes,[2] the two parts, medulla and cortex, remain separate through life. Now, an interesting corollary to our observed analogy of action between the suprarenals and the pituitary is the fact that morphologically we could reasonably conceive of these two organs as having something in common. The pituitary body, like the suprarenals, consists of two parts; and again like the adrenals, each part has a separate derivation. The anterior lobe has its origin from one of the branchial clefts in a pouch of buccal mucous membrane.[11] The posterior is derived, like the medulla of the adrenal, from the ectoderm. It comes from the floor of the third ventricle, to which it remains attached by a stalk, viz., the infundibulum. According to some, the larger anterior lobe has two sources, the primitive oral tissue in early life and the anterior portion of the alimentary canal.[12] Wiederscheim[13] says that "the secretion from the pituitary gland formerly passed into the ventricles, and one of the more recent theories assumes that the pituitary corresponds to the primitive mouth (palæostoma) of the proto-vertebrata, which to a greater or less extent is represented by the combined impaired nasal and pituitary passage of cyclostomes." In certain mammals there can yet be seen evidences of the passage which connected the anterior part with the posterior part and thence with the third ventricle.[11] These facts by themselves are of interest, and in connection with our observations they are not in discord. That an organ so anatomically remote as the pituitary should have a definite influence on a gland in possible morphological relation to it is therefore less surprising.

As with the adrenals, it is that part derived from the nervous system which gives rise to the blood-pressure as well as the inhibitory element. For neither the epithelial portion of the pituitary nor the cortex of the suprarenals, however, is there any recognized function. The two parts

11. Herring: Jour. Physiol., Cambridge, xxxvi, No. 6.

12. Stengel: Text-Book of Pathology, Philadelphia, Saunders, 1906. Davidoff, Böhm: Text-Book of Histology, Huber, 1900, p. 380.

13. Wiederscheim: Comparative Anatomy of Vertebrates, Parker, 1897, p. 155

of the pituitary can be worked up and extracted separately, as noted above, but this has not yet been possible with the adrenal, so far as its inhibitory action is concerned, although from the suggestive analogies between these two organs and the very evident limitation of the inhibitory feature of the pituitary to its nervous moiety, it seems probable that the adrenalin inhibition has the same point of origin as the blood-pressure factor, viz., the medulla; still, this can not be postulated at present, and it may be, indeed, that we have here an expression of one of the functions of the suprarenal cortex.

Since the completion of our experiments some work has been reported by Botazzi, D'Errico and Jappeli,[14] in which they obtained an inhibition of flow from the salivary gland by painting it with adrenalin. Stimulation of the chorda tympani then failed to give a response. Without questioning the accuracy of their findings, which are at variance with the work quoted by Cushny, the question as they present it does not argue an inhibitory action on the salivary gland analogous to that observed by us on the pancreas. In the first place, they are dealing with a gland excited by purely nervous means and not by a chemical substance which reaches it through the blood. Again, and more important, the inhibited salivary gland is stated by the above Italian workers to be in the highest degree anemic after local application, a condition in which it is hard to conceive of its having an activity of any sort, since it is for the time being out of commission. This is, of course, in no way comparable to the action of adrenalin on the pancreas (if its action *is* on the pancreas) when the flow of juice in the latter organ is inhibited by a systemic injection into the jugular vein. And, furthermore, this view of the matter does not explain the action of the pituitary which has, as far as we know, no such reported action on glands. Finally, to ascribe to an ischemia of the pancreas the inhibition of pancreatic flow after jugular injection of a small dose of adrenalin, supposes that most or all of the organs of the body become anemic to such a degree that they can no longer act, which is stretching a hypothesis beyond the facts to support it.

It is somewhat immaterial, however, whether adrenalin acts on the pancreas alone or also on other organs, since the point of interest is that in affecting it at all in this way it affects the one gland of the body whose connection with diabetes is best established. That it might also affect certain other analogous structures with inhibition would not be surprising, though the evidence now is against it.

14. Botazzi, D'Errico and Jappeli: Physiol. Inst. Univ., Naples; Biochem. Ztschr., January, 1908, vii, 431.

One feature of our work demands some notice and is of suggestive interest. On the day when we experimented with the pituitary and suprarenal extracts of our own manufacture we made our first injections about 1 p. m. The preparations used for this purpose had been made between 10 a. m. and 12 m. from the animals killed early that morning as noted. The samples of suprarenal extract first injected were vigorously active. Because of press of work under the desire to utilize our preparations before they were affected by decomposition, we were unable to use the pituitary extracts before evening, about 8 p. m. Although tried then for the first time, about eight hours or more after their manufacture, they acted vigorously, as stated. On endeavoring to repeat with the suprarenal extracts our work with them of the early afternoon, however, we were able to get no inhibitory action, although the blood pressure was still raised. To control this conflicting observation we tried a preparation of adrenalin made some weeks previously from the dried extract of the suprarenal gland put on the market by Parke, Davis & Co. in small grain vials and said to be free from preservatives. This solution corresponded purposely, in adrenalin strength, to the usual commercial article containing the preservative chloretone. It was remarked by one of us immediately prior to the injection, while filling the syringe, that the solution showed a slight mould. It had been used many times before and had in every instance been powerfully and emphatically active, though there had been a lapse of perhaps a week since its last use. To our surprise, this preparation raised the blood pressure decidedly, but was absolutely without influence on the flow from the pancreas. We then tried an injection of the commercial adrenalin chlorid solution, also some weeks old but containing chloretone, which both raised the blood pressure and inhibited the flow, as we had repeatedly observed before.

The absolute significance of these observations can not be established until we repeat our experiments in this particular connection, but the most obvious and reasonable deduction is that the extracts from the suprarenal glands contain two or more substances, one of which acts on the blood pressure and one of which acts to inhibit the flow of juice. The former of these seems the more stable of the two and resists decomposition for a considerable time, but the latter loses its activity very shortly, perhaps in a few hours. In the instance of the preparations of our own manufacture, from dog organs, the tissues and the extracts from them were, of course, contaminated from the start with the ordinary postmortem putrefactive agents, and in order in no way to impair the efficiency of the extracts no attempt was made to introduce preservatives or sterilize them. The "dried extract" of the gland, however, was presumably

sterile to start with and the solution made from it remained fairly free from infection except in so far as it was contaminated by the initial weighing of the dry powder. Sterile salt solution was added to this and the solution kept on ice in a corked bottle, the only further contaminating agent, beyond contact with the air when the cork was removed, being the needle of the syringe. This was always thoroughly cleansed with water after each injection, though not sterilized. Under these circumstances decomposition would surely proceed rapidly from the start in the case of our dog preparations, but slowly in the case of the others. We can offer no explanation for the apparently greater stability of the pituitary inhibitory factor except that the pituitary glands, being small, were easily mashed in a small agate mortar and quickly transferred to small flasks, while the suprarenals required longer and more vigorous treatment with sand in a mortar, had also first been run through a hash machine, and were hence more open to infection.

The process which operated to destroy the activity of these preparations may be simply that of decomposition by putrefactive organisms, or it may be, on the other hand, of an oxidative nature more like that to which Bayliss and Starling have ascribed the slow deterioration of secretin and its more rapid loss of activity on evaporation in efforts to concentrate it. All the points here suggested are yet to be worked out, however, in their relation to our work.

We are by no means sure, at the present writing, of the full interpretation of the results under discussion. They are but the earliest steps in a line of work on which further observations may throw much light. They seem to us, however, to be very suggestive in their possible bearing on other interglandular relations, on the medium in which these are maintained, and possibly on a new conception of the interdependence of various organs now the subject of speculation. For these reasons it seemed advisable to publish our results at this stage and make their further amplification the subject of later contributions.

In studying the records, and indeed through a consideration of all our work, it must be borne in mind that we are dealing with a balance of power between various factors, no one of which is susceptible of exact definition or measurement. As with the study of the pharmacologic action of drugs, there must be taken into consideration, besides the size of the dose, the activity of the organ under consideration, and the condition and size of the animal as a whole. What may be quite sufficient markedly to affect one animal may be altogether inadequate in the treatment of another.

Popielski[15] has recently taken issue with Bayliss and Starling as to the method of action on the pancreas of acid extracts of the intestinal mucosa and indeed as to the existence of secretin at all, as a specific excitor. He also claims to be able to produce pancreatic activity with extracts of stomach and large intestine. The main point of discussion in this controversy is somewhat beside our present issue, though there are a number of incidental features which have a close relation to some observations of our own.

Popielski thinks that the secretion of pancreatic juice after excitation by secretin is dependent on a fall of blood pressure and that if the blood pressure be maintained high no flow results. He uses adrenalin to raise the blood pressure and notes with the high pressure that there is no flow. He concludes also, as an incidental point, that adrenalin, in itself, does not inhibit pancreatic activity. He considers that stimulation of the pancreas by secretin and stimulation by HCl in the duodenum are different processes. Now, it seems to us that our work throws some light on several of these questions. In the first place, we have obtained some further results with adrenalin (already mentioned and to be referred to again presently). Popielski's use of it seems to have been solely to raise the blood pressure. In so doing he has apparently overlooked the other feature of it, for, while he notes incidentally that it does stop the pancreatic flow, he thinks this phenomenon due to the high blood pressure and not to the adrenalin proper. He specifically states that adrenalin in itself does not influence the flow of juice. Now, as we mentioned above, one of our series of experiments conclusively proves that it is possible to obtain a flow after the injection of secretin, despite the fact that the blood pressure is raised to a high point. We refer to those observations, happened on by chance, in which exposure to air and apparent decomposition had destroyed the inhibitory factor of a solution of adrenalin, but allowed the blood pressure element still to act. Whatever the true explanation of this—and we offer nothing positive on this point—it is a fact that on several occasions such a solution distinctly raised the blood pressure sometimes to a very high point, and yet the juice flowed. To have noted this once would be sufficient to prove it possible. We have a number of such records. Not only does this prove that it is not the blood-pressure element alone of adrenalin which affects the flow of juice, but it also proves that, as just stated, a flow may take place following secretin when the pressure is high and that, therefore, a low blood pressure is *not*, as Popielski claims, a feature necessary to it.

15. Popielski: Arch. f. d. ges Physiol., 1907, cxx, 451; 1908, cxxi, 239.

His findings in regard to the failure of atropin to affect the flow are in agreement with ours, viz., that no inhibition results from it. We have as yet been unable to effect a secretion from the pancreas by the injection of extracts of other tissues, though we have not yet tried those particular tissues (i. e., stomach and large intestine) used by Popielski. He states that a watery solution is sufficient to extract the exciting factor, and we used also water and normal salt solution in our work. We obtained no flow, but, on the contrary, from certain tissues, as mentioned above, we obtained an inhibition. We also made an acid extract of the pancreas with 0.4 per cent. HCl, and treated the whole exactly as we did a coincidently prepared and active solution of secretin. No flow resulted, however, from the acid extract of pancreas.

It should be mentioned also that after section of both vagi we still obtained the inhibitory effect from suprarenal and pituitary extracts.

Some further interesting observations have recently appeared which deserve reference. Fleig[16] reports on the physiologic properties and toxicity of normal pancreatic juice and that provoked artificially. He considers as normal, juice elaborated under the influence of chyme secreted through a duodenal fistula in an otherwise sound dog and then injected into the duodenum of the dog whose pancreas is under consideration. The quantities of chyme required under these circumstances are considerable (20 to 30 c.c.) and they must be repeatedly injected (every ten to twenty minutes) to induce a proper flow. The secretion thus provoked differs much from that which follows intraduodenal injections of 0.3 per cent. HCl, the time required is much greater and the quantity of juice furnished "infinitely less." Under the influence of chyme thus conducted the juice remains very thick and viscid from beginning to end, whereas juices secreted after more artificial stimulation differ in this and other physiologic respects until after repeated injections of secretin. For example, the pancreatic juice may have hardly any of its normal physical characters.

Natural and artificial secretions also vary in their toxicity when injected into animals, the former being more powerful in this respect. The lowered toxicity of secretin juices, Fleig thinks, is in consonance with their poor content of solids rather than their relative tryptic inactivity. He says that the above conditions are true also in general of the biliary and salivary secretions.

Now it seems to us that the above results are what might be expected. That a purely artificial and foreign substance, such as secretin, full of other extraneous matter and differing itself not only in quantity but in

16. Fleig: Compt. rend. Soc. de biol., May 8, 1905, No. 15.

quality from the normal pancreatic excitant, should produce the same juice as does the slow extruder gastric chyme, acting over perhaps many hours, seems unlikely in the highest degree. It would, indeed, be extraordinary if the results of such varied stimulation were the same. The amount of excitant which reaches the pancreas normally from the duodenum is surely a small or moderate quantity; that which is injected with secretin is not only concentrated in preparation from many feet of gut, but is injected in a few seconds to spend its whole force at once. It is hard to see how any gland could long continue to elaborate a normal product under such vigorous treatment. We hope to investigate shortly the effect of adrenalin and pituitary extracts on the pancreatic flow after stimuli other than secretin, especially chyme from a gastric fistula in an otherwise healthy dog, but it seems probable that the principles are much the same on which depends secretion after all of these and that the results of such work will be in harmony with what we have already seen. If adrenalin and pituitary extract inhibit the sudden and violent initial flow from secretin, it is conceivable that they would also affect the mild response from other stimuli. It must be remembered that the altered nature of pancreatic juice after secretin comes as the result of protracted and powerful stimulation and not from the initial dose.

It is interesting to note in connection with our work the observations of Meyer[17] and Frouin,[18] which afford some evidence that extirpation of the suprarenals, after the induction of diabetes in depancreated animals, modifies the severity of the diabetes and reduces the elimination of sugar.

We hope to concern ourselves now with the question of the site of this antagonism between the pituitary and suprarenal glands, on the one hand, and the pancreas, on the other; with the question of whether it is a chemical action, in the general sense of the word, which occurs in the circulation, or whether it is the result of some influence exerted on the pancreas alone; or whether, again, it is accomplished through a nervous mechanism. The solution of these problems should give information of value in studying the influence of such factors on the so-called "internal secretion" of the pancreas, and its relation to diabetes. Whether, on hypodermic injection, adrenalin produces glycosuria, which it does in a few minutes, by virtue of an inhibition of the internal secretion of the pancreas analogous to the inhibition of its external and visible discharge, is yet to be investigated. We have been unable to produce a glycosuria after either the subcutaneous or intravenous injection of 4 c.c. of pituitary extract. The solution used was made for us without

17. Meyer: Compt. rend. Soc. de biol., Feb. 14, 1908, p. 219.
18. Frouin: Compt. rend. Soc. de biol., Feb. 14, 1908, p. 216.

chloretone by the manufacturers, but we have not as yet controlled its inhibitory activity on the external pancreatic flow and, therefore, can not be positive on this point.

It yet remains to investigate more thoroughly the degree of specificity by trying the effects of other tissues and other methods of extraction; but, whatever the result of this, it appears reasonably certain that this feature to which we have called attention is one peculiar to certain structures, and from the data now available the expression of hitherto unknown properties of several organs.

In conclusion, it is a pleasure and a duty to express our great obligation to Dr. David L. Edsall for his constant and helpful interest in the work, and we also wish to thank Dr. John Marshall for many courtesies in the loan and equipment of apparatus.

CONCLUSIONS.

1. The suprarenal glands and the nervous moiety of the pituitary body in dogs contain something which, on extraction with salt solution and intravenous injection into dogs, cuts short the flow of pancreatic juice, after the administration of secretin. It also prevents the stimulation of the gland by secretin if its injection precedes the secretin.

2. This feature has been found, to date, in no other tissues.

3. It is independent of the general rise in blood pressure seen after the intravenous injection of adrenalin and pituitary extracts.

4. The inhibitory factor of extracts of the suprarenal glands seem to disappear by decomposition, oxidation, or other process, before the blood-pressure raising element is gone. It would appear that the suprarenal and the pituitary bodies have at least one property other than those qualities generally recognized as present in them.

1953 Locust Street.

ADDENDUM.

The accompanying records are illustrative of this article. They show the inhibitory effects of the intravenous injection of extracts of the suprarenal and pituitary bodies into dogs whose pancreatic juice has been excited by secretin.

It is to be regretted that it is impossible to reproduce more of the records, especially those which illustrate the prevention of excitation of pancreatic flow when the dose of secretin is preceded by an injection of suprarenal or pituitary extract. Under these circumstances the inhibition is more marked, but its proper exposition requires the consideration of a number of lengthy control records whose publication is impracticable. This is also true of those records which illustrate the inhibitory factor of suprarenal extracts as something apart from the effect on blood pressure. The reproduction of still other features is omitted for the same reason.

In the accompanying chart the upper line in each series of tracings represents the respiration as recorded by a manometer in the trachea; the next line represents the blood pressure as recorded by a manometer in the femoral artery; the line next to the lowest marks the time in seconds, and the lowest line records the injection of secretin and the injection of extracts, both of which are marked by a triple interruption of its continuity. This line also marks the flow of pancreatic juice, each isolated interruption indicating the flow of the juice past a division marked on a glass canula introduced into the pancreatic duct.

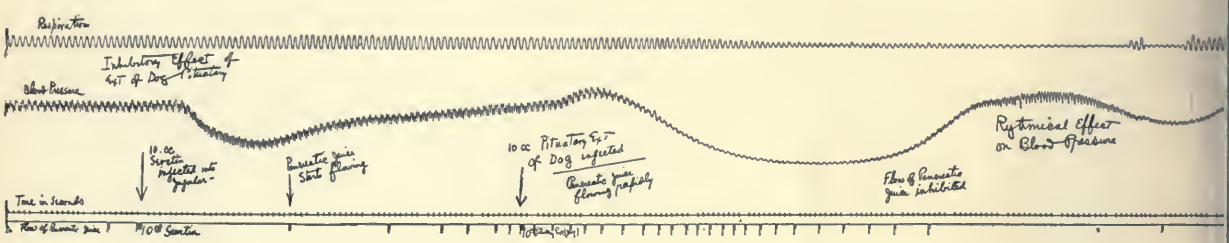
It should be stated for a proper understanding of the records that the normal response to the given dose of secretin is a prolonged flow of pancreatic juice, lasting sometimes many minutes, in contrast to which the accompanying records of flow show a distinct slowing and early cessation. Space will not permit of the reproduction of such a lengthy tracing as the normal.

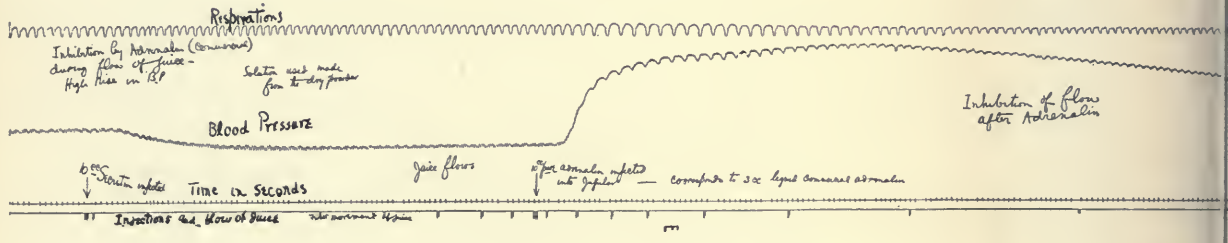
The upper series of tracings shows the stoppage of pancreatic flow by an extract of the pituitary body of dogs, with a coincident high rise in blood pressure.

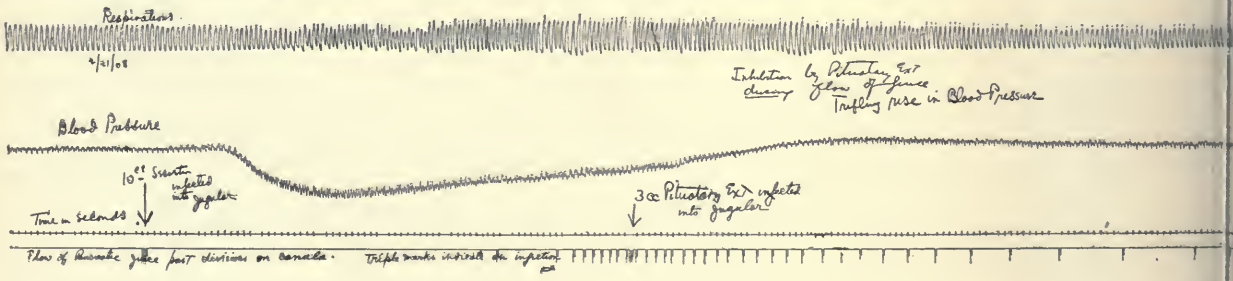
The middle series shows the same following an injection of adrenalin.

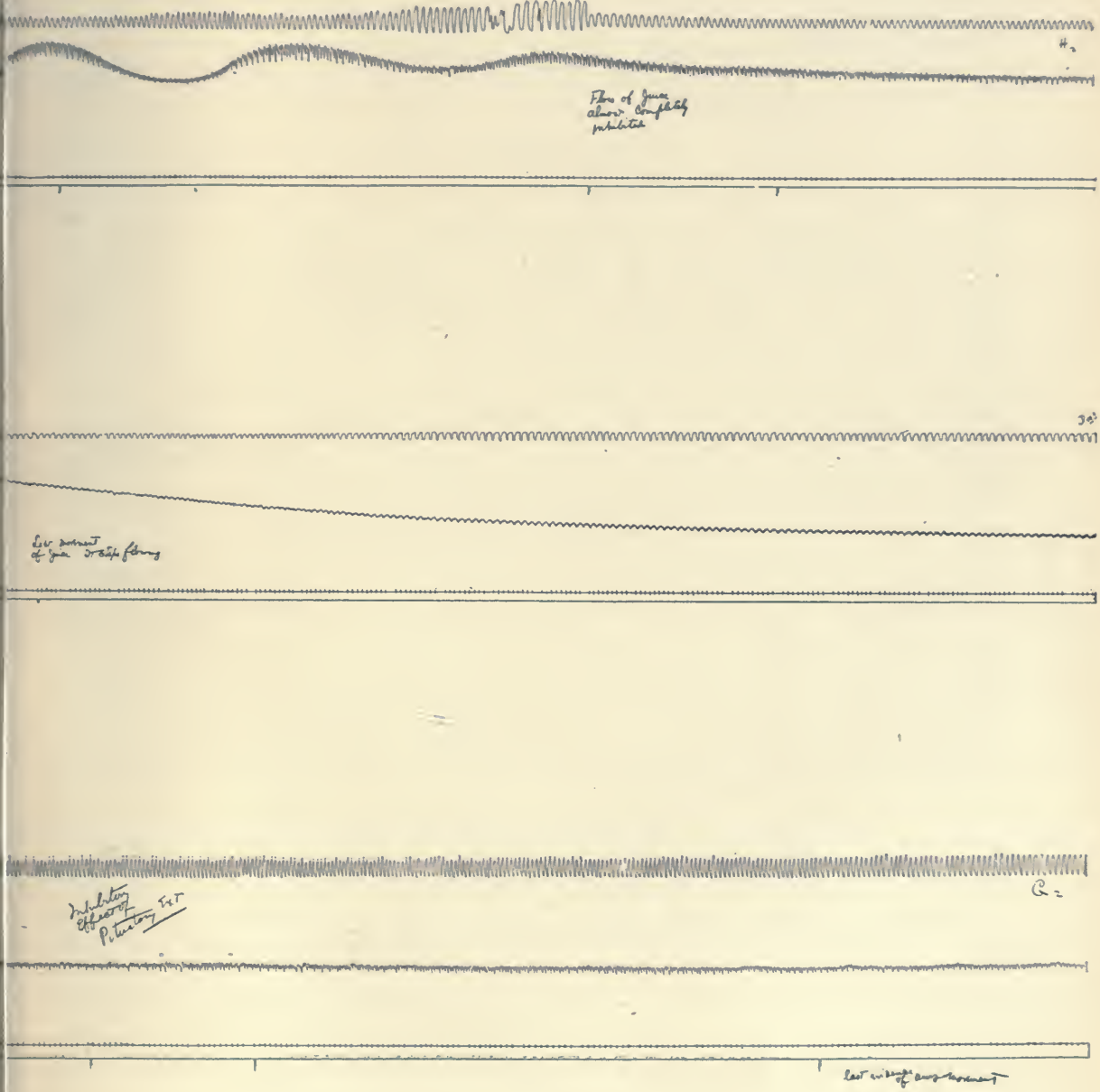
The lowest series shows the inhibitory effect following an injection of pituitary extract with a very slight rise in blood pressure.

(OVER)


Respiration
Inhibitory Effect of Ext of Dog Pituitary
Blood Pressure
10 cc Secretin injected into Jugular
Pancreatic juice starts flowing
10 cc Pituitary Ext of Dog injected
Pancreatic juice flowing freely
Rhythmical Effect on Blood Pressure
Flow of Pancreatic juice inhibited
Time in Seconds
Flow of Pancreatic Juice
10 cc Secretin
Notes Lost


Respirations
Inhibition by Adrenalin (Concurrent) during flow of Juice - High Rise in B.P
Solution used made from dry powder
Blood Pressure
Inhibition of flow after Adrenalin
10 cc Secretin injected
Time in Seconds
Juice flows
1 cc Adrenalin injected into Jugular — corresponds to 3 cc liquid commercial adrenalin
Injections and Flow of Juice
Slow movement of paper


Respirations
4/21/08
Inhibition by Pituitary Ext during flow of Juice
Trifling Rise in Blood Pressure
Blood Pressure
10 cc Secretin injected into jugular
Time in Seconds
3 cc Pituitary Ext injected into jugular
Flow of Pancreatic juice from divisions on cannula
Triple marks indicate the injections


Flow of Juice almost completely inhibited
Ext
Inhibitory Effect of Pituitary Ext
Last vestige of movement

EXPERIMENTAL OBSERVATIONS ON SECRETIN.

WITH SPECIAL REFERENCE TO DIABETES AND MALNUTRITION.*

J. EDWIN SWEET, M.D.

AND

RALPH PEMBERTON, M.D.

PHILADELPHIA.

The work of Bayliss and Starling† in ascribing pancreatic activity to so-called "secretin," a product of union of the acid chyme and intestinal epithelium, has opened a new field of research in certain branches of pathologic physiology. It has been known for some time that the introduction of acid into the duodenum would be followed by a flow of pancreatic juice, but this had always been ascribed, even by Pawlow, to a nervous mechanism. It remained for Bayliss and Starling to show, by a series of elaborate experiments in which they completely separated the gland from all innervation, that the pancreas responded to something which was formed when the hydrochloric acid of the chyme came in contact with the mucosa of the upper part of the intestine.

This substance, they proved, was normally absorbed where formed, and carried by the blood to the pancreas, which it at once caused to secrete. Certain other substances were found to unite similarly with the mucosa and produced the same results. The ultimate nature of this exciting agent is not yet known, but it appears to be a fairly stable chemical compound which can be extracted with alcohol and resists boiling, proving quite conclusively that it is not in the class of ferments, as we ordinarily understand that term. The discoverers of this compound named it secretin, and to the contributory factor resident in the epithelium they gave the name prosecretin.

The question of glandular action by chemical messenger or "hormone" is one of much importance and possibly of wide application to many physiologic processes hitherto poorly understood, especially where no clearly demonstrable nervous mechanism is concerned; thus Edkins[1] has described an analogous mechanism which seems responsible, in some part, for gastric secretion.

In connection with secretin, it has been thought by some that since

* From the Pepper Laboratory of Clinical Medicine and Laboratory of Experimental Surgery, University of Pennsylvania.

† Recent Advances in Physiology of Digestion, by E. H. Starling, Chicago; W. T. Keener & Co., 1906.

1. Jour. Anat. and Physiol., Lond., 1906, xxxiv, 133.

it causes an external secretion of the pancreas, it might also induce an internal secretion having some relation to diabetes. Work has been done on this line to which we shall have occasion to refer later. It seemed to the present authors, however, that apart from any specific property of secretin or prosecretin, its precursor in the intestinal mucous membrane, such a fundamental feature of pancreatic activity must be of wider significance. To find pancreatic secretion referable to a definite and well localized substance occurring in a certain place only, suggests the query, "What would happen if this substance were lacking?" As a function of the animal economy it must be subject to disturbances, and such disturbances might be of the utmost importance to health.

Cohnheim[2, 3] has shown that perhaps the most important of our digestive functions, proteolytic digestion, takes place not alone by virtue of the pancreatic juice, but also by means of certain other ferments (which act in the mucosa of the small intestine), and Vernon[4] seems to have proved that this same ferment action occurs in the other tissues of the body as well; but, however this may widen our conceptions of tissue destruction and construction, there can be no doubt of the prime importance of the pancreas and its juice for the purposes of intestinal digestion, not only of proteid, but also of the other elements of our diet. A failure of this secretion would, in the nature of things, lead us to expect a condition of perverted nutrition. It is true that Pawlow has produced permanent pancreatic fistulæ in dogs which survived for some time after the operation, but they were fed on special diet, with special care, in order that digestion and assimilation might take place.

With these facts in mind it occurred to us that it might be possible to demonstrate a deficiency or absence of these excitors of pancreatic activity in various conditions of malnutrition, and, perhaps, establish some etiologic relationship. Edsall[5] proposes the same thing in connection with some suggestive work by him on the rôle played in these same perverted states by the ferment eropsin, mentioned above as being resident in the small intestine and first discovered by Cohnheim. Some time since we began our work Wentworth[6] reported some cases of marasmus in which he found no evidence of prosecretin, and he regards this deficiency as the cause of the disease. We will refer to this work later. Bainbridge and Beddard[7] have reported six cases of diabetes which they investigated for the presence of prosecretin with similar negative results.

2. Ztschr. f. physiol. Chem., Strassb., 1901, xxxiii, 451.
3. Ztschr. f. physiol. Chem., Strassb., 1902, xxxv, 134.
4. Jour. Anat. and Physiol., Lond., 1904, xxxii, 33.
5. The Journal A. M. A., 1907, xlviii, 1469.
6. Jour. A. M. A., 1907, xlix, 204.
7. Bio.-Chem. Jour., Liverp., 1906, i, 429-445.

We originally meant to work on the line of pathologic physiology indicated above, but on attempting to establish some standard of normal action we encountered so many points of interest and difficulty that we had first to undertake a considerable series of purely physiologic experiments. It is the result of these, chiefly, that we wish to discuss.

We began, therefore, with efforts to excite the pancreas in dogs in which a temporary pancreatic fistula had been formed. We injected into them, through either the jugular vein or a vein of the hind leg, material obtained at the autopsy table, from various pathologic subjects. Our methods of work were essentially as outlined by Bayliss and Starling, and as far as possible, except where otherwise indicated, we endeavored to duplicate the conditions of each experiment in the attempt to be uniform. The human autopsy material was obtained in most instances as soon as possible after death, and the periods elapsing between death, autopsy and preparation of extract noted. They appear in the protocols.

The mucous membrane was scraped from the upper four to six feet of the small intestine with a piece of plate glass having a smooth edge, after the gut had been opened, washed in plain tap water and drained as well as possible. It was found that the nature of the gut varies considerably in different individuals, making it very difficult at times to remove the epithelial lining. In certain elderly subjects the membrane seems to be firmly adherent, requiring firm pressure in scraping to separate it, while in younger individuals it is removed with less difficulty, though rarely giving much bulk of material. In this respect the human gut differs radically from that of the dog, sheep and calf, from all of which, preparations were made. Although the intestine of a dog is less in lumen than that of a human being, the epithelium is not only relatively more abundant but actually so as well, and, furthermore, it can be removed with the greatest ease by light pressure, making in practically every case examined a greater bulk of scrapings than that from a human being. Not only is this true of dogs, but also of sheep and calves, in the former of which the gut is very much smaller both in lumen and thickness than in man, and it is also scraped more easily.

The membrane thus removed from the upper four feet of the small intestine, except where six feet were used, as noted in the protocols, was covered with a small amount of dilute hydrochloric acid and ground up with sand in a mortar. Inadvertently, acid of slightly less than 0.2 per cent. strength was used in the early experiments instead of 0.4 per cent. strength, which was adopted later, as noted.

The mortar contents, after being ground for about ten minutes, were slightly more diluted with as little acid as possible (the amounts are

given in each case), and transferred to a porcelain dish, where they were brought to boiling. A few drops of fairly strong caustic soda solution were then added, while stirring, until litmus paper showed faint alkalinity, and then the reaction was made slightly acid with glacial acetic acid, diluted one to three or four with water. A very few drops sufficed for this, and with the precipitation of the precipitable proteids the supernatant liquid, which had before been thick and opaque, became clear and could be decanted. In the earlier experiments the whole contents of the porcelain dish were strained through unbleached muslin by squeezing. It was found, however, that even with most of the proteid constituents precipitated as above, it was very difficult to filter the solution thus obtained. By the time it ran fairly clear and was free from opacity, even with a suction filter, the delay was so great and the amount of fluid obtained was so slight that we feared oxidation would render the preparation less active, if not inert, as stated by Bayliss and Starling. Later preparations were, therefore, made by simply decanting from the porcelain dish after addition of acetic acid and filtering this hot liquid quickly through coarse paper. At different times filtrates at varying stages of preparation were used, some of great opacity and some clear, while the supernatant fluid was used at other times without further treatment; but as far as could be seen the active properties were contained no more in one than in the others. Filtration, therefore, seems not to affect the activity of the extract, though we can not insist on this point as yet. The above solutions were then transferred to small Erlenmeyer flasks, sterilized in an Arnold steam sterilizer and used as soon as possible. After injection unused residues were resterilized for subsequent use.

The mechanical problems involved in making a pancreatic fistula in a dog are peculiar and deserve a short notice. The incision, like all physiologic incisions, is of importance secondary to the question of satisfactory exposure. Our method was to make a two-inch incision directly over the pancreas well to the right of the mid-line. The lower end of that portion of the pancreas which is closely attached to the intestine is withdrawn, together with the intestine. One can then locate the duct by palpating between the thumb and finger the tissue which lies between the pancreas and the intestine. The duct will be found lying within an inch from the lower end of the attached portion. The duct is then freed by careful blunt dissection and traced into the intestinal wall; a longitudinal incision is made in the duct, as far as possible into the intestinal wall, and the canula introduced and tied in place by means of a ligature, which passes entirely around the duct. A form of canula which has

given us satisfaction is that made with a tip of platinum fused into a graduated glass tube.

The necessity of adopting this technic evolved itself during the course of the work. The reason for exposing the duct external to the intestine is that the pancreas is one of the most delicate organs of the body, and attempts to introduce an adequate canula through the normal opening of the duct cause hemorrhages from the mucous membrane of the intestine. The actual mouth of the duct is smaller than the lumen as a whole, and hemorrhage is prone to occur also from the mucous membrane of the duct itself. The hemorrhages thus caused are persistent and induce coagulation of the pancreatic secretion. It is advisable to trace the duct well into the intestinal wall because part of the duct which is common to the upper and lower ends of the pancreas is extremely short; often so short, in fact, as to preclude tying a canula in place without excluding, by the ligature, the duct of the lower third of the organ.

We were led to the adoption of a canula with a tip of platinum because that metal can be wrought very thin and still possess ample strength. The lumen of the tip can then be made as great as the lumen of the canula, and, indeed, but little smaller than the lumen of the duct itself. On the outside of the extreme tip of the canula is a small ridge for a ligature, which is necessary to prevent the canula from slipping out of place during movements of respiration and peristalsis.

Extreme care must be taken in manipulating the pancreas, as very small hemorrhages frequently occur from the wall of the duct, and the admixture of the least amount of serum with the pancreatic secretion may cause a coagulum which will effectually block the canula. This can be materially prevented by coating the interior of the platinum tip and the lower end of the glass with paraffin. The caliber of the duct varies so greatly that we have two sizes of canulæ, using always that caliber which most closely approximates the caliber of the duct.

It will be seen from a study of the protocols that our first attempts with human preparations injected into dogs were failures, despite the fact that every possible care was exercised to have the conditions of preparation of extracts identical with those in preparation of extracts from dogs. Of a total of nine human cases from which we tried to obtain active extracts, in only two did we meet with certain success. The dog extracts, on the contrary, as also the sheep and calf extracts, were obtained active at the first attempt. We have not recorded a single instance of failure to obtain a very violent and pronounced reaction from them, though in many of the experiments the acidity of the extract more

nearly approached the acidity of the chyme in man than that in lower animals.*

It was noted that the extracts from man's intestines were harder to filter than those of animals, and after several failures we decided not to attempt much filtration (for which considerable liquid was required), but to use less fluid and decant sufficient for use from this more concentrated preparation. This was done, and, as seen in the records, a response was obtained on injection. Active animal preparations were obtained from both 0.2 and 0.4 per cent. strength hydrochloric acid, but in our series, human preparations of undoubted activity were obtained only from the acid of 0.2 per cent. strength.

In making our first controls we used secretin extracts made from dogs, and later on we made extracts from the sheep and calf, just mentioned, in order to satisfy ourselves that there was no specificity of secretin for any particular genus. The response given by the sheep extract was, perhaps, the most violent and pronounced of any witnessed, and it seems most improbable that a difference in the nature of the human secretin, *per se,* was in any way responsible for the failures following its injection.

During the course of the experiments fresh extracts were prepared from dogs, solely as controls of known activity, in testing human preparations under consideration. It, therefore, seems that although the acid extract of human intestinal membrane is higher in those presumably proteid and gelatinous constituents which make it difficult of filtration, the human intestine is not only relatively but actually lower in its content of prosecretin than is the intestine of some lower animals. The greater bulk of epithelium which can be removed from the animal gut doubtless accounts for this, and it appears that this is, perhaps, a provision of Nature, in keeping with other differences shown in the various species. For example, the acidity of the gastric secretion in a dog is greatly in excess of that in man, reaching 0.5 per cent. in order that he may digest the large pieces of meat swallowed without mastication. R. Meade Smith[8] gives a series of analyses of gastric contents in man, dog, sheep and horse, of which the hydrochloric acid in man, in 1,000 parts, was 3.19; in sheep, 4.05; in a horse (diet of oats), 4.9; in a dog, 17.13, from which it will be seen how greatly in excess of the human average all of these are. It seems probable, therefore, that the greater provision of epithelium (and, therefore, presumably of prosecretin) is to keep pace

* Since writing the above, we have made additional secretin preparations, in another connection, from about eight more dogs, and in every instance have obtained extracts of great activity.

8. Physiology of the Domestic Animals, 1889.

with this large amount of acid and to excite a copious and equal alkaline secretion from the pancreas. Certain it is that under the above conditions the preparation of an active extract of secretin is more difficult from man than from animals, and it may be for the reason stated above.

We intended, at one time, to take equal weighted amounts of intestinal scrapings from man and dog and dilute them with large and equal amounts of acid. We hoped to show by this that, whereas, the dog epithelium would yield an active extract even with considerable dilution, none would be obtained from the human, for the above reason. Unfortunately, however, we had to stop work temporarily at this point, but the same fact is indicated to all intents and purposes by the last human case tried, reference to which will show that only 65 c.c. hydrochloric acid were used. The preparation was inactive, or at best but slightly and very questionably active, whereas a coincident extract of a dog was diluted with over twice that amount of acid and still gave a violent response. The respective amounts of intestinal epithelium removed were not weighed, but were roughly comparable in bulk.*

In view, therefore, of the difficulties recorded in obtaining active human preparations, we feel that caution should be exercised in basing conclusions on negative results which are not fully controlled and in which the flow of juice is not accurately measured. The measurement is not so much for comparison between the individual animals injected, because each is (within limits) a law unto itself as to the rapidity and amount of flow, but for each case there should first be established some dependable standard of secretion as a normal on which can be based exacerbations due to injections.

It seems that entirely apart from differences in the sizes of animals, which would determine variations in flow, the rate of flow and amount of pancreatic juice obtained vary with the period of digestion. It thus seems easier to excite a flow of pancreatic juice when the animal has been fed within a few hours than when it is fasting. Furthermore, the copious flow thus obtained is calculated better to prevent the formation of clots which form so readily both in the canula and within the excretory duct itself, as mentioned above. Consequently, in our later experiments, we used dogs which had been recently fed.

For the above reasons and for others which will appear later we are led to accept with reservation, the finality of Wentworth's findings in

* Since above was written we have obtained a violently active preparation from a dog's intestines, with a dilution of 310 c.c. $\frac{4}{10}$ N HCl.

cases of malnutrition because we know how easy it is to obtain an inactive extract in a subject from which there is every *a priori* reason to expect a response. To turn to his interesting work in which he records an absence of secretin in a number of cases of marasmus examined, several points call for consideration.

In the first place, he details a series of cases of marasmus and some also of new-born children, in which he finds secretin absent. He believes this deficiency of secretin to be due to an insufficient quantity of hydrochloric acid in the stomach of these children, this, in turn, being caused by the fact that the milk of each species has some specific element which is necessary to its perfect digestion by that species, and in the case of marantic human infants fed on cow's milk, for example, this is lacking. Without questioning the evidence in favor of the latter contention, in this particular connection, let us consider the reported absence of secretin in the newborn.

The citation of this deficiency is evidence, it seems to us, in support not of the unknown and unlikely possibility that a child is thereby unqualified for pancreatic digestion of its mother's milk (which we know clinically is not the case), but rather that this "absence" of secretin is another instance of the difficulty of obtaining it under a considerable variety of circumstances and in, perhaps, a number of pathologic conditions. In point of fact, secretin has been found in both the embryo and the newborn, and in the human as well as in the animal species,[9, 10] which would go to prove that some of the many factors to which we refer as making secretin at times difficult of extraction, have been operative with Wentworth, not only in these children at birth, but, perhaps, as well in those cases of malnutrition on which he bases his report. Failure to detect it in the newborn seems an evidence against the very specificity of its absence in pure marasmus.

In both of these conditions, as we have tried to indicate, the evidence for the absence of secretin as against a frequent general difficulty of its extraction under many circumstances, is very incomplete. We feel, therefore, that the whole question of the activities of digestion is much too complicated to justify the assumption at present that marasmus is referable to a factor so difficult of exact definition as the absence of secretin.

That this absence should, furthermore, be dependent on a deficiency of hydrochloric acid, and this, in turn, on a specificity of milk, seems an hypothesis calculated beyoud the facts at our command. With our pres-

9. Camus: Compt. rend. Soc. de biol., Par., 1906, lxi, 59.

10. Hallion et Lequeux: Id., 33.

ent knowledge of the subject, we feel that the properties and activities of secretin are much too unmapped and too little understood for us intelligently to ascribe a great morbid state to its deficiency alone, and when it comes to building further on this foundation the question becomes one of almost pure hypothesis. As a general principle, we know that the interdependence of the various digestive and assimilative processes is against such specificity, and we are beginning to recognize this interdependence as much wider than was hitherto thought. In illustration of this Abelmann and Sandmeyer[11] have shown that complete extirpation of the pancreas from dogs is followed by the absorption of 33 to 45 per cent. of non-emulsified fat. Again, if the connection between the pancreas and the intestine is cut off completely and permanently, the pancreas itself remaining wholly or partially in the system, it is found that the absorption of fat may be maintained (80 per cent.) for a considerable length of time.[12] The work of Brücke, Voit and Bauer, Heidenhain, Friedländer and others[13] abundantly proves that the protein of flesh, as well as both serum and egg albumin, may be, in part at least, absorbed as such; from which alone we see the abundant provision of Nature against the weakness of a single part in her complicated system of nutrition.

That some disturbance of the amount of secretin may be a link in the chain of events which produces infantile atrophy we readily grant, and, in fact, had started work on the basis of an analogous hypothesis; but that the other links of the chain are known, or that a causative deficiency or absence of secretin has been established in that interesting condition, we can not at present believe.

An examination of the work of Bainbridge and Beddard on diabetics will show that they measured the flow of juice in drops and cubic centimeters. This method of measurement seems to be open to some criticism. The output of such an organ as the pancreas is, in the nature of things, a relatively small quantity, and exacerbations of flow can not be appreciated within small limits when the index is so crude. The method of Bayliss and Starling is certainly the most graphic and satisfactory for recording the flow, where at all practicable, but it requires that the tube be filled and the juice allowed to drop on a recording tambour. With weak preparations or where, for any reason, there is difficulty in obtaining a steady flow, the first output may be ample to indicate the activity of a given preparation and yet quite insufficient to fill a canula of five

11. von Noorden: Metabolism and Practical Medicine, i, 30.
12. Sandmeyer, Abelmann, Rosenberg, loc. cit.
13. Von Noorden: Metabolism and Practical Medicine, i, 19.

inches, much less to drop from the end of it. For these reasons, we found a graduated canula better adapted to our needs.

In regard to the estimates of flow given by Bainbridge and Beddard, it can be said that with an actively functionating gland there is, at most times, a flow, and the statement that a drop or a cubic centimeter resulted from an injection is somewhat questionable information as to whether the gland was stimulated or not, in the absence of data giving the normal rate of secretion. It assumes that the tube must be full at all times, but from such a tube drops might fall with varying speed, due, for example, to changes in blood pressure, which is appreciably lowered by the injection. Again, if such a tube be filled, more powerful respiration or any unusual movement of the animal may induce a change of level in the tube and consequently cause a drop to fall. Bainbridge and Beddard give no data of time elapsed when recording flows which took place or failed to take place after injection. In Case 5 of their diabetic series they obtained 0.6 c.c., a response greater than that from some of their normal preparations, as, for example, that from a normal cat, and yet this response is recorded as moderate. Case 6 gave persistently one drop in response, and Case 4 gave two drops on two occasions, and it seems to us that in both instances these were indications of responses which might have been more marked had there been, perhaps, less dilution of the secretin. or more regard for the relative difficulty under many circumstances of extracting it from human intestines. A deduction from this that secretin is diminished in amount in these particular cases seems to us hardly to be justifiable. The same authors, unfortunately, omit also to give the amounts of juice secreted in their series of controls, and state merely that they were abundant, fair or moderate, by which very little comparison can be made with their later work. Bainbridge and Beddard conclude that "in only one of six cases of severe diabetes was prosecretin present in amount approximating the normal," and in the other five cases they say that prosecretin "was either absent or present in very small quantities," but we feel that without more accurate methods of establishing a standard of reaction and of measuring the flow such results must be accepted with reserve. Bainbridge and Beddard speak, for example, of a maximum and minimum dose without stating what either is, and it would be of interest to know the dilution with acid of the intestinal scrapings. Other observers, as Moore, Edie and Abrams, quote the above work as evidence that secretin is absent in many cases of diabetes, but it may well be that the failure to react was at times due to some of the factors which have prevented us from getting responses. It is to be remembered, furthermore, that in an individual the subject of a chronic

wasting disease, such as diabetes or marasmus, the intestinal epithelium shares with the other bodily structures a degree of atrophy, perhaps secondarily, and the reduced bulk may require different treatment to develop the properties still present within it. This, again, may have been the cause of a certain number of failures.

Therefore, we are forced to conclude that, while the absence or deficiency of secretin may be a factor in certain varieties of diabetes, the evidence of this, hitherto adduced, is not convincing to all of those who have worked on the pancreas and its excitation.

In order to obviate the possibility that postmortem change was responsible for some of our failures, we killed a dog, kept the body on ice for thirty-six hours and then removed the upper part of the small intestine. This we kept on ice for another fourteen hours, and then worked up as usual, with the result to be mentioned presently. It had occurred to us also that another possible source of failure was the necessarily restricted diet of most hospital patients who come to autopsy, so that the dog above mentioned was fed for about one week prior to death on a pure milk diet. Evidence of the fact that he had been well starved was the condition of the stomach and small intestine, both of which were full of sawdust, which had formed part of his bedding. He had, of course, attempted to satisfy his hunger by eating it. The extracts from the intestine of this animal were powerfully active.

We wish to emphasize the fact that in testing the human preparation a response was in all cases first obtained by means of a known active extract in order to obviate failure from causes other than inactivity of the preparation in question, and following its injection known active extracts were again used wherever possible. This inclusion of an inactive human preparation between two plainly active animal extracts would seem to narrow down the failure of response to some feature of the preparation itself.

Another thought which suggested itself was that the strength of the acid used in working up the preparations might be responsible for some negative results, but reference to the records will show that we eventually obtained active extracts from dogs, with both weak and strong hydrochloric acid, as referred to earlier, so that the formation of secretin apparently is not dependent on the peculiar acidity of the chyme in any particular animal. It would appear probable also that neither fasting nor the nature of the diet has any marked influence on the qualities of an extract.

Some of our active preparations were used a number of times, and we found that if kept sterile, an extract will retain its efficiency for many

weeks, though it deteriorates slowly, as stated by Bayliss and Starling. The reactions caused by the injection of equal amounts grow less intense as time goes on and finally cease altogether. One of our extracts showed activity for at least nine weeks, which is the longest recorded period of which we have any knowledge.

Finally, we come to the consideration of those human cases in which we found secretin positively present. They were two in number, respectively Cases 8 and 10, out of a total of nine examined. In two other cases there was some evidence that it was present also, though we were not convinced of the fact at the time of the experiment. They were Cases 14 and 15. It may be, of course, that failure to demonstrate any secretin in the remaining cases was due to the fact that these cases presented some of the pathologic conditions originally the subject of our investigation. This can not be asserted, however, with our present knowledge of the subject. As a corollary to this is the record of the presence of secretin in a case of pulmonary phthisis (Case 8) and a case of cholelithiasis with jaundice and cardiorenal disease (Case 10). Two cases are, of course, inadequate in number to warrant definite conclusions, but it might seem from them that the absence of secretin is not a causative or accompanying feature of these diseases.

It is of some interest to consider the nature of the various cases in which no secretin could be detected positively after repeated injection of various preparations from them into different dogs (which responded to other stimuli). These cases represented, respectively, the following diseases: tabes dorsalis, lobar pneumonia, fracture of the skull, pseudohypertrophic muscular dystrophy complicated by phthisis, uremia (or possibly epilepsy), phthisis, and erysipelas following debauch.

It will be noted that one of our active extracts was from a case of phthisis (Case 8), and yet we were unable to get positive results from two other instances of this disease. In one of them (Case 14) there was some evidence of a response, but, as indicated above, we do not feel warranted in regarding it as certain. The other was complicated by muscular dystrophy, which is a rather suggestive result, though, of course, by itself of no value whatever. It is conceivable, however, that this last interesting and baffling condition may be found to be due to some factor, perhaps as yet undiscovered, which affects the construction of tissue. In this connection, one of the present authors has made some attempt, as yet unsuccessful on account of the paucity of cases and the difficulty of the procedure, to investigate the proteolytic and protoconstructive ferments found by Vernon to be present in nearly all tissues. An absence of one or more of these from muscular tissue might possibly stand in some

relation, primarily or secondarily, to the well known metamorphoses of this disease.

We have been unable to account satisfactorily for an initial spurt in the flow of juice which often occurs when a canula is first introduced successfully into the common duct. The more ready and the quicker the introduction, the more marked the initial spurt, which in a minute or so subsides to what may be called the normal rate of flow. Bayliss and Starling state that there seems to be little or no diminution in activity after prolonged stimulation of the pancreas with secretin, and they quote one case which seemed to have lost an activity after stimulation for a total of 8 hours. Without questioning this finding, our experience has been that the pancreas reacts best to early injections, and that after repeated excitations the response is less marked in amount and violence. It would seem much more in the nature of things that the organ should become exhausted in time, but we made no observations directly to this end and can not, therefore, offer anything more positive on this point.

There can be no question that there remain a great many features in connection with this interesting subject of pancreatic excitation which call for investigation. It is our hope to pursue some of them in the near future, and it is only because of the growing activity in this line of work as well as the evident need for accurate observations that we wish to publish, at this time, the results of our own experience.

CONCLUSIONS.

1. There would seem to be some factor which makes the preparation of secretin from human intestines more difficult than from the intestines of some animals.

2. This factor may depend on the relatively great abundance of membrane in these animals and consequently greater amount of prosecretin.

3. The abundance of mucosa may be, in part, a provision of Nature in order that the strongly acid chyme of some animals may meet with a quantity of pancreatic juice sufficient to neutralize it and effect digestion.

4. Active preparations of secretin can be made with hydrochloric acid of widely varying strengths, and activity, *in vivo,* is apparently not dependent on the peculiar acidity of the chyme in any particular animal.

5. Dieting and fasting seem to have no appreciable effect on the activity of an extract.

6. Time elapsed between death and the preparation of the extract (within limits) does not seem to be a factor.

7. Caution should be exercised in basing conclusions on work not thoroughly controlled, as the demonstration of secretin may be prevented by many factors not easy of determination.

8. In investigating for its presence, the normal flow and the exacerbations should be measured carefully by means of some accurate gauge, such as the rate of flow through an accurately spaced canula or by the recording of time drops with a tambour.

9. The evidence so far adduced that secretin is absent in some varieties of diabetes does not seem conclusive.

10. The specific absence or deficiency of secretin in marasmus seems to remain as yet unproven.

We wish to express our thanks to Dr. A. J. Smith, Dr. Samuel Leopold and Dr. L'Engle for courtesies shown at the autopsy table in obtaining material, and especially to Dr. David L. Edsall for his helpful interest in the work.

PROTOCOLS.

It should be stated that the flow of juice was at times hard to record, because after introducing the canula into the pancreatic duct, the intestine and attached duct were replaced in the abdominal cavity where they were more or less out of reach and somewhat covered over. The canula generally became partly coated with blood, which often obscured both the markings upon it and the juice within it. The deep position within the abdomen of the duct and proximal end of the canula increased this difficulty, so that it became necessary at times to count from the outer end of the tube instead of from the inner. Where this occurred it is so stated.

The caliber of the canulæ used varied somewhat as did the markings on them. In cases where the flow was slow, fine gradations were required to measure its advance. In cases where it was very rapid, we were often unable to note its rate by the one-eighth inch gradations alone and had time to measure the progress at intervals of five divisions only.

When the canula became filled, it was emptied by sucking through a still finer glass tube, introduced within it to the lowest gradation desired.

The notes of our cases are as they were made at the time. The strength of acidity of the preparations was not measured regularly, but from several titrations, made at various times, they approximated the following:

$$8 \text{ cc. secretin extract} = 0.1 \text{ cc.} \frac{4}{10} \text{ N NaOH.}$$

In our first experiments, having then no controls of known activity, we established a flow of juice by the injection into the duodenum of 25 c.c. of $\frac{4}{10}$ N HCl.

Several attempts were made to obtain permanent pancreatic fistulæ in dogs, but the difficulties in the way of the proper after-care of the animals caused us to work with temporary fistulæ instead. Our animals were kept under complete ether anesthesia, and at the end of the experiments they were killed.

We desire to give our observations at length, because they seem to us to show the difficulty in reaching dependable conclusions even when every effort is made to be accurate. That this difficulty must be greater with estimations which are more approximate, is self-evident.

Case 1.—Feb. 28, 1907. A. M., male, white, age 53 years. Philadelphia Hospital. Died, 7:45 p. m., February 27. Autopsy performed 4 p. m., February 28.

Pathologic Diagnosis: Emphysema and edema of lungs; brown atrophy of heart; chronic cystitis; pyemic kidney; hypertrophy of prostate; tabes dorsalis.

Thirty-six hours after death, upper four feet of intestine extracted and put over night in ice-chest. Scraped with much difficulty, as it was very tough. Whole quantity (what could be held in man's hand, perhaps) covered with 0.2 per cent. HCl (100 c.c.) and ground in a mortar with sand. About 300 c.c. HCl then added; whole squeezed through mesh, filtered and then sterilized in autoclave.

No reactions were obtained with this preparation.

Case 2.—March 31, 1907. J. C., male, colored, age 42 years. Philadelphia Hospital. Died, 4 a. m., March 31. Autopsy performed, 1:30 p. m. same day. Pathologic Diagnosis: Croupous pneumonia, gray stage, with cavity from poor resolution; acute fibrinous and chronic adhesive pleurisy; chronic adhesive perisplenitis and chronic interstitial splenitis; fatty infiltration of liver and cholelithiasis; acute parenchymatous nephritis, superadded to slightly fibroid kidney.

Upper four feet of intestine used; 125 c.c. 0.2 per cent. HCl; boiled, neutralized, acidified, etc., at night, March 31, 1907.

April 1, 1907, almost impossible to filter; most of solution lost in attempt; about 40 c.c. left, which were used. No result, though good reactions were obtained with 0.2 per cent. HCl thrown into duodenum twice; secretion of juice unusually free, both when canula first introduced and when HCl was injected into duodenum; presumably because of recent feeding, as gut at first was full of food.

Case 3.—April 5, 1907. Large black bitch, very fat, killed with gas. No previous operation on animal. Four feet of intestine cut out (with pylorus) within one-half hour of death, and scraped, ground and diluted with 225 c.c. of 0.2 per cent. HCl; some fat in filtrate, which filtered slowly but better than last. Sterilized and finally free from evident fat.

Case 4.—April 16, 1907. C. M., female, white, age 52 years. Philadelphia Hospital. Died, 8:30 p. m., April 14. Autopsy performed 5:30 p. m., April 15. Coroner's case. Pathologic Diagnosis: Chronic parenchymatous nephritis; tuberculosis of lungs; chronic myocarditis; right-sided subdural hemorrhage. The tuberculous involvement was relatively slight and in no way the cause of death. Clinical Diagnosis: Fracture of skull.

Intestines easily scraped, normal in appearance; 250 c.c. HCl used; run through quite rapidly and not filtered perfectly clear in order to avoid possible oxidation. No reactions were obtained with this preparation.

Case 5.—April 17, 1907. Medium large, male, woolly dog. Ulcers and worms in intestines; dog had been bled five days before; killed 12:30 p. m. Intestines worked up instantly.

Case 6.—April 23, 1907. E. B., male, white, age 15 years. Philadelphia Hospital. Died, 5:30 a. m., April 22. Autopsy performed about 4 p. m. same day. Pathologic Diagnosis: Fibrinous pleuritis of right side; fibrous pleuritis of left side; purulent bronchitis, peribronchial pneumonia, pseudo-lobar pneumonia, edema, congestion and emphysema of lungs; subacute nephritis with passive congestion; acute congestion of spleen; passive congestion with fatty metamorphosis of liver; pseudo-hypertrophic muscular dystrophy.

Intestines scraped April 23, 12:30 p. m.; 200 c.c. 0.2 per cent. HCl used. Intestines thin but not anemic; small amount of mucosa relatively, much less than small dog; filtered quickly. No reactions were obtained with this preparation.

Case 7.—May 1, 1907. Rather large fox terrier bitch. Dog fed on milk for five to six days; killed on morning of April 29, and put on ice. Dog quite thin and stomach and upper part of bowel filled with dark brown sawdust. At 3 p. m., April 30, four feet of bowel were cut out and put on ice. May 1, 3 p. m., worked up for secretin. Bowel pale and membrane came off rather less easily than usual, and made rather small amount; 150 c.c. 0.2 per cent. HCl required altogether; filtered quickly and clear at once.

Case 8.—May 4, 1907. H. Z., male, white, age 21 years. Philadelphia Hospital. Died 9:15 p. m., May 3. Autopsy performed at 4:30 p. m., May 4. Pathologic Diagnosis: Hydropericardium; serofibrinous pleuritis; atelectasis and chronic pulmonary tuberculosis; chronic parenchymatous nephritis; slight fatty infiltration of liver; pneumo-thorax.

Body of a fairly well nourished man. Dark grumous material in lower bowel. Upper five feet of intestines look green-yellow as though from bile; tuberculous ulcer low in ileum (ten feet down or more), Peyer's patches swollen; 0.2 per cent. HCl used; six feet of intestine taken; made considerable bulk, more sand than usual needed; 300 c.c. HCl altogether; filtered with much difficulty and slowly; various filtrates used, and sterilized May 4, 8 p. m.

Above preparation active.

Case 9.—E. F., male, black, age 40 years. Philadelphia Hospital. Died 6 p. m., May 6. Autopsy performed, 3:30 p. m., May 7. Pathologic Diagnosis: Brown atrophy of heart; edema and healed tuberculosis of lungs; slight chronic interstitial nephritis and parenchymatous nephritis; chronic passive congestion of spleen. Clinical Diagnosis (in part): Uremia or epilepsy.

Body well developed and nourished. Intestines worked up, 4 p. m., May 7; six feet used, 250 c.c. HCl, 0.2 per cent. Considerable scraping, which came off much more easily than usual. Small pieces of pancreas left on the back of bowel, possibly some scraped off too; filtered quickly and various filtrates and supernatant portions taken.

e. g., Supernatant plus HCl without anything else.

Supernatant plus HCl plus alkali and acid.

The latter was much more liquid than the former because the albumin coagulated and settled. Supernatant portions and those treated with alkali, etc., were filtered and finally some supernatant fractions were squeezed through muslin as usual and filtered. In working up this preparation it seemed to us most probable that it would be active, but it was not.

Case 10.—K. F., female, white, age 52 years. Philadelphia Hospital. Died 12:30 a. m., May 18, 1907. Autopsy performed, 4:30 p. m. same day. Pathologic Diagnosis: Cloudy swelling of myocardium; dilatation of both ventricles; chronic passive congestion of spleen; cholelithiasis; general biliary pigmentation; hypertrophic cirrhosis of liver.

Body well developed. Six feet of bowel used; worked up, 3:30 p. m., May 19. Bowel membrane dark green, small amount of scraping which is watery and fluid; 75 c.c. of 0.2 per cent. HCl required, and mixture treated as usual. Rushed through without delay, and supernatant fluid as well as filtrate used.

This preparation was active.

Case 11.—Calf. Intestines from abattoir. Animal several months old probably; membrane much like dog; bowel smaller; four feet of intestine and 120 c.c. 0.2 per cent. HCl used; unfiltered and filtered both taken; none squeezed through mesh. Membrane came off very easily, as does dog's, and made quite a little pile, though less than a large dog, as intestines are smaller, the size of a fountain pen.

Case 12.—Sheep. Intestines from abattoir; smaller than calf, though animal (sheep) probably one year old. Scraped with greater difficulty and connective tissue came off with membrane, giving long strands in mortar; made a relatively small amount of scraping which did not seem to become digested by the 0.2 per cent. HCl, and made a gelatinous mass; 85 c.c. acid used. Supernatant fluid and filtrate both used.

Case 13.—On May 21, 1907, a large puppy, setter type, was unsuccessfully operated on for a fistula and injected with secretin, and then the bowel removed and put on ice same day, about 6 p. m.

May 26, 3 p. m., bowel worked up. Membrane very loose and some loose material adherent to membrane, within bowel, apparently being cast off. No odor; in good condition; scraped easily, upper part more easily than usual; made considerable bulk; 125 c.c. 0.2 per cent. HCl used. All filtered, none squeezed through mesh.

Case 14.—A. R., female, white, age 17 years. Philadelphia Hospital. Died 12:30 a. m., May 27, 1907. Autopsy performed 5 p. m. same day. Pathologic Diagnosis: General miliary tuberculosis; chronic parenchymatous nephritis; pneumonia; typhoid (?); fatty infiltration of liver.

Secretin worked up morning of May 28, and 0.4 per cent. acid used (4.1 c.c. of 1.2 sp. gr. HCl taken and diluted to 400 c.c. with H_2O); 75 c.c. acid required. Considerable bulk of membrane, which was thin, pink and scraped easily; filtered rapidly.

This preparation was unquestionably active.

Case 15.—T. McK., male, white, age 50 years. Philadelphia Hospital. Died 7:40 a. m., June 16, 1907. Autopsy performed, 12 noon. Clinical Diagnosis: "Drink," erysipelas. Pathologic Diagnosis: Edema of lungs; acute vegetative endocarditis; cloudy swelling of myocardium; recent fibrous pleurisy; cloudy swelling of liver with fibrosis; acute diffuse splenic hyperplasia with multiple infarcts; acute parenchymatous nephritis.

Worked up, 1:30 p. m., same day. Abundant scrapings; bowel somewhat red and injected on scraping, but not before; considerable loose superficial mucoid material, as though there had been a catarrhal process. Scrapings made considerable bulk; six feet of intestine taken; 0.4 per cent. acid, only 65 c.c. used altogether; mixture was quite concentrated. Supernatant fluid was decanted and some filtered once only. The remainder not filtered at all.

This preparation was questionably active.

Case 16.—June 18, 1907. Intestine of Irish terrier worked up; operation for fistula to-day failed; considerable scrapings; 150 c.c. 0.4 per cent. acid used; all filtered.

Observations on the levels reached by the pancreatic juice as it flowed in the canula, before and after injection of secretin. Markings are ⅛ inch apart. Canula about ⅛ inch in diameter.

April 2, 1907.—Small Fox Terrier. Canula Used Here Contains Fifteen Divisions.

At 3:34 p. m. at No. 6. Count from 0. Had been between 5 and 6 for several minutes; flowing pretty steadily after original spurt until within past ten minutes.

3:37, still at 6.

3:40, at 8.

3:42, at 9.

3:44, at 14.

25 c.c. HCl thrown in duodenum at 3:37; at 3:40 juice in canula sucked out by means of fine glass tube.

3:47, at 3¼.

3:48, going slowly.

3:51, nearly 5 (nearly 9 from outer end).

3:52, going slowly now.

3:53, still hardly reached 9 from outer end.

4:00, still at 9.

Secretin, (Case 2, J. C.) thrown in. 4 c.c.

4:06, has just passed 9.

4:08½, has not moved.

4:11, at 8½.

10 c.c. (Case 2, J. C.) thrown in at 4:11 (left leg vein).

4:13, no movement.

10 c.c. more injected (4:13).

4:15, moving apparently at normal rate, very slowly, has not touched 8.

4:20, barely at 8.

4:21, 25 c.c. HC. thrown in duodenum.
4:25, has moved and left 8.
4:27, at 7½, evidently moving, but rather slowly.
4:28, apparently stopping at 7½ from far end.
4:29, at 6.
4:30, at 5.
4:30½, at 4.
4:31, at 2.
4:32, at 1.
4:33, at 0, tube filled.
4:33½, emptied to 10 from outer end.
4:35, not quite to 9.
4:36, apparently stopping just short of 9.
4:39, stopped at 9.
4:43, stopped at 9.

Apparently a very faint reaction to HCl in bowel, probably because of clot, but none to secretin.

April 6, 1907.—Fox Terrier Dog, Operated On.

3:11, tube nearly filled; juice hardly moving.
3:16, 8½ from outer end.
3:22, at 8¼.

About 3 c.c. dog secretin (Case 3) thrown in, about 3:25.

3:30, at 8.
3:33, at 2.
3:35, filled up.
3:36, sucked out to 11; tube filled with air bubbles and effort to remove them consumed some moments.
3:39, movement apparently over.
3:39½, at 9 ½.
3:41, at 8, moving still, but moves slowly.
3:43, nearly at 7. First big jump was made in about 2 minutes.
3:45, at 7½.
3:47, nearly at 6.
3:50, just at 6.
3:51½, at 5½.
3:54, at 5½.
3:56, at 5¼.

Amounts were thrown in: were hard to estimate, but the syringe held 10 c.c. Much of it escaped behind the plunger, though a few c.c. could be seen going into vein.

4:01, at 4.
4:04, at 3¼.
4:05, at 3.

A few minutes after first injection another was made, time not noted in confusion, but about 3:30; a marked reaction followed first injection, promptly, violently, and about the same time the other (second) injection was given.

4:10, at 2. Moving quite uniformly, though not nearly so rapidly as at height of activity.
4:13½, at 1.
4:17½, tube filled, zero.
4:18, emptied to 11.

Some secretin (Case 3) thrown in at 4:21.

4:21, at 9½.
4:22, barely at 9.
4:24, at 8¾.
4:25, at 8½.
4:26, moving faster than it has for some minutes, at 8 now.
4:27½, has passed 8.
4:29, at 7½.
4:31½, at 6¾.
4:33½, at 6 2/5.
4:35, at 6.
4:38, at 5¼.
4:39½, at 4 4/5.
4:45, emptied to 10¾.
4:45½, nearly 10.
4:46½, at 10.
4:47, at 9¾. Same rate of flow as before; 10 c.c. thrown in.
4:48, at 9 1/5.
4:49, at 8.
4:49½, at 7.
4:50½, at 6.
4:51, at 4¾.
4:51½, at 4.
4:52, at 1. Slight coughing.
4:52½, tube filled.
4:53½, sucked out to 10.
4:54, at 9.
4:54½, at 8.
4:55, at 7.
4:56, apparently going a little slower, at 6⅛.

4:56½, at 5 3/5.
4:57½, at 5.
4:59, at 4.
5:01½, at 3.
5:04, at 2.
5:09, tube filled.
5:10, sucked out to 11.
5:11½, at 10.
5:12, 25 c.c., 0.2 per cent. HCl thrown into duodenum.
5:13½, at 9.
5:14½, at 8, moving visibly faster.
5:14¾, at 6.
5:15, at 4; 2 divisions in 15 seconds; tube overflows at 5:15½.
5:16½, sucked out to 8. Flowing faster than ever yet seen.
5:17, tube filled. Dog struggling somewhat from lack of ether.
5:18½, at 2.
5:18¾, at 1.
5:19—at 0, full.

Sucked out and count made from proximal end.
5:19½, at 0.
5:19½, at 1.
10 seconds later, at 2.
5 seconds later, at 3.
5 seconds later, at 4.
5 seconds later, at 5.
5 seconds later, at 6.
8 seconds later at 7.
5 seconds later, at 8.
5 seconds later, at 9.
Filled up.
5:21½, at 0.
5 seconds later, at 1.
5 seconds later, at 2.
8 seconds later, at 3.
10 seconds later, at 4.
10 seconds later, at 5.
18 seconds between next mark, getting slower.
Dog killed, at 4:25.

Results marked. Second injection did not enter veins as they were blocked up. Third injection of secretin was made into left leg by a new opening and new syringe; all went in, 5 c.c.. Reaction most violent to the HCl in duodenum; went so fast as to be uncountable, even when called out by a watcher.

(Dog secretin successful; none other tried.)

April 17, 1907.—Cocker Spaniel, Medium Sized; Tube Introduced Into an Opening in the Pancreatic Duct, Outside of Gut.

4:38, at 6 from outer end.
4:38½, at 5.
4:39, at 4.
4:39½, at 3.
4:40¼, at 2.
4:41, at 1.
4:41½, at 0.
Sucked out to 10.
4:42½ at 9 from outer end.
4:43 at 8.
4:44, at 7.
4:45′ 10″, at 6.
4:46′ 50″, at 5.
Going slower, but moving constantly.
4:48′ 20″, at 4 from outer end.
4:50½, at 3.
Considerably slowed.
4:53′ 45″, at 2 from outer end, much slower.
4:58′ 30″, at 1¼.
Sucked out to 10½.
5:00′ 30″, at 10 from outer end.
5:02′ 15″, just barely passed 10, going extremely slowly.
4.5 c.c. secretin (Case 4, McM.) thrown in at 5:02′ 30″, into vein of leg.
5:07, moving very slowly, at 9⅓.
5:09′ 30″, moved slightly, nearly at 9.
5:12′ 30″, at 9 from outer end.
5:15, nearly past 9.
5:21′ 45″, at 8½.
5 c.c. secretin (Case 4, McM.) thrown in at 5:22′ 30″; 5:25 at 8½ from outer end; 5 c.c. more thrown in.
5:30, moving, but slowly.
5:35, has barely reached 8.
5:40, has barely passed 8.
5 c.c. dog secretin thrown into vein of leg, at 5:41.
5:43 at 8.
5:45, at 8.
5:50, at 7¾ from outer end.

5:54, at 7¼, barely.
5:54, 5 c.c. dog secretin (Case 5) thrown in.
5:55, 5 c.c. more new dog secretin thrown in.
5:58, bile in large quantities oozing out; big clot in canula.
6:02, moving fast, too fast to count; went 7 divisions in about 1 minute.
6:04, at 2 from end.
6:05, quieting down, but moving.
6:05, tube full.
6:05, sucked out to 7½.
6:07, at 7 from outer end.
6:07½, at 6½.
6:08′ 20″, at 4.
6:08′ 20″, at 3.
6:08′ 50″, at 2.
6:09 30″, at 1.
6:10′ 30″, nearly full, sucked out to 17.
6:14½, at 14.
6:16, at 9⅔ from outer end.
6:16′ 30″, at 9.
6:17½, at 8.
6:18½, at 7.
6:20, at 6.
6:21¾, at 6.
Secretion at bottom of tube at 6:32½.
5 c.c. human secretin thrown in then.
5 c.c. more human secretin thrown in at 6:33½.
6:42, bile flowing furiously through canula introduced into common bile duct.

In the light of later experiments, clots in canula evidently prevented good action, but the dog secretins seemed to cause a reaction.

No conclusions based on such responses as the above, however.

April 18, 1907.—Small Fox Terrier.

3:08½, at 3½ from outer end.
3:09, at 5.
3:09′ 50″, at 10.
3:10′ 12″, at 11.
3:11, at 12⅓.
3:11′ 20″, at 13.
3:12, at 14.
3:12′ 50″, at 15.
5 c.c. dog secretin (Case 5), at 3:14; going slowly at 3:14.
3:14′ 30″, at 16.
3:15, moving faster.
3:15′ 30″, at 18.
3:15′ 45″, at 19, marked response.
3:16′, at 20, marked response.
3:16′ 16″, at 21, marked response.
3:16′ 30″, at 22.
3:16′ 42″, at 23.
3:17, at 24.
3:17′ 15″, at 25.
3:17′ 43″, at 26.
3:18′ 30″, at 27; slower.
3:19′ 10″, at 28.
3:19′ 57″, at 29.
3:21′ 45″, at 30.
Sucked out to 25 at 3:22; moving slowly at 2:23′ 30″.
3:24, just over 25.
5 c.c. human secretin (Case 4. McM.) thrown in at 3:24.
3:24′ 23″, at 26.
3:25, at 27.
3:26′ 08″, at 28.
3:26′ 50″, at 29 (sucked on).
3:27′ 50″, at 30.
Sucked out to 24½, at 3:28′ 30″.
3:30′ 30″, at 25.
5 c.c. new dog secretin (Case 5) thrown in at 3:30′ 45″.
3:31′30″, at 26.
3:32′ 40″, at 27.
3:32′ 50″, at 28 (fast).
3:33′ 08″, at 29.
3:33′ 25″, at 30.
3:33′ 50″, at 31.
3:34′ 16″, at 32.
3:34′ 40″, at 33.
3:35′ 08″, at 34, slower.
3:35′ 38″, at 35.
3:36′ 08″, at 36, slowing to normal.
3:37′ 16″, at 37.
3:38′ 30″, at 38.
Sucked out to 25, at 3:39.
3:39′ 50″, at 25½.
5 c.c. dog secretin (Case 3) thrown in at 3:40.
3:40′ 30″, at 27.
3:40′ 50″, at 28, fair response.

Blood in bottom of canula.

3:41′ 10″, at 29, fair response.
3:41′ 43″, at 31, fair response.
3:42′, at 32.
3:42′ 20″, at 33.
3:42′ 42″, at 34.
3:42′ 10″, at 35.
3:43′ 40″, at 36, slower.
3:44′ 18″, at 37, much slower.
3:44′ 52″, at 38.
3:46′ 05″, at 39, very slow.
Sucked out to 24.
3:49′ 00″, at 24.
3:50′ 15″, at 24⅓.
3:50′ 30″, at 25.
5 c.c. human secretin (Case 4) at 3:50′ 45″.
5 c.c. more human secretin (Case 4) at 3:51′ 30″.
3:51′ 52″, at 26.
3:52′ 40″, at 27.
3:53′ 50″, at 28, slow, apparently stopped.
3:57′ 30″, at 28½, hardly moving; sucked out to below lowest gradation.
About 2 divisions below at 4 p. m.
Moved about ½ division at 4:02 p. m.
5 c.c. dog secretin (Case 5) at 4:02′ 30″.
5 c.c. more (Case 5) at 4:03′ 20″.
4:03′ 30″, at 1, fast.
4:03′ 50″, at 2, fast.
4:04′ 05″, at 3, fast.
4:04′ 08″, at 4, fast.
4:04′ 15″, at 5, fast.
4:04′ 20″, at 6, fast.
4:04′ 25″, at 7, fast.
4:04″ 30″, at 8, fast.
4:04′ 38″, at 9.
4:04′ 45″, at 10.
4:04′ 48″, at 11.
4:04′ 53″, at 12.
4:06′ 00″, at 13.
4:06′ 10″, at 14.
4:06′ 15″, at 15.
4:06′ 20″, at 16.
4:06′ 25″, at 17.
4:06′ 32″, at 18.
4:06′ 38″; at 19.
4:06′ 47″, at 20.
4:06′ 54″, at 21.
4:07′, at 22.
4:07′ 07″, at 23.
4:07′ 19″, at 24.
4:07′ 25″, at 25.
4:07′ 37″, at 26.
4:07′ 48″, at 27.
4:07′ 58″, at 28.
4:08′ 10″, at 29.
4:08′ 28″, at 30.
4:08′ 40″, at 31.
4:08′ 51″, at 32.
4:09, at 33 (dog moved).
4:09′ 07″, at 34.
4:09′ 18″, at 35.
4:09′ 27″, at 36.
4:09′ 36″, at 37.
4:09′ 47″, at 38.
4:10′, at 39, full up.
Sucked out to 0, at 4:10′ 30″.
4:11′ 10″, at 3.
Pencil dropped.
4:11′ 30″, at 5.
4:11′ 45″, at 6.
4:12′, at 7.
4:12′ 18″, at 8.
4:12′ 34″, at 9.
4:12′ 55″, at 10.
4:13′ 12″, at 11.
4:13′ 37″, at 12.
4:13′ 53″, at 13.
4:14′ 25″, at 14.
4:14′ 50″, at 15.
4:15′ 13″, at 16.
4:15′ 44″, at 17, slowing down.
4:16′ 20″, at 18.
4:16′ 57″, at 19.
4:17′ 55″, at 20.
4:18′ 48″, at 21.
4:19′ 45″, at 22 (normal rate).
4:21′ 25″, at 23.
Bile duct now exposed, 4:22; canula put in duct.
4:30, flow of bile almost stationary in tube.
4:32′ 20″, 5 c.c. human secretin thrown in.
4:33′ 30″, bile moving very slightly.
4:34, faster (?).
4:37, pancreatic flow not changed.
4:38, apparently slower flow of bile (no marks on tube in bile duct).
4:39, new dog (Case 5) thrown in.
4:40, pancreatic juice stationary at 29.
5 c.c. more secretin at 4:40′ 30″.

Little or no result from human secretin on bile; none on pancreas.
4:41′ 30″, sucked out; pancreas started to flow slightly; 3 divisions.
Pancreas started up, rapidly moving; as before, too fast to put down.
10 divisions to 30 seconds, at 4:43′ 30″.
Stomach contents furiously pouring out at 4:43.
Pancreas, 3½ divisions in 30 seconds.
4:45 p. m., slower, no evident effect on bile in canula.
4:50, dog killed.

April 27, 1907.—Fairly Large Woolly Dog.

No movement at 12 noon, at mark 3.
No movement at 12:01′ 20″.
Very old dog secretin (Case 3) thrown in, 12:10, with no result.
12:33′ 30″, HCl introduced into bowel, juice stands at 1.
12:38, no movement.
12:41, at 2, hardly moved at all.
12:43, at 2½, just barely moving.
12:51, barely moving, after sucking, etc.; now at 9¾.
12:53′ 30″, at 10, peristalsis active.
12:56, at 10.
12:57′ 30″, at 10½.
1:03, barely moving.
1:03′ 30″, 5 c.c. new dog secretin (Case 5).
Fluid bloody since start.
1:10, hardly at 11.
1:15, dog killed.

Gall bladder not over full; little bile in guts; no food except in rectum.
No response; evidently due to invisible clots or some undetermined factor.

April 28, 1907.—Small Bitch, Size of Fox Terrier.

Duct opened instead of gut; canula directly in duct.
Juice clean and runs freely at once.
Ran to 19, and then slowed down at 11:47.
11:50′ 30″, at 23.
11:51, at 24.
11:52, at 25.
11:52′ 10″, at 26.
11:52′ 45″, at 27.
12:02, sucked out to 0.
12:03, 4 c.c. new dog secretin (Case 5) injected, right thigh.
Level constant, practically at 0.
16 divisions to ½ minute at 12:03′ 50″.
Too fast to count, reaction in less than 45 seconds.
Full up at 12:04′ 45″.
12:04′ 45″, at 35.
Sucked out to 0, at 12:06.
12:06′ 20″, at 10.
12:06′ 50″, at 20.
12:07′ 08″, at 25.
12:07′ 30″, at 30.
12:08, at 35.
Sucked out to 0.
12:09′ 08″, at 5, slower.
12:09′ 50″, at 10.
12:10′ 55″, at 15.
12:12′ 20″, at 20, slower.
12:14′ 40″, at 23, very slow.
Sucked out to 0, at 12:15.
12:16′ 05″, at 1.
5 c.c. secretin (Case 6, E. B.), at 12:17.
12:19, no movement.
12:20, at 3.
12:21′ 40″, at 4.
12:23′ 30″, at 5.
5 c.c. old dog secretin (Case 3) at 12:24′ 30″.
First movement at 12:25.
12:25′ 10″, fast.
12:25′ 40″, at 20.
12:26′ 03″, at 25.
12:26′ 40″, at 30.
12:27′ 08″, at 35.
Sucked out to 0 at 12:27′ 30″.
Slowing.
12:29′ 50″, at 5, slowing.
12:30′ 40″, at 6, slowing.
12:31′ 15″, at 7, slowing.
Almost normal rate now.
12:32, at 9.

12:32′ 15″, 5 c.c. secretin (Case 6, E. B.) thrown in.
12:33, at 10.
12:34, at 11.
12:35′ 20″, at 12.
12:36′ 30″, at 13.
12:37′ 20″, at 14.
12:38′, at 15.
12:39′ 30″, at 16.
12:40′ 45″, at 17.
12:42′ 05″, at 18.
Sucked out to 0, at 12:42′ 45″.
12:43′ 20″, 5 c.c. new dog secretin (Case 5).
12:43′ 55″, first slight movement.
12:44′ 20″, at 5.
12:44′ 30″, at 10.
12:45′, at 20.
12:45′ 29″, at 25.
12:46′ 45″, about full.
Good marked reaction, but not so violent, though just as prompt as first new dog.
12:51′ 30″, at 4½.
5 c.c. 0.2 per cent. HCl injected into vein at 12:51′ 40″.
12:52′ 40″, at 6.
No movement.
12:55′ 25″, at 7.
Dog killed.

Almost nothing in the small intestines, except bile; a few stray strands of yellow feces, a few hard feces in rectum; considerable bile in gut. Gall bladder not so filled as in dog of April 27, 1907.

May 2, 1907.—Small Brown Terrier, Well Nourished.

4:55′ 45″, at 10½.
4:57′, at 11½.
4:58, at 12.
5:00, at 13¼, pretty constant and slow.
5:01′ 40″, at 14.
5:04′ 30″, at 15.
Starting anew, flow constant and slow,
5 c.c. newest dog secretin (Case 7) left leg, at 5:05′ 15″.
Flow started at 5:06.
Going very fast at 5:06′ 10″.
Full at 5:07.
Sucked out to 0 at 5:07′ 15″.
5:07′ 30″, at 5.
5:07′ 50″, at 10, slower.
5:08′ 20″, at 15.
5:08′ 55″, at 20.
5:09′ 45″, at 25.
5:11, at 30.
5:14′ 30″, slow, and 5 c.c. secretin (Case 6, E. B.) thrown in.
5:14′ 40′, at 2.
No movement at 5:17; no reaction.
No movement at 5:18′ 30″.
No movement at 5:19′ 30″, only normal rate, very slow; no reaction five minutes later.
5 c.c. very old dog secretin (Case 3) thrown in, 5:19′ 50″.
5:20, at 4.
First movement at 5:20′ 07″.
5:20′ 54″, at 20.
5:21′ 20″, at 25.
Marked reaction.
5:21′ 37″, at 30.
5:21′ 52″, at 35, slower.
Sucked out to 0.
5:22′ 24″, at 5.
5:23′, at 10.
Much slower now.
5:23′ 35″, at 15.
5:26, slowed to almost normal.
5:26′ 50″, at 20.

May 5, 1907.—Small Black Bitch.

12:39′ 35″, juice at 0, and 5 c.c. Case 3 (very old dog) secretin thrown in.
Barely moving.
12:40′ 33″, first movement.
12:41′ 07″, at 5
12:41′ 53″, at 10
12:42′ 30″, at 15
} Not so fast as usual: a small clot visible in tube: moving on.
Very slow.
12:45′ 20″, at 16.
12:46′, 5 c.c. very old dog secretin (Case 3) different flask. thrown in.
12:46′ 20″, at 16½.
First movement at 12:47′ 28″.
12:48′ 42″, at 20.
Very slow, but evidently accelerated.
12:49′ 21″, at 21.

12:50′, at 22.
12:50′ 30″, at 23.
12:51′ 03″, at 24.
12:51′ 27″, at 25.
12:52′ 15″, at 26.
12:54′ 20″, at 27½.
Sucked out to 5.
12:55′ 30″, at 5, not moving.
12:56′ 10″, 10 c.c. human secretin (H. Z., Case 8) thrown in, right hind leg.
12:58′ 10″, at 6.
1:00′, at 7.
No movement.
1:04′, at 8.
Not moving visibly.
10 c.c. old dog secretin of a dilution of 1 to 4 (2 c.c. secretin, 8 c.c. H_2O, distilled) thrown in then.
1:11′ 30″, at 9 1/5.
No movement.
10 c.c. dilution of 1 to 1 (5 c.c. secretin, old dog) to 5 c.c. distilled water, thrown in at 1:14′ 45″.
1:14′ 30″, at 9 1/5.
First movement at 1:16′ 30″.
1:16′ 45″, at 10.
1:17′ 20″, at 11.
1:18′ 15″, at 12.
1:18′ 57″, at 13.
1:19′ 40″, at 14.
1:20′ 15″, at 15.
1:21′ 45″, at 16.
1:22′ 50″, at 18.
1:24′ 10″, at 19.
1:25′ 20″, at 20.
1:26′ 50″, at 21.
1:30′ 45″, at 22½.
5 c.c. very old dog secretin, first flask, thrown in at 1:31′ 25″.
1:32′ 40″, at 23.
1:33′ 10″, moved visibly, very slightly.
1:34′ 10″, at 24.
1:34′ 50″, at 25.
1:35′ 15″, at 26.
1:35′ 30, at 27.
1:35′ 50″, at 28.
1:36′ 16″, at 29.
1:37′ 10″, at 30 (irregular meniscus).
1:37′ 40″, at 31.
1:38′ 35″, at 32.
1:39, at 33.
Sucked out to 3.
1:39′ 45″, at 3.
1:40′ 15″, at 4.
1:42′ 05″, at 5.
1:43′ 15″, at 6.
1:47′ 15″, at 7, nearly.
10 c.c. (Case 8, H. Z.) thrown in at 1:47′ 48″.
1:49′ 07″, at 7.
1:50′ 30″, at 8.
1:50′ 50″, at 9.
1:51′ 15″, at 10.
1:52′ 15″, at 11 almost (upper meniscus).
1:52′ 35″, at 11.
1:53′ 03″, at 12.
1:53′ 30″, at 13.
1:54′ 40″, at 14.
1:56′ 25″, at 14½.
1:57′ 30″, not yet 15.
5 c.c. secretin (Case 8, H. Z.) thrown in at 1:57′ 50″.
5 c.c. more secretin (Case 8, H. Z.) thrown in at 1:59′ 10″.
1:59′ 20″, at 18.
1:59′ 40″, at 19.
2:00′ 18″, at 20.
2:01′ 10″, at 21.
2:01′ 50″, at 22.
2:02′ 45″, at 23.
2:04′ 50″, at 24.

Two distinct responses, of the human, equal or almost equal to the dog. Reaction of dog to all stimuli very slight, relatively, to most dogs tried so far; the reaction was slow to set in and seemed to gather speed slowly and to last longer proportionately for the speed, though, perhaps, the delayed response accounted for that.

Slight amount of yellowish fluid in upper part of gut and slight amount of dark green feces throughout bowel, but practically nothing of consequence.

MAY 8, 1907.—SECRETIN. IRISH TERRIER, FAIRLY GOOD SIZE. CANULA IN DUCT, NOT IN GUT.

2:01′ 10″, at 5.
2:02′ 05″, at 10.
2:03′ 13″, at 15.
2:07′ 30″, at 20.
Going much slower after the usual initial spurt.
Sucked out to 0 at 2:12′ 50″.
2:10′ 30″, practically stopped, hardly at 1.
2:13′ 45″, at 1 (hardly there).
2:14′ 10″, 5 c.c. (Case 7) newest dog secretin in right thigh.
First movement at 2:15′ 20″.
2:16′ 10″, at 2, very slow.
2:17′ 40″, at 3, very slow.
Very atypical response.
2:20′ 30″, at 3 (practically stopped).
2:20′ 40″, 10 c.c. (Case 7) newest dog.
2:22′ 30″, started.
2:22′ 35″, at 5, response better than last, but slow.
2:22′ 50″, at 6, response better than last, but slow.
2:23′ 58, at 8.
2:25′ 25″, at 9.
Slowing down much.
2:40′ 45″, at 11½.
2:43′ 15″, at 12.
10 c.c. secretin (Case 8, H. Z.) at 2:43′ 15″.
No response, same flask as last time.
10 c.c. (Case 3) very old dog, at 2:51′ 50″.
A response from this, faster than before, but not fast. However, tube filled up.
Sucked out to zero.
2:59, at 0.
10 c.c. secretin (Case 9, E. F.) at 2:59′ 30″.
Moving at same rate at 3:00′ 30″.
Clot in canula, apparently of juice chiefly.

SECOND DOG.—SMALL FOX TERRIER BITCH.

5 c.c. (Case 8) newest dog secretin, at 3:33. Juice at bottom of canula.
Response at 3:34.
Going fast at 3:34′ 45″.
3:35′ 05″, at 5.
3:35′ 30″, at 7.
3:35′ 42″, at 8.
3:36′ 09″, at 9.
3:37′ 22″, at 10.
3:37′ 36″, at 11.
3:37′ 40″, at 12.
3:37′ 52″, at 13.
3:38′ 08″, at 14.
3:38′ 53″, at 15.
3:39′ 10″, at 16.
Slower.
Sucked out to 0, at 3:40.
Good response.
3:41′ 25″, at 1.
3:42′ 30″, at 1 1/5.
10 c.c. (Case 9, E. F.) secretin at 3:42′ 55″.
No response.
Clogged up, large red clot in tube and vessels.
Pancreas seems sclerosed.

MAY 9, 1907.—FOX TERRIER BITCH, THIN AND RATHER SMALL.

2:15′ 50″, at 0.
2:16′ 20″, at 1.
2:17′ 45″, at 2.
Very little initial spurt.
2:21′ 30″, at 2.
5 c.c. newest dog (Case 7) secretin at 2:21′ 45″.
First movement at 2:22′ 25″.
2:22′ 30″, at 5.
2:22′ 39″, at 10.
2:22′ 50″, at 15, too fast to count and jot down.
2:22′ 55″, at 20, too fast to count and jot down.
2:23′ 00″, at 30, too fast to count and jot down.
Sucked out to 3.
2:23′ 25″, at 5.
2:23′ 40″, at 10.
2:24′ 00″, at 15, slower.

2:24′ 32″, at 20.
2:25′ 05″, at 25.
2:26′ 38″, at 29.
2:27′ 26″, at 30, about normal rate.

Sucked out to 3.
2:30, at 3⅓.
10 c.c. secretin (Case 7, H. Z.) at 3:30′ 20″.

First movement at 2:31.
2:31′ 04″, at 5.
2:31′ 45″, at 10.
2:32′ 25″, at 12½.
2:32′ 40″, at 13.
2:33′ 07″, at 14.
2:34′ 10″, at 15.
2:35′ 38″, at 16.

10 c.c. secretin (Case 9, E. F.) first unfiltered, supernatant, at 2:36′ 20″.
2:38′ 10″, at 17, same rate.

No response. Result of both injections clear.

First tuberculous case (H. Z.) gave a distinct response, slower than dog and apparently not quite so soon (though see figures).
2:44′ 30″, at 18 (constant).

10 c.c. secretin (Case 9, E. F.), treated with both HCl and alkali, etc.
2:47′ 25″, first movement.
2:48′ 48″, at 19, no response.
2:49′ 52″, at 20, no response.
2:53′ 40″, at 21 (nearly) no resp.

10 c.c. newest dog secretin (Case 7) again at 2:54′ 34″.

First movement, at 2:55′ 25″.
2:55′ 38″, at 25.
2:55′ 48″, at 30.
2:55′ 53″, at 35.

Lost; too fast to count.
2:56′ 10″, at 10.
2:56′ 18″, at 15.
2:56′ 26″, at 20.
2.56′ 34″, at 25.
2:56′ 45″, at 30.
2:56′ 57″, at 35.

Sucked out to 3.
2:57′ 12″, at 5.
2:57′ 52″, at 10, slower.
3:02′ 45″, at 12.

10 c.c. (Case 9, E. F.) squeezed and filtered, at 3:03′ 20″.
3:06′ 25″, at 13, no response.
3:09′ 00″, at 13½.

10 c.c. secretin (Case 8, H. Z.) late filtrate, injected at 3:11′ 30″.

At time of injection, juice not moved from 13½.

First movement at about 3:13′ 40″.
3:13′ 10″, at 15.
3:13′ 48″, at 16.
3:15′ 04″, at 17.

Slight response, less than the other from same case, but distinct.
3:17′ 25″, 10 c.c. secretin (Case 8) earlier than last, but perhaps later filtrate than that first injected.
3:19′ 15″, at 18.
3:24′ 55″, at 19, no response.

10 c.c. secretin of (Case 9, E. F.) later filtrate, over night, at 3:26′35″.
3:28′ 00″, at 19⅓; no response.

10 c.c. very old dog secretin (Case 3) at 3:29′ 35″.

First movement at 3:30′ 35″.
3:30′ 58″, at 20, active; preparation must be some 5 or more weeks old.
3:31′ 13″, at 30.

Sucked out to 3.
3:31′ 38″, at 5.
3:32′ 07″, at 10.
3:32′ 55″, at 13½.
3:34′ 00″, at 16, slowed down.
3:35′ 03″, at 17.

10 c.c. of a solution made up of HCl, NaOH and CH_3COOH in the proportions used in making secretin extracts, was injected at 3:35′ 40″.

No response.
3:46′, at 19.

10 c.c. most active flask of (Case 8, H. Z.) heavy precipitate, at 3:47′ 10″.

First movement, at 3:48′ 55″.
3:50′ 20″, at 20.
3:54′ 15″, at 21.

Very slow response, if any, probably the slightest possible.
3:56′ 15″, at 21⅓.

10 c.c. (Case 8) much alkali and acid, at 3:56′ 47″.
3:59′ 10″, at 23.
4:00′ 45″, at 24.

A response, but not great. Curiously, the preparation first used just before this did not act, when it did earlier in the day.
4:04′, at 25.

10 c.c. newest dog (Case 7) secretin at 4:04′ 15″.
Tube sucked out to 4⅓.
First movement at 4:06′ 28″.
4:06′ 29″, at 5.
4:06′ 50″, at 7.
4:07′ 05″, at 8.
4:07′ 20″, at 9.
4:07′ 33″, at 10.
4:07′ 58″, at 11.
4:08′ 50″, at 12.

Distinct response, but not so marked as before. Does the general condition of the dog account for it? At one time she nearly died from too much ether. Canula worked beautifully to-day and no clot in end.

None of the E. F. (Case 9) preparations worked. Several of Case 8 preparations worked. None of the Case 9, E. F., preparations were put in Arnold sterilizer.

The preparation (Case 9) marked "much alkali and acid" was one carried somewhat beyond neutrality, and then brought back to relatively strong acidity to get out all possible proteid. It worked.

Stomach full of well digested fluid and food. Upper part of intestine contains some light yellow food, then becomes pretty free and further down contents are fecal in nature and pretty profuse. Bowel therefore much fuller than with recent dogs. (Last two not examined, but not fed beforehand; this one was, at 10:45 a. m.)

May 21, 1907.—(1) Small Fox Terrier.

A failure, as canula would not go in and tissues became too bruised and torn to be of any use.

(2) Large Puppy, Setter Type.

4:30, at ¾.
4:30′ 25″, at 1.
4:31′ 10″, at 2. Divisions are ¼ inch instead of ⅛ inch.
4:32′ 30″, at 3, usual initial flow followed by decrease.
4:37′ 30″, very slow.
4:38′, barely at 4.
5 c.c. dog secretin of April 17 (Case 5) at 4:39′ 30″.
Not yet 4.

Both failures, mechanically. Pancreatic duct of second dog branched so early that the common duct was too short to allow of satisfactory tying in the canula. In both dogs the canulæ were introduced outside of bowel; bowel not opened.

May 22, 1907.—Fox Terrier Bitch.

Juice flowing fast when canula first put in. Marks on canula about ⅜ apart.
3:00 p. m., at ¾.
3:01′ 30″, at 1.
5 c.c. secretin Case 5 (dog of April 17) thrown in at 3:02′ 20″.
First movement, at 3:02′ 50″.
3:03′ 30″, at 3.
3:03′ 53″, at 4.
3:04′ 15″, at 5.
3:04′ 40″, at 6.
3:05′ 10″, at 7.
3:06′ 12″, at 8.
3:07′ 35″, at 9.
3:09′ 35″, at 10, much slowed down.
Sucked out to 2.
3:14′ 30″, at 2.
5 c.c. secretin (Case 10, K. W.) filtered.
3:15′ 00″, at 2¼.
3:18′ 30″, at 3, no response.
5 c.c. secretin (Case 10, K. W.) supernatant, at 3:19′ 50″.
3:22′ 45″, no response, juice at 3⅓.
3:24′ 30″, 5 c.c. same active dog secretin of April 17 (Case 5) thrown in.
3:27′ 30″, apparently no response, though canula sucks as though not blocked up.
3:28′ 30″, at 4.

3:34′ 50″, 10 c.c. dog secretin of April 17, (Case 5); level only at 4⅓.

Respiration affected.

3:36′ 20″, first movement.

3:36′ 35″, at 5.

3:37′ 15″, at 6.

3:38′ 25″, at 7 (slower, though a distinct response).

3:40′ 45″, at 8.

A thrombus in canula may have slowed flow. Also left leg vein may have thrombosed or injection may have been in artery. Last active injection made into right jugular.

3:44′ 30″, at 9.

10 c.c. calf secretin (Case 11) at 3:44′ 35″.

3:45′ 40″, first movement.

3:45′ 52″, at 10.

3:45′ 59″, at 11.

3:45′ 06″, at 12.

3:46′ 12″, at 13.

3:46′ 18″, at 14.

3:46′ 22″, at 15.

3:46′ 26″, at 16.

Juice now dropping into test tube to be saved for another purpose. The clot above mentioned was pushed out; juice viscid.

Sucked out to 2, at 3:49′ 10″.

3:50′ 05″, at 6; still very fast.

3:50′ 55″, at 7, slower.

3:53′, just over 8.

10 c.c. sheep secretin (Case 12) filtered and supernatant, at 3:53′ 15″.

3:54′ 05″, first movement.

3:54′ 10″, at 12.

3:54′ 20″, at 15.

Filled.

Violent reaction.

Sucked out.

3:55′ 13″, at 8, slower.

3:55′ 23″, at 9.

3:55′ 33″, at 10.

3:55′ 45″, at 11.

3:56′ 06″, at 12.

3:58′ 20″, at 16, full up.

Slowing, but violent response.

Sucked out, and at 4:04 has ceased flowing and stands at 2.

4:09′ 00″, at 2 1/6, hardly moved at all.

4:19′, at 2¼.

Sucked out to nearly 1.

10 c.c. calf secretin (Case 11) filtered, injected at 4:27′ 15″ to see if canula clear.

4:27′ 40″, response as before.

4:29′ 15″, at 3 (started at about 4:28′ 55″ or so).

4:29′ 43″, at 5.

4:29′ 57″, at 6.

4:30′ 12″, at 7, much slower than first.

4:30′ 30″, at 8, much slower than first.

4:30′ 43″, at 9.

4:30′ 54″, at 10, response.

4:31′ 10″, at 11, dog has been in poor shape for some time.

4:31′ 28″, at 12.

4:31′ 45″, at 13.

4:32′ 10″, at 14.

Slower.

4:33′ 08″, at 15, much slower.

10 c.c. sheep secretin (Case 12) supernatant, injected through gut wall into duodenum above pancreas at 4:38, and then 10 c.c. more.

4:37′ 30″, at 3 2/5, hardly moving.

4:38′ 45″, at 3 3/5.

4:40′ 30″, at 4.

4:48′, at 4¼, no response.

10 c.c. secretin (Case 10, K. W.) filtered and squeezed and filtered, injected into carotid.

4:49′ 15″, at 6.

4:49′ 23″, at 7.

4:49′ 30″, at 8.

4:49′ 50″, at 9, response.

4:50′ 05″, at 10.

4:50′ 29″, at 11.

4:51′, at 12.

4:52′ 20″, at 13.

4:54′ 20″, nearly 14.

4:55′, at 14 3/5.

Sucked out to 2⅓, almost constant.

10 c.c. supernatant secretion (Case 10, K. W.) at 4:58′ 30″ (dog nearly dead).

4:58′ 40″, started.

4:59′, at 6.

4:59′ 07″, at 7.

4:59′ 25″, at 9.

4:59′ 32″, at 10.

4:59′ 48″, at 11.

5:00′ 00″, at 12.

5:00′ 18″, at 13.

5:00′ 50″, at 14, slower.
Distinct response.
Sucked out to 2, at 5:05.
10 c.c. secretin (Case 4, McM.) at 5:05′ 50″, juice at 2¾ then.
5:06′ 20″, at 3.
Apparently no response.
10 c.c. calf secretin (Case 11) at 5:09′ 45″.
Response relatively mild.
Dog killed.

MAY 31, 1907.—SMALL MALE PUPPY, BULL TYPE.

12:47′ 10″, at 1 (marks ¼ inch apart).
12:50, at 2⅓, partly by sucking through fine tube introduced into canula.
Flowing very slowly.
5 c.c. secretin of Case 13 (setter dog kept on ice) at 12:52′ 50″, in right jugular.
12:53′ 15″, at 3.
Started in about twenty seconds or so.
12:53′ 48″, at 4.
12:53′ 57″, at 5, response.
12:54′ 10″, at 6.
12:54′ 24″, at 7.
12:54′ 42″, at 8.
12:55′ 08″, at 9.
12:57′, at 10, slow and possibly plugged up.
Small plug removed by making a "cork screw" out of catgut.
Sucked out to 9.
5 c.c. more secretin Case 13 put in, to wash out canula.
1:03′ 10″, 5 c.c. more secretin of Case 13.
1:04′ 08″, moved.
1:04′ 24″, at 14, too fast to count.
1:04′ 32″, at 15.
1:04′ 42″, at 16.
1:04′ 52″, at 17.
1:05′ 02″, at 18.
1:05′ 13″, at 19.
1:05′ 28″, at 20.
1:05′ 33″, at 21.
Full.
1:09, still moving.
Sucked out to 6.
5 c.c. secretin (Case 14, A. R.) young girl with tuberculosis, at 1:12′ 50″.
1:13′ 20″, at 7¼, practically stopped.
1:14′ 45″, at 7½, no response yet.
Trouble, canula out.
1:29′ 05″, 5 c.c. secretin (5-day-on-ice-dog) to clear tube.
Response, but canula evidently blocked.
5 c.c. more secretin (Case 13) at 1:34′ 30″, to clear duct.
More secretin Case 13; respiration affected, but it has not been much noticed to-day.
A slight sluggish response.
Canula seems clear yet movement atypical and not so good as at first.
5 c.c. more secretin (Case 13) again gave a slow response.
5 c.c. active calf secretin (Case 11) gave a slight movement, not sufficient to record (1 div.).
5 c.c. sheep secretin (Case 12) injected.
About 5 minutes later a quite marked flow, evidently a response.
5 c.c. more secretin of Case 13 (5-day-dog) gave a relatively slow but distinct response.
10 c.c. human secretin (Case 14, A. R.) cloudy, that is, but little filtered, at 2:21′ 45″.
Level at 3½, response in 35 seconds.
2:22′ 45″, at 5.
Cleansing wire taken out, level fell back.
2:23′ 05″, at 6.
2:23′ 35″, at 7, response.
2:24′ 15″, at 8.
2:25′ 15″, at 9.
10 c.c. clear secretin (Case 14, A. R.) young girl with tuberculosis.
2:29′ 15″, at 2.
2:30′ 33″, at 3.
2:31′ 15″, at 4.
2:31′ 56″, at 5.
2:32′ 45″, at 6, response.
On dissection, gland looked edematous under peritoneum; much alkaline pancreatic juice.

JUNE 18, 1907.—BROWN IRISH TERRIER.

Tried with secretin of Case 15 (McK.); canula about ⅜ inch in size, much larger, and fitted with platinum point.

No movement in tube, just a drop or so in bottom.

10 c.c. Case 15 (McK.) at 11:23.

Breathing changed at once.

Seemed to be a response from motion in canula, but injection used chiefly to start a free flow.

11:32′ 30″, flowing freely (marks ⅛ inch apart).

11:34′ 20″, at 5.

11:37′, at 6 (slower, though moving).

11:41′ 20″, very nearly 7.

11:41′ 20″, 10 c.c. more of Case 15.

At 8, a clot in tube, clearly seen, long feathery and red.

The above apparently a response, but hardly dependable, as normal flow may have been very active.

JUNE 20, 1907.—LARGE BLACK DOG, SETTER TYPE.

11:15′ 35″, at 0.

11:16′ 05″, at 1.

11:17′ 25″, at 2⅓.

11:18′, at 3.

10 c.c. secretin Case 16 (dog of June 18) injected into carotid, at 11:18′ 40″.

11:19′, at 4.

First movement at 11:19′ 45″.

11:19′ 50″, at 7.

11:19′ 56″, at 8.

11:20′ 03″, at 9.

11:20′ 10″, at 12.

11:20′ 18″, at 15.

11:20′ 26″, at 19. } Too fast to
11:20′ 28″, at 20. } count, even
11:20′ 37″, at 25. } with biggest
11:20′ 43″, at 28. } tube.
11:20′ 48″, at 30. } Violent reac-
11:20′ 55″, at 32. } tion.

11:21′, at 34.

11:21′ 06″, at 35.

11:21′ 16″, at 36.

11:21′ 27″, at 38.

11:21′ 43″, at 40.

Sucked out to 0, at 11:23′ 15″.

11:24′ 40″, at 1½.

11:25, at 2.

10 c.c. secretin Case 15 (McK.) injected into right jugular at 11:25′ 20″.

11:26′ 35″, at 3.

11:26′ 48″, at 4.

11:27′ 34″, at 5.

11:27′ 57″, at 6.

11:28′ 28″, at 7.

Response, but much less marked than that of dog.

10 c.c. more secretin of Case 16 (dog) tried, to obviate possibility of clot, at 11:30′ 35″.

Now slowed down.

11:30′ 45″, at 8.

11:31′ 40″, at 9.

11:31′ 50″, at 10.

11:31′ 58″, at 11.

11:32′ 03″, at 12.

11:32′ 08″, at 13.

11:32′ 13″, at 14.

11:32′ 17″, at 15.

11:32′ 22″, at 16.

11:32′ 28″, at 17.

11:32′ 32″, at 18.

11:32′ 38″, at 19.

11:32′ 43″, at 20.

11:32′ 49″, at 21.

11:32′ 53″, at 22 (lacteals show plainly in gut).

11:33, at 23.

11:33′ 07″, at 24.

11:33′ 15″, at 25.

11:33′ 28″, at 26.

11:33′ 58″, at 29.

Small clot somewhere, visible in material sucked out.

10 c.c. secretin Case 15 (McK.) unfiltered and simply decanted, at 11:38.

11:38′ 20″, at 3.

11:41′ 13″, at 4.

11:46′, at 5.

11:48′ 05″, at 6.

11:48′ 35″, at 15. } Marked response *very much delayed* and persistent when present.
11:49′ 15″, at 19.
11:49′ 40″, at 21.
11:50′ 15″, at 20.
11:50′ 25″, at 25. } Dog's heart action better than when human secretin was first thrown in this last time.
11:50′ 45″, at 26.
11:51′ 08″, at 27.
11:51′ 25″, at 28.
11:51′ 55″, at 29.
11:52′ 25″, at 30.
11:52′ 50″, at 31.
11:55′ 00″, at 32.
11:55′ 30″, at 35.

Cardiac depression perhaps a factor in slow response, but there was no cyanosis.

11:59′ 40″, at 1 (going very slowly).
12:03′ 45″, at 2.
12:05′, at 3.

10 c.c. secretin Case 15 (McK.) thrown in jugular vein at 12:06′ 05″.

12:06′ 37″, at 4.
12:07′ 40″, at 5.
12:08′ 40″, at 6.
12:09′ 35″, at 7.
12:11′, at 8.
12:14′ 45″, at 9½.

Even with accurate figures and timing, etc., it was very hard to tell whether the above human injection was a response or not. Certainly it was less than that of a dog, but possibly a response even so.

12:19′ 15″, at 10¾.
12:20′ 55″, at 11.

10 c.c. secretin Case 16 (dog of June 18) at 12:21′ 10″.

12:22′, at 12.
12:22′ 15″, at 13.
12:22′ 20″, at 14.
12:22′ 23″, at 15.
12:22′ 40″, at 20.
12:22′ 50″, at 25.
12:23′, at 30.
12:23′ 10″, at 35.
12:23′ 20″, at 40.
12:23′ 30″, at 45 (estimated).

Sucked out to 0.

12:23′ 57″, at 10.
12:24′ 07″, at 15.
12:24′ 15″, at 20.
12:24′ 20″, at 25.
12:24′ 40″, at 30.
12:24′ 55″, at 35.
12:25′ 09″, at 40.
12:25′ 24″, at 45 (estimated).
12:25′ 30″, at 0.
12:25′ 48″, at 5.
12:26′ 03″, at 10.
12:26′ 20″, at 15.
12:26′ 45″, at 20.
12:27′ 30″, at 25.

Dog breathing rapidly and respiration shallow, flow has slowed down considerably since last figures.

12:29′ 30″, at 30.
12:31, at 32.
12:33′ 30″, at 33.
12:36′ 20″, at 34.

10 c.c. secretin Case 15 (McK.) filtered, at 12:37′ 40″.

Sucked out.

12:38′ 15″, at 0.
Missed time at 1.
12:39′ 50″, at 2.
12:40′ 57″, at 3.
12:42′ 14″, at 4.
12:44′ 30″, at 5.

Seems to be a response, but vague like the last, and vastly below the dog preparations in efficiency.

VARIABILITY AND UNRELIABILITY IN THE DETERMINATION OF THE OPSONIC INDEX.*

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PHILADELPHIA.

Huxley has said, "The man of science has learned to believe in justification, not by faith, but by verification." With this in mind, throughout the past nine months, I have been engaged in a study of the practical utility of the opsonic index as a factor in the diagnosis, prognosis and therapeusis of disease.

Lest my attitude on this question be misinterpreted, I desire primarily to state that I have no reason to doubt, and, on the contrary, entertain implicit faith in the theory of opsonins; but as to the practicability of the index in medicine, my experiments have occasioned the gravest skepticism, if not absolute pessimism, relative to its utility for the profession at large.

Slow as the perfection of the delicate technic for the determination of the phagocytic power of the blood necessarily was, it is rather surprising to note that approximately but one year has elapsed since the opsonic wave cast its waters on American soil. Although tardy in initiation, the aggressiveness of its influence throughout the states is unprecedented in the history of research and discovery. Indeed so widely disseminated at the present time is this overvaluation of an impractical, yet attractive and ingenious hypothesis, that many in the profession are expecting veritable miracles in the treatment of disease.

Personally it is of little import what may be the relationship of opsonins to antitoxins, coagulins, precipitins

* From the William Pepper Laboratory of Clinical Medicine; Phoebe A. Hearst Foundation.

and agglutinins, or possibly to amboceptors, complement, etc., but thus far my observation and experience have dictated the belief that Wright's methods have occasioned an unsuccessful attempt, figuratively speaking, to enthrone on a practical basis Ehrlich's side-chain hypothesis. Until the recent session of the American Congress of Physicians and Surgeons, held in Washington, diffidence alone prevented any public utterance of opinion, inasmuch as barely nine months' experience with a problem of experimental medicine, to which Wright and his associates, Leishman and Douglas, have devoted five years for its perfection, did not invite negations prematurely bold. The enthusiastic advocates of the utility of the opsonic index may claim that the causes of failure in the hands of those who have found it impossible to obtain consistent results are breaches in technic and lack of experience, and that such individuals should, after mastering the technic from one of Wright's circle of co-workers, experiment (I beg to ask, for four or five years) before indulging in criticism. To such a statement I can only reply that any technic so intricate as to be impossible of satisfactory solution after four to six weeks in laboratory association with a pupil of its originator, must be relegated to a field of usefulness so limited for the general profession as to render it well-nigh valueless.

It is not my intention to detail the present perfected technical methods for the determination of the opsonic index. Suffice it to say that they are two: The phagocytic index of Wright and the percentage index of phagocyting leucocytes of Simon, and to the latter I extend unqualified preference because of its greater simplicity and comparative ease of determination and because it has always served as a valuable check on the former, confirmation of which is apparent on inspection of Chart 3. One point, however, should be emphasized, namely, the impossibility of gathering from the extant opsonic literature a perfectly satisfactory working technic, it being necessary, although theoretically familiar with the principles, to see at least one demonstration in the hands of an associate of Wright or one who has directly inspected his methods. Even then the difficulties, some of which it is my purpose to enumerate, are so considerable as to render its utility, from a medical standpoint, practically *nil*.

EFFECT OF STRENGTH OF BACTERIAL EMULSION.

Over ten months ago the idea occurred to me that variability in the "strength" of the bacterial emulsion was responsible, to a degree at least, for fallacious re-

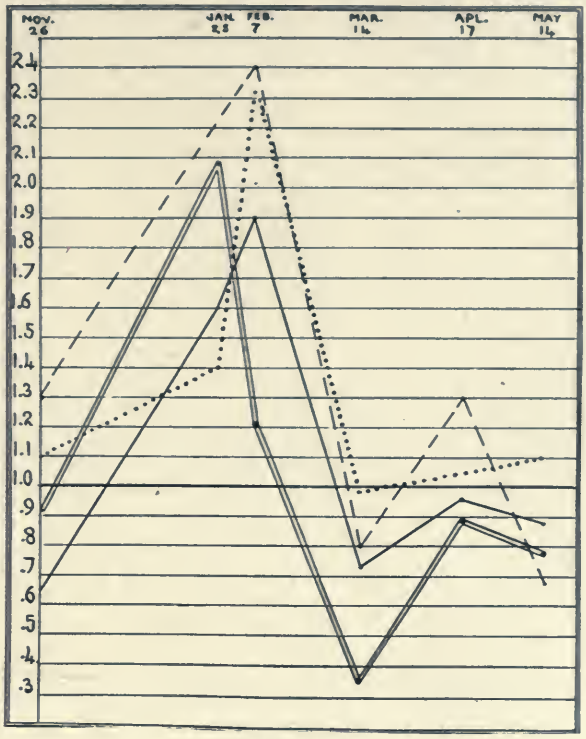


Chart 1.

—— Bacterial emulsion centrifuged for 10 minutes, then dilution of supernatant suspension so that 1 c.mm. contained approximately 10,000,000 bacteria.
.... Bacterial emulsion centrifuged for 10 minutes.
---- Bacterial emulsion centrifuged for 10 minutes and supernatant suspension diluted with 3 volumes of 0.85 per cent. saline solution.
═══ Bacterial emulsion standardized by McFarland's "nephelometer."

sults. Therefore I proceeded, in a series of determinations of opsonic indices, employing emulsions, standardized by various methods, to depict graphically by Chart 2 the indices for their respective bacterial emulsions. Pursuant of this, in association with other observations

that I desired to present, I selected from the service of Dr. Charles H. Frazier, in the University Hospital, the case of a patient with tuberculous arthritis of the knee.[1] After treatment by extension and plaster cast for two months, an arthrotomy was performed Nov. 22, 1906, and four days later, the opsonic index was found to be low, 0.66, using an emulsion averaging approximately 10,000,000 bacteria per c.mm. Shortly thereafter the patient was discharged and sent to Atlantic City, only to be readmitted for resection of the knee joint Jan. 23, 1907, since which time monthly determinations of the opsonic index, employing on each occasion four differently standardized bacterial emulsions, were made.

A study of Chart 1 should demonstrate the fact that no constant parallelism exists between the curves of the indices of their respective bacterial emulsions. At times this relationship is fairly uniform, but occasionally, especially during January, when the indices for all four emulsions seemed to be ascending admirably in the "positive phase," or the period of increased resistance, and Wright's so-called "high tide of immunity" was apparently about to be maintained, at the determination made February 7, the indices for three emulsions continued to mount in the positive phase, while for one emulsion, that standardized by McFarland's "nephelometer," the index dropped almost into "negative phase." Again on April 17 the indices for two emulsions are in the "positive phase," while for the other two they continue in the "negative phase."

This irregularity in the relationship of the indices, characterized by crossing and intercrossing of the various opsonic curves, indicates, I believe, that the strength of the bacterial emulsion plays an important rôle conducive to fallacious results—indeed worthy, perhaps, of more consideration than has been accorded it. For example, figuratively speaking, the amount of grass consumed by the herd on the rugged mountain side depends not necessarily on the hunger of the sheep but rather on the amount present. Just so with the unfortunate phagocyte, the amount of bacterial pabulum in-

1. In the presentation of the points which I desired to make, it seemed to me that perhaps the results would be attended with more significance if my contemplated experiments were carried out on a single individual who probably would be in the hospital ward for several months, and to this end all the data in the three incorporated charts are referable to the same patient.

gested is directly proportionate in a large measure to that available, and any deprivation limiting its capability will be conducive to fallacious indices. Believing, therefore, at the beginning of my studies that a constant bacterial emulsion of known strength should be invari-

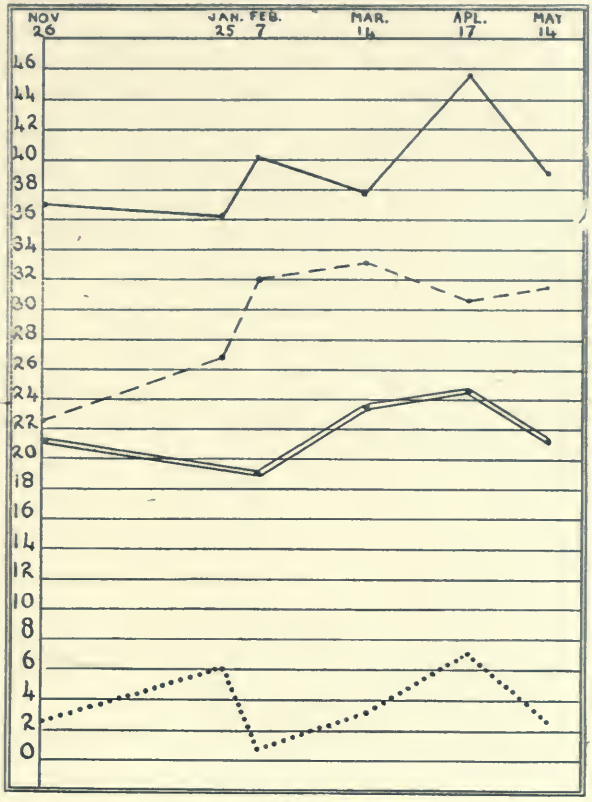


Chart 2.

—— Patient's serum plus washed leucocytes plus bacterial emulsion employing NaCl solution of 0.6 per cent. and sodium citrate 1 per cent.

.... No serum. Washed leucocytes plus bacterial emulsion employing NaCl solution of 0.6 per cent. and sodium citrate 1 per cent.

---- Patient's serum plus washed leucocytes plus bacterial emulsion employing NaCl solution of 0.85 per cent. and sodium citrate 1 per cent.

═══ Patient's serum plus washed leucocytes plus bacterial emulsion employing NaCl solution of 1 per cent. and sodium citrate 1.5 per cent.

The figures from 0 to 46 in the vertical column represent the average number bacteria pro phagocyte.

ably employed, I have utilized in conjunction with my other experiments one containing 10,000,000 bacteria per c.mm., but, as will be pointed out later, even this curve of opsonic indices does not agree with the clinical symptomatology. Knorr[2] has stated recently that by employing an emulsion of *Staphylococcus aureus* of definite strength and by progressive dilutions, estimating in each instance the phagocytic index and percentage of phagocyting cells, that the indices were directly proportional to the strength of the bacterial emulsion. My results are entirely in harmony with Knorr's experience.

Wright,[3] however, in a former communication on the preparation of the bacterial emulsion, advises the use of the supernatant suspension of bacteria following centrifugation. This, without a supplementary definite enumeration of the bacteria per c.mm., I believe capable of the production not infrequently of erroneous results; first, in that a variability in the strength of the original emulsion prior to centrifugation is productive of inconstancy in its strength after centrifugation, although the emulsion is centrifuged always for a specified time, which is very essential; second, in that, although the time element may be observed, the speed or number of revolutions per second of the centrifuge, whether operated by hand, water or electricity, is variable on different days and hours in the same day, depending on the power of the operator, the water pressure or strength of the electric current. These points may appear insignificant, but, when taken into consideration with other detrimental influences concerned in opsonic work, play a more important part than is surmised.

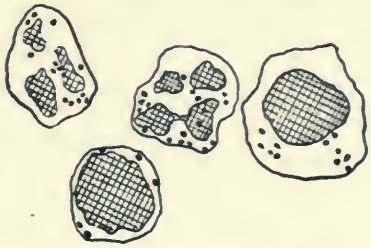
RELATION OF PHAGOCYTOSIS TO PERIOD OF INCUBATION.

Phagocytosis is dependent directly on the length of time the leucocytes and bacteria are allowed to incubate. Its degree is variable with different bacteria and is influenced by temperature, 37 C. (98.6 F.) being most desirable for the majority of bacteria, although phagocytosis has been observed to occur at room temperature. A comparatively weak emulsion, one containing approximately 1,000,000 bacteria per c.mm., was required in my experiments, because as time progressed the ingested

2. THE JOURNAL A. M. A., April 13, 1907, 1255.
3. Potter, Ditman and Bradley: THE JOURNAL A. M. A., Nov. 24, 1906, 1722.

bacteria became too numerous for easy enumeration. For an hour to an hour and a half phagocytosis was apparently directly proportional to the period of incubation. After that time the leucocytes began to degenerate, because of the action of the leucocidin formed by the *Staphylococcus pyogenes aureus,* and an accurate estimation was rendered impossible. My experience has justified the belief that an incubation of a half-hour is more reliable than a shorter period in that it furnishes a more trustworthy opsonic index. At least in the cases where I have employed the longer incubation period the agreement between the opsonic index and the clinical symptomatology has been more constant.

Explanatory of this, it seems reasonable to suppose that in the longer period the opsonins are given a greater opportunity to exert their full influence on the bacteria



Two large mononuclear and two polynuclear leucocytes exhibiting apparently spontaneous phagocytosis.

and consequently the result is a more truthful exponent. On the contrary, during the longer period the ingestion of bacteria by the leucocytes is ofttimes so extensive as to make an exact enumeration almost impossible. At room temperature phagocytosis for *Staphylococcus pyogenes aureus* was markedly retarded, and five to six hours were insufficient to produce the same degree of bacterial ingestion as is usually noted for an incubation of fifteen minutes in the thermostat. After this time further observations are useless, because the leucocytes lose their vitality and lead necessarily to erroneous results.

SPONTANEOUS PHAGOCYTOSIS.

Apropos of the thought that all the bacteria counted within the circumference of a phagocyte were not perhaps the result entirely of opsonic influence, but that possibly spontaneous phagocytosis or the mere adhesion

of bacteria to leucocytes was a factor, I was prompted to make comparative determinations in which a rather concentrated bacterial emulsion of the *Staphylococcus aureus* was employed. For this purpose the customary technic was used, excepting that in one instance the patient's serum was added, while in the other no serum was employed. The results of those observations are graphically described by a comparison of the continuous, broken and dotted curves in Chart 2.

In all determinations it is my practice to wash the "leucocytic cream" at least three times so that the leucocytes should have been free from serum, as the volumes of salt solution employed were several times that of the blood corpuscles. Although it has been claimed that no spontaneous phagocytosis exists for staphylococci, I desire to append these observations with the explanation that perhaps the bacterial emulsion may not have been sufficiently concentrated, or that the apparent spontaneous phagocytosis may have been referable to mere adhesion between the bacteria and leucocytes, although the latter has been characterized by a marginal arrangement of the organisms, which was not the case constantly in my studies, as will be seen by the accompanying diagram.

The above condition was observed when using a decalcification fluid of 1 per cent. sodium citrate in 0.6 per cent. saline solution and subsequent washing of the leucocytes with a 0.6 per cent. saline solution, this strength saline solution apparently favoring spontaneous phagocytosis.

As will be noted in Chart 2, the addition of serum greatly accelerated phagocytosis, which, however, seemed to be directly influenced, that is, diminished by the employment of an increase in the strength not only of the saline solution but also of the sodium citrate. The thought has occurred to me that possibly the use of 1½ per cent. sodium citrate in a 1 per cent. saline solution may be too strong, exerting an inhibitory, if not deleterious, influence on opsonins. Certainly the environment of the phagocytes *in vitro* is not so propitious as it was *in vivo*. Wright and Douglas[4] claim to have demonstrated, however, that the addition of the necessary quantity of sodium citrate had no influence whatever on the behavior of the blood corpuscles. Whether or

4. Proceedings of the Royal Society of London, lxxxii, 357, 1904.

not this statement is applicable to strengths of sodium chlorid greater than normal saline I am at present unprepared to say, but an inspection of the chart will reveal the fact that the number of the bacteria ingested by the leucocytes was less with the saline solutions of increased strength.

Wright has observed spontaneous phagocytosis of tubercle bacilli in certain concentrations of salt solution. Davis[5] very recently has demonstrated beyond question spontaneous phagocytosis for the influenza bacillus. Opsonins, therefore, are apparently not the sole factors concerned in the ingestion of bacteria by leucocytes, and the theory that they are derived, according to Metchnikoff, in part at least, from the leucocytes (in spite of the fact that there seems to be no relation between opsonins and leucocytosis) may yet deserve credence.

ENUMERATION OF LEUCOCYTES.

It has been my experience, naturally, that the larger the leucocyte count the more the reliance on the opsonic index. Counts of less than 100 leucocytes are especially likely to be misleading, and in my work it has been the practice to enumerate from 100 to 200 leucocytes, preferably the latter number, which is not so difficult using the percentage method of Simon. In estimating the number of phagocyting leucocytes both the large lymphocytes, transitionals and polymorphonuclears were considered because of the not infrequent phagocytic activity of the first and third as shown in the above diagram. This I believe to be just as important as the total enumeration of all three varieties of leucocytes, whether phagocyting or non-phagocyting.

TEMPERATURE.

I have also found that my results are more consistent since the employment of bacterial suspensions, decalcification fluids and saline solutions of a temperature maintained as nearly as possible at 37 C. (98.6 F.). In accordance with this I have endeavored also to insure a like temperature for the blood serum and "leucocytic cream."

NORMAL AND PATHOLOGIC VARIABILITY.

It would seem improbable to believe that any index very variable for the normal could be of great signifi-

5. THE JOURNAL A. M. A., May 11, 1907, 1567.

cance and utility in the determination of pathologic conditions. McFarland[6] has found the phagocytic count, in individuals giving no history of any suppuration or disease whatsoever, to vary from 4.125 to 23.2. In justice, however, to the opsonic index, we must remark that we regard standardization by the "nephelometer" as very unreliable, inasmuch as it is impossible for the naked eye to differentiate the degree of turbidity even after the addition of thousands of bacteria. Potter, Ditman and Bradley's[3] normal indices varied from 0.81 to 1.18; Wright and Douglas'[7] from 0.85 to 1.2, and my own from 0.75 to 1.25. Park has recently drawn attention to the fact that the index varies greatly in comparative tests with leucocytes obtained from selected normal individuals.

AGE OF CULTURE AND LIFE OF OPSONINS.

Knorr,[2] in experimentation using forty-six-hour-old and forty-two-day-old cultures, demonstrated that the aging of the culture seems not to affect the phagocytic or percentage indices. In my work I have employed only twenty-four and six-hour-old cultures, recently using exclusively the six-hour-old cultures, with identical results. On the contrary, different strains of the same organism give variable indices.

Knorr's results show that "the serum loses one-half of its opsonic power in twenty-four hours; after this there is practically no further loss in the following twenty-four hours. The value then rapidly drops, but, however, does not wholly disappear until after five days."

PERSONAL EQUATION.

As many and varied as are the opportunities cited above that may lead to erroneous results, impairing the value of the opsonic index, that factor, paramount among its fellows, blighting the practicability of the opsonic determination on its present basis, is the personal equation. The importance of this negatively and positively can not be overestimated and plays an even more important rôle, considering the intricate technic, than the determination of slight variations in leucocytosis in a given case by different observers. On the contrary, it can be readily appreciated that it is utterly impossible

6. Medicine, April, 1906.
7. Proc. of Royal Soc., lxxii, 357.

for any single observer to master all the work on more than one or a very few cases, even though he may sacrifice all his time for the cause. Consequently the necessity arises of employing a corps of low-salaried workers or "leucocyte counters," in most instances an impractical procedure.

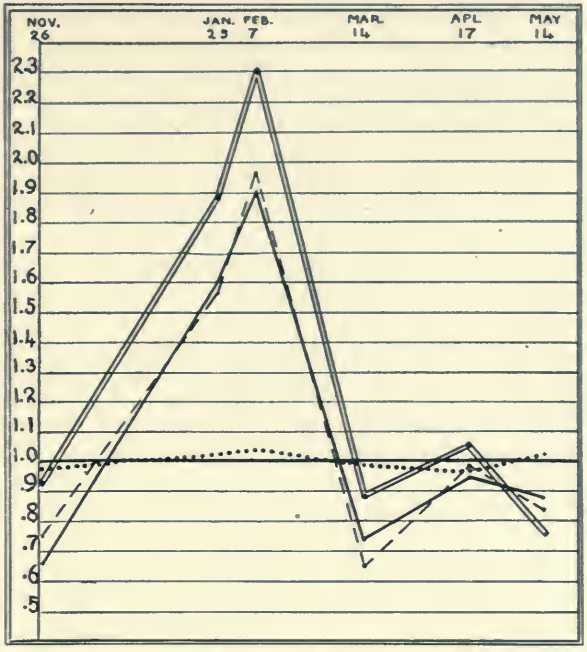


Chart 3.

—— Wright's phagocytic index using emulsion of approximately 10,000,000 bacteria to c.mm.

---- Simon's percentage index using emulsion of approximately 10,000,000 to c.mm.

═══ Simon's percentage index using supernatant suspension of bacteria of an emulsion centrifuged for 10 minutes and diluted with three volumes of 0.85 per cent. saline solution.

.... Simon's percentage index using supernatant suspension of bacteria emulsion centrifuged for 10 minutes.

WRIGHT VERSUS SIMON.

It has been found of great interest in my determinations to measure the constant ratio existing between Wright's phagocytic index and Simon's percentage index of phagocyting leucocytes, especially the percentage

index because of its greater value. A consideration of paramount importance in this connection and never to be disregarded is not to use a too concentrated bacterial emulsion, especially when employing Simon's method, as the percentage of phagocyting leucocytes will be too great, reaching 100 constantly, thereby nullifying the index. Simon[8] himself appreciates this, and in a late communication writes: "The percentage of phagocyting cells is to a certain extent dependent on the number of organisms present, it is advantageous to work with an emulsion which, with normal blood serum, should not give a higher percentage than 50." In accordance with his suggestion, we have found it is also desirable to dilute the blood serum from twenty to forty times.

A review of Chart 3 will serve to elucidate this point by a comparison of the double line (===) curve (using a weak emulsion) with the dotted line (....) curve (using a concentrated emulsion).

OPSONIC DIAGNOSIS.

The value of the opsonic index as a diagnostic measure depends on the specificity of opsonins. The methods are three: 1. Derivation of the opsonic index from the blood serum. 2. Comparison of the indices of heated and unheated serum. 3. Comparison of indices of blood serum and exudate or transudate of the same case. The results obtained by Wright and Douglas and Bulloch[9] relative to the specificity of opsonins have not been confirmed by Simon, Potter, Ditman, Bradley and others, so that at the present time the diagnostic value of the opsonic index is minimal.

OPSONIC PROGNOSIS AND THERAPY.

Pottenger,[10] in an excellent article on tuberculin therapy recently, attributes no inconsiderable amount of importance to the prognostic value of the opsonic index. He states that in 150 cases of lupus in which the patients had done badly a low opsonic index persisted, while in those that had responded to the treatment the index was higher. With Wright, Bulloch,[9] Lawson and Stewart[11] he contends that the therapeutic use of tuberculin (Koch's T. R.) in tuberculosis invariably produces

8. The Journal A. M. A., Jan. 12, 1907, 139.
9. Lancet, Dec. 2, 1603, 1905.
10. The Journal A. M. A., May 11, 1907, 1570.
11. Lancet, Dec. 9, 1905.

a rise in the opsonic index. Not only this, but in sanatorium treatment he has secured 20 per cent. more cures apparently with tuberculin than without, and, moreover, he has confirmed the opinions of Trudeau[12] and Turban[13] that the tendencies to relapse are fewer and the results more permanent following tuberculin therapy. Unfortunately I have had no experience with tuberculin therapy in conjunction with the opsonic index, but in the case cited above on whom determinations of the opsonic index were made periodically it will be noted by a glance at Chart 1 that the general trend for the last three months of the opsonic index has been toward or in the "negative phase," in spite of the fact that the clinicians persistently assert that the patient's condition is steadily improving.

In 1833 a German advanced the idea expressed in the title of a monograph that all contagious diseases contain in their contagium the materials necessary for their cure. Therefore, the theory which underlies therapeutic inoculations in infectious diseases is by no means new, although, as Ohlmacher[14] says, "it remained for Wright to so modify the vaccine of Pasteur as to arouse in the serum of Buchner a substance which prepared the disease-producing microbe for destruction by the phagocyte of Metchnikoff, thus bringing to practical humanitarian usefulness the laboriously studied theories of three pioneers in biologic therapy."

Although my experience thus far with artificial autoinoculation has been most gratifying and my results in close harmony with those of other observers, I am disposed to believe there is a tendency to over-valuation even in this method of therapy. Certainly its application has not been sufficiently prolonged, and the results, *pro* and *con*, have not been so numerous as to warrant a decisive opinion, but I am satisfied that time and again patients recover spontaneously, coincident with "vaccine" therapy. Fortunately brilliant results are obtained independently of routine determination of the opsonic indices, the quantity of "vaccine" and the frequency of inoculations being controlled solely by the clinical symptomatology.

Koch's new tuberculin (T R) is undoubtedly more

12. Tr. Amer. Physicians, 1900.
13. Quoted in Welcker's Beitrag. z. Frage d. Volksheilstaetten, 22.
14. The Journal A. M. A., Feb. 16, 1907, 572.

reliable and preferable as a therapeutic agent in tuberculous infections. For the infections other than tuberculous a suspension of the organisms cultured on agar is made in physiologic salt solution. After sterilization by exposure to a temperature of 65 C. (149 F.) for an hour, and the addition of a preservative, this material, which is known as the "vaccine," is ready for inoculation. This emulsion is always standardized by determining the number of bacteria per c.c. of fluid.

The impracticability of Wright's method is further apparent from the fact that he urges daily determinations to ascertain the condition of the positive or negative phase, or whether the high tide of immunity has been reached or, on the other hand, is being maintained, thereby regulating the amount of "vaccine" to be inoculated from time to time and avoiding any "cumulation in the direction of the negative phase." I do not doubt the wisdom of these precautions theoretically and, were the application universally feasible, would enjoin its constant employment. Unfortunately, through errors in technic and especially not infrequent disagreement between the opsonic index and clinical symptomatology, we have invariably resorted to the latter as our guide in artificial autoinoculation therapy.

On the other hand, the dangers from over dosage or too frequent administration of the "vaccine" are not insignificant, and errors through carelessness or uncurbed enthusiasm in the employment of "vaccine" therapy in the untrained hands of the general practitioners will lead inevitably to results, if not disastrous, at least avoidable.

SUMMARY.

1. The phagocytic index is, as a rule, directly proportional to the strength of the bacterial suspension, which in all cases where consecutive comparative studies are to be made should be standardized by definite enumeration of the bacteria pro c.mm. Opsonic indices dependent on the supernatant suspension of bacteria, following mere centrifugation and the bacterial suspensions obtained by standardization with McFarland's "nephelometer," are fallacious.

2. For a certain time phagocytosis is directly proportional to the period of incubation. After this time degeneration of the leucocytes renders a trustworthy de-

termination of phagocytosis impossible. Phagocytosis does occur at room temperature, but incubation at 37 C. (98.6 F.) for most bacteria is more conducive.

3. Spontaneous phagocytosis or mere adhesion of bacteria to leucocytes may be a factor in the production of erroneous opsonic indices. In any event, opsonins do not appear to be the sole agents concerned in the ingestion of bacteria by leucocytes.

4. Not fewer than 100 leucocytes should be counted in estimations of phagocytosis, and these enumerations should include large lymphocytes and transitionals as well as polymorphonuclears. In short, the higher the leucocytic count the truer the index.

5. Maintenance of body temperature during the process of technic seems to influence beneficially the phagocytic index. Sudden fall of temperature acts conversely.

6. The inconsistency of the phagocytic index for normal individuals is apparently confirmed by the unreliability of the opsonic index for pathologic cases.

7. Aging of bacterial cultures (6 to 24 hours) seems not to affect materially the phagocytic index.

8. Knorr states that the opsonic power of the serum is diminished one-half in twenty-four hours, and that after forty-eight hours there is a gradual diminution, complete loss occurring after five days.

9. Aside from the technical difficulties, the question of personal equation involved in opsonic determinations is so serious as practically to nullify the value of the method in most instances.

10. Simon's percentage index is apparently of more value from the practical standpoint than Wright's phagocytic index because of its relative constancy and comparative ease of determination.

11. The experiences of the majority of observers indicate that the diagnostic value of the opsonic index is minimal.

12. The consensus of opinion favors the belief that, prognostically, some utility attaches to the opsonic index, especially in the field of tuberculosis and in the laboratory where it can be applied to test the virulence of organisms and the strength of sera whose value depends on opsonins.

13. In the heralded unlimited field of therapy, where

the opsonic index is ordained to play a star rôle, its utility seems destined to pass into oblivion, not only because of its inconstancy in agreement with the clinical symptomatology but especially because of its impracticability.

I desire to thank Dr. M. P. Ravenel of the Phipps Institute, who studied Ross' methods at the Rockefeller Institute, for valuable technical suggestions.

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STUDIES FROM THE BACTERIOLOGICAL LABORATORY.

I. Some Observations on Three Members of the Bacterium Mucosus Capsulatus Group. II. A Note on the Effect of Toxin and Anti-toxin Injections on the Phagocytosis of Diphtheria Bacilli.

By Herbert Fox, M.D.,
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(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

I. SOME OBSERVATIONS ON THREE MEMBERS OF THE BACTERIUM MUCOSUS CAPSULATUS GROUP.

These observations were undertaken after the isolation of two strains of the Bacterium mucosus capsulatus from the lungs of very young infants who died from pneumonitis, one of which was reported by Dr. Lavenson and the writer in the Bulletin, June, 1906. The Friedländer pneumobacillus was included for comparison.

Appended is a chart of the morphological and biological characters of the three strains.

PHAGOCYTIC AVERAGE OF FRIEDLÄNDER, LAV. II, AND X.

Normal average phagocytic index of the rabbits was, respectively, 1.2, 1.4, and 1.15. Immunization with twenty-four-hour serum bouillon cultures of the several strains (May 31st).

Friedländer blood with Lav. II, index 3.18. Friedländer blood with Lav. X, index 5.45. Friedländer blood with Friedländer, index 3.36.

Lav. II blood with Friedländer, index 1.9. Lav. II blood with Lav. X, index 2.9. Lav. II blood with Lav. II, index 3.8.

Lav. X blood with Friedländer, index 4.6. Lav. X blood with Lav. II, index 3.9. Lav. X blood with Lav. X, index 2.6.

Rabbits were immunized against all three cultures, so that Lav. II animal was able to withstand 10 c.c. of a twenty-four-hour serum bouillon culture into the peritoneal cavity; Lav. X and Friedländer rabbits were each able to resist 20 c.c.

No agglutinin was found in the blood of any of them except the Friedländer for itself, reacting only in the dilution of 1 to 5.

The serum of the Lav. II rabbit contained a precipitin for the homologous filtrate to the limit of 1 to 200, but not for the filtrates of Lav. X or Friedländer. Immunization with Lav. X produced no precipitin even for the homologous filtrate. The serum of the anti-Friedländer rabbit precipitates with the filtrates of the Friedländer and Lav. II growths. The reaction was positive with the former in dilutions of 1 to 400, which limit also gave a result with Lav. II, but much less clearly. With the filtrate of Lav. X the precipitation is only feeble in the dilution of 1 to 200. These sera were drawn nine days after the last injection. The growths used for inoculation were made in serum

Media 1.5 +	Lav. II.	Lav. X.	Friedländer (Pepper Laboratory).
Morphology.	Gram-negative bacteria capsules in milk and animal blood, plump rod; polar staining.	Same.	Same, but no polar staining.
Agar slant.	Smooth, flat, even, regular, glistening, slimy, creamy pearl, edges wavy, stroke becoming concave, spreading only to condensed water.	Same.	Color pearl gray, not so slimy, not concave.
Agar plates.	Forty-eight hours, superficial, round, discrete, convex, entire, slimy, creamy, yellow-brown, deep, round or whetstone, brown-yellow, coarse granular	Same smaller and not so yellow	Color pearl gray and microscopically yellow, not slimy.
Glycerin.	Gas, acidity.	Very little gas, slight acidity.	No gas, neutral.
Gelatin.	Filiform along stab; no liquid, few bubbles gas, surface convex, slight umbilication, no true nail growth.	Same.	Surface more convex, but not true nail growth; all surface growths creamy yellow.
Gelatin plates	Forty-eight hours, small, round or elliptical, entire, even, finely granular.	Same.	Same, but less yellow.
Milk.	Acidification, in forty-eight hours, coagulation, no digestion, whey pink.	Acid in twenty-four hours, no coagulation till seventy-two hours; otherwise same.	After forty-eight hours lilac which remains; no coagulation.
Potato.	Luxuriant, moist, slimy, creamy white, cheesy odor gas bubbles.	Same, but no odor.	Same, but no odor and not so luxuriant
Bouillon	Very turbid, viscid, thick pellicle, stringy sediment, pellicle fragile.	Same.	Same, but not so luxuriant.
Peptone water.	Slightly cloudy, no pellicle, indol feebly positive.	Same. No indol.	Same. Indol faint.
Glucose agar.	Twenty-four hours, acid and gas	Same.	Same.
Lactose agar.	Twenty-four hours, acid and gas.	Same, but not so much gas.	No gas; slightly acid.
Saccharose agar.	(Lost after first subculture) twenty-four hours, acid and much gas.	Same.	Same.
Mannite agar	Twenty-four hours, acid and gas.	Same.	Acid; very little gas.
Lactose N. Red.	Acid yellow, after four days no return of color, gas.	Acid yellow lower half, seventy-two hours partly returns, gas.	No change beyond deepening of the red.
Pathogenicity.	1 c.c. twenty-four-hour bouillon culture fatal in twenty-four hours, guinea-pigs, rabbits and mice.	1 c.c. twenty-four-hour bouillon culture fatal in twelve hours, guinea-pigs, not mice or rabbits.	1 c.c. twenty-four-hour bouillon culture fatal in 72 hours, guinea-pigs and mice, not rabbits.

bouillon. It will be seen that Friedländer produces a small amount of group precipitin, which body reacts to a higher limit with the filtrate of that bacterium (Lav. II) farthest from it in a biological sense.

On the other hand, phagocytosis with the anti-Friedländer blood is quite high with Lav. X, 5.45; while with the homologous organism it is only 3.36 and with Lav. II 3.18. The Friedländer seems to be able to produce a phagocytic as well as precipitating serum for these strains.

Lav. X, which was able to produce no precipitin, elaborated a high phagocytic power for all strains, for itself less than for the other two; viz., Lav. X, 2.6; Lav. II, 3.9; Friedländer, 4.6.

Lav. II produced relatively more phagocytic power for itself in the immune blood than for the other two bacteria or than these latter could call forth for themselves in their respective immune bloods. With the blood of Lav. II rabbit phagocytosis averaged 3.8 for the homologous organism, 2.9 for Lav. X, and 1.9 for the Friedländer. Here we notice that Lav. II was able neither to produce a precipitin nor phagocytosis for the Friedländer organism.

These biological, physiological, and chemical properties of the three strains under consideration are quite interesting, inasmuch as they show the vagaries of this group. The first two, that is, Lav. II and X, belong to the Aërogenes division, while the Friedländer is typical. That the physiology and chemistry of this latter should in any way interact with the first two is remarkable, since they are biologically distinct divisions, even though the Lav. X be nearer to the Friedländer type than is the Lav. II.

In summing up these points we see that Lav. X produces no precipitin, but its anti-blood attains a fairly high phagocytic value; Lav. II elaborates homologous precipitin, but very little increase in the phagocytic power; while Friedländer produces group precipitation and phagocytosis. These facts, however, offer little assistance in the determi-

nation of these species, since they are not sufficiently clear and bear no relation to the cultural characteristics. Nor does the pathenogenicity seem to clear the sky much. Inasmuch as this study was begun with the idea of examining the pneumonic processes set up by Lav. II, X, and Friedländer, the following is a *resume* of the findings in the lungs of the two babies from whom the first two were isolated, a preparation of Friedländer pneumonia in an adult, and the experimental lesions produced by all three in guinea-pigs.

When compared with the gelatinous croupous pneumonia produced by the Friedländer organism spontaneously in adults, the process produced in the lungs of the babies and experimentally bore no resemblance. The most striking thing throughout was the extensive hemorrhagic extravasation. This was marked also in all other organs. In the lung of the baby from whom Lav. II was obtained this was very pronounced and the experimental lesions were also largely hemorrhagic. The catarrhal process was seen in all the animals, but in the animal injected with Lav. X to the most marked degree. No fibrin formation was observed in any lesion. The Lav. II culture seems to have been the most virulent, since it caused death in the shortest time and gave rise to the most extensive disease. In the lungs of all the animals infected with this organism the lesion assumed the massive type and did the greatest amount of destruction. With the experimental Friedländer pneumonitis the tendency was toward the formation of miliary abscesses, or areas of catarrhal desquamation and leukocytic invasion. The pronounced feature of the Lav. X lesions was the epithelial desquamation and degeneration. The number of the mononuclear leukocytes was in direct ratio to the tendency to hemorrhagic extravasation, and in that case, *i. e.*, Lav. II, where this was at its height, they were in by far the largest number. In the lung of the animal injected with Friedländer showing the small foci of des-

quamation and infiltration, however, the polynuclear type predominated. When the pure desquamative changes were most prominent, as in the case of Lav. X, the two types of cells were almost equally represented. The animals were all injected into the abdominal cavity with twenty-four hours' bouillon cultures. The distribution of the bacteria is not very clear, and it is difficult to say where they lie by preference. It seems, however, that they are most abundant wherever the hemorrhagic extravasation or leukocytic infiltration is greatest. They are frequently seen in the septa and are not abundant where the pure desquamation predominates. Such a distribution, of course, might be expected, since the bacteria were carried to the lungs by the blood stream.

II. A NOTE ON THE EFFECT OF TOXIN AND ANTITOXIN INJECTIONS ON THE PHAGOCYTOSIS OF DIPHTHERIA BACILLI.

This report concerns the results of one experiment on the effects of variously combined injections of diphtheria bacilli, toxin and antitoxin (commercial) upon the phagocytic power of rabbits' blood. The toxin was the filtrate of a four weeks' old culture of the bacterium, and was fatal for guinea-pigs in doses of 1.5 c.c. in forty-eight hours. The results set down in the table are phagocytic averages and not opsonic indices.

Rabbits were subcutaneously injected (in different localities when more than one injection was made) in quick succession and the first observation was made after the lapse of four hours. Both blood and serum were drawn, the former being defibrinated by sodium citrate solution. In preparing the emulsion of corpuscles the same amount of blood was drawn in order to have the number of leukocytes approximately the same. The emulsion of the bacilli was made in normal salt solution and washed twice. In order that the

results might be comparable, the number of bacilli in the emulsion at the three tests was counted, and the figures in the table are on the common basis of the lowest count. In setting the tests 0.1 c.c. of the various emulsions and sera was pipetted into tubes and the whole made up to 0.6 c.c. with normal salt solution. The smears were made after the tubes had been one hour at 37° C.

The first thing which strikes one's attention in looking over the table is the marked decrease in the average phagocytosis at the test made three days after the injection, the negative phase of opsonification. Even in the blood of the animal which had received the antitoxin alone is this true, but to a relatively less degree than in the others.

The immediate (after four hours) effect of the injections seems to be negligible except in the case where the toxin was injected alone. Here the average rose from 3.6 to 4.5, a rise of 0.9. This may have been due to a sudden stimulation of the leukocytes "in vivo" and carried on when the blood was shed; the same thing was not observed with the normal corpuscles and "B" serum, nor in the blood of rabbit "C," which received both bacilli and toxin, probably because the organisms anchored the opsonin stimulated to action by the toxin. The marked drop in phagocytosis after seventy-two hours in this "B" rabbit's blood may be an excessive negative phase due to the presence of overwhelming poison. (This animal and Rabbit "A" died in ten days, preventing the extension of the experiment to five tests as primarily intended.) The lower average with normal leukocytes may be because they had not been stimulated by a virus.

From the reactions of the blood of Rabbits "D" and "E" it would seem probable that the injection of antitoxin into animals has little to do with phagocytosis, since the averages of these bloods throughout permit of comparison with that of "A," which received the bacilli only.

When we look at the reactions which occurred after eight

days we notice an increase over those which were found in the previous test, except with "C" serum and normal blood, a low figure which I am unable to explain. I am also unable to explain the marked rise of the phagocytic average with "C" serum and corpuscles.

The last averages of the rabbit receiving toxin are relatively lower than the averages of the blood of the animals receiving bacteria, either alone or in combination, and lower relatively than the animal receiving antitoxin alone. It would seem that the toxin depresses the action of the opsonins when acting "in vivo," that is, the phase of stimulation is succeeded by a lasting depressing or negative stage.

The results of this experiment are offered with the full realization that they, of themselves, have little value, but they may supplement the work of some other observer or suggest a line of work to him. They were suggested by Prof. Stengel, and it is with his sanction that I offer them.

PHAGOCYTOSIS OF DIPHTHERIA BACILLI.

		4 hours.	72 hours.	8 days.
Normal serum and leukocytes (simultaneously with below) +Bact. diphtheria		1.7	1.2	1.6
A. Injection of washed diphtheria bacilli, 1 c.c. emulsion.	"A" blood and serum + Bact. diphtheria	2.0	1.0	2.3
Before injection 2	"A" serum + normal leuk. + Bact. diphtheria	2.2	0.8	1.7
B. Injection of toxin alone, 1 c.c.	"B" serum and leuk. + Bact. diphtheria	4.5	1.3	1.8
Before injection 3.6	"B" serum + normal leuk. + Bact. diphtheria	2.4	1.0	1.1
C. Injection washed diphtheria bacilli emulsion 1 c.c. and toxin 1 c.c.	"C" serum and leuk. + Bact. diphtheria	3.5	0.5	4.2
Before injection 3.9	"C" serum + normal leuk. + Bact. diphtheria	4.0	1.7	1.0
D. Injection washed diphtheria bacilli emulsion 1 c.c. and antitoxin 250 units	"D" serum and leuk. + Bact. diphtheria	4.6	1.6	3.8
Before injection 4.8	"D" serum + normal leuk. + Bact. diphtheria	5.0	2.0	3.3
E. Injection of antitoxin 250 units	"E" serum and leuk. + Bact. diphtheria	3.5	1.3	2.5
Before injection 3	"E" serum + normal leuk. + Bact. diphtheria	3.4	1.3	2.5

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SOME OBSERVATIONS UPON THE STRUCTURE OF THE SPIROCHETA PALLIDA (SCHAUDINN).

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The object of this communication is to record some observations on the morphology of the spiral body found by Schaudinn and Hoffmann in preparations from syphilitic eruptions. The material at hand consisted of smears from six chancres, three mucous patches, three maculopapules, three secondary variolous syphilides, one venereal wart, sections of one of the mucous patches and of the venereal warts. A comparative study of the secondary eruptions with a chancre (author's case) was made possible by the gift of an excised mucous patch and venereal wart from Dr. Rosenberger, whom I wish to thank at this point.

Pressure preparations were made on slides exclusively, avoiding as much as possible any rubbing which might alter the position of the organisms, or distort them. Tissues were preserved in 4 per cent. formalin.

The staining methods used were: Giemsa (ten minutes' fixation in absolute alcohol and one to two hours' staining), Goldhorn's borax methylene blue, Wright's blood stain,

filtered saturated aqueous solution of gentian violet, iron-hematoxylin, and the silver precipitation method modelled after Levaditi but somewhat modified for use with slide smears. The first two are very good for diagnostic purposes, especially the second when differentiated with Lugol's solution; but for study of the form, shape, and especially the ends of the spirals the last three were found to be the best. The silver precipitation method is as follows: Fixation in 10 per cent. formalin thirty minutes, 95 per cent. alcohol thirty minutes, 1.5 per cent. solution silver nitrate twenty-four hours, pyrogallol solution (pyrogallol 4 per cent., formol 5 per cent.) four hours, wash in running water, clear with alcohol and bergamot oil, and mount. This may or may not be stained. The field is quite dirty but it has been impossible to obviate this so far. The organisms may be seen quite clearly when found free from precipitate. This method is only useful for study and has no value in diagnosis.

It is hardly necessary to go into the percentage of findings in my material further than to say that the results are in accord with those of others. The variations of size will be considered later, but the evidences of flexibility indicated by the position of the spirals in pressure preparations, and the irregularities of staining have been reported many times. These appearances seem to be more characteristic of the Sp. refringens than of the Sp. pallida.

Herxheimer and Loeser have reported the finding of spindle-like bundles and rosette arrangements of these spirochetæ, simulating segmenting trypanosomata. Such an arrangement has never been seen in any of my preparations. In smears the organisms are usually single; two or three may be seen more or less closely intertwined at some point of the length; two individuals are sometimes encountered lying parallel with their coils closely interlocking, giving the appearance of longitudinal division. In tissue they are most frequently single, and when present in large numbers lie more or less parallel to the tissue structure; masses of

spirochetæ are without definite arrangement. The long axis of the body of the organism is commonly straight when seen in tissue, but in slide stains, no matter how carefully made, the spirocheta is most often bent, even to the extent of forming a circle, which fact is not difficult to explain if we imagine one end drying before the other. In all probability these shapes are largely artificial.

Examination with high apochromatics and compensation oculars has not developed any undulating membrane or contractile pore either in the moist or stained (iron-hematoxylin) state.

Evidences of what might be considered longitudinal division have been observed four times in all the preparations studied, while undoubted transverse division has been seen many more times. The transverse division is characterized by the appearance of a palely staining area at or near the middle of the spiral, with subsequent thinning and separation of the extremities into two new individuals. On one occasion transverse division into three elements was noted. It seems that the newly formed or newly forming spirals have more curves in relation to their length than the individuals apparently older.

On the other hand the indications of longitudinal division are not clear, the best example being shown in the drawing (*B*). Here the free end is fine and tapering, while the end near the larger spiral has the same diameter as that body at their point of contact. They must have be enclosely associated, since no power of the microscope at my command could dissolve them at their point of junction. This was seen in a stain from a chancre.

Many times intertwined spirals were met with, but in almost every instance both ends of each body could be discovered by diligent search.

A word will be added here in reference to this matter of division which will have a relation to what will follow. Only the large typical forms of the "pallida" show this simulation

of longitudinal division, the shorter type always segmenting transversely.

When comparing the preparations made from chancres and from secondaries, I was struck with the fact that the forms of the "pallida" met with in the initial sore are more typical and regular in their shape and size than those met in the later manifestations. They are spirals of an average length of 11.14 microns with an average number of windings of 10.2; their curves form the large arc of a small circle. By careful observation with high powers of magnification in all preparations, even the azur stains, one end may be seen to be thicker than the other. The thinner end fades away into a fine filament called by Schaudinn the flagellum, but which appears to be more exactly a continuation of the body of the spirillum, a view expressed by Norris, Pappenheimer, and Flournoy in regard to Sp. Obermeieri. With the silver method this extremity is blunt and has not the appearance of a whip. On one spiral, by this method, a straight tail was seen to come off this finer end and appears to be a flagellum (Fig. 1). The thicker end is not only wider but takes the stain more deeply, especially when the silver or gentian-violet methods are used. A filamentous extension of this end was never observed, nor could any definite structure be made out. Beyond this blunter end no prolongation can be discovered and there seems to be no spot at or near the *fine* end of the body which is comparable to the clubbing, in other words no thickening from which the terminal filament or flagellum comes off. Nor could this terminal filament be traced back into the body of the spiral as a differentiated line. Fig. 1 *A* (gentian violet) and *E* (silver preparation) in the drawing show the appearance of a typical "pallida" from a chancre; and in both, the clubbed and fine ends are easily made out. I was unfortunate in photographing the large form and am obliged to substitute a drawing. Fig. 1 *B* represents longitudinal division, if it be division, proceeding from the fine end of this form.

FIG. 1.—*A*, typical Sp. pallida (gentian violet); *B*, evidence of longitudinal division (gentian violet); *C*, shorter form with regular coils and more equal ends seen in secondaries (silver preparation); *D* and *F*, irregular large type seen in secondaries (silver preparation); *E*, typical Sp. pallida showing how the relations between the ends are maintained in silver preparation; *G*, Sp. refringens (silver preparation).

Schaudinn supposes that when two flagellæ are seen, division is beginning, a reasonable assumption if this spiral be a protozoon. If it be a protozoon one might expect to find a basal body at the root of the flagellum, but such a spot cannot be made out at the fine end of the spiral. The blunt extremity of the spirocheta may contain such a body but this study can offer no elucidation upon this point since

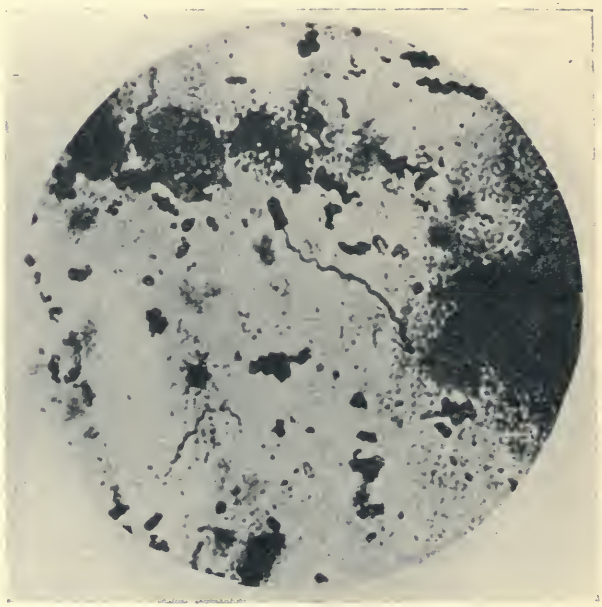

Fig. 2.—Spirocheta pallida, large atypical, by circa 2000 (silver).

sufficiently clear evidences of longitudinal division were observed so seldom. The picture in the drawing was encountered only once. The blunt end *may* be the blepharoplast itself, with the body unstained, the spiral we see being the undulatory membrane or the two latter combined.

In the secondaries, besides the form described above, one meets such types as shown in Fig. 1 *D* and *F*, also in Fig. 2.

These represent some of the atypical spirochetæ which appear to be the same as the ones described above. They have been observed before and explained as artificial productions. Their curves assume for the most part the usual large arc of a small circle, but portions of the length may be found without any curvature. They are not infrequently seen with one or the other end nearly straight, as in the

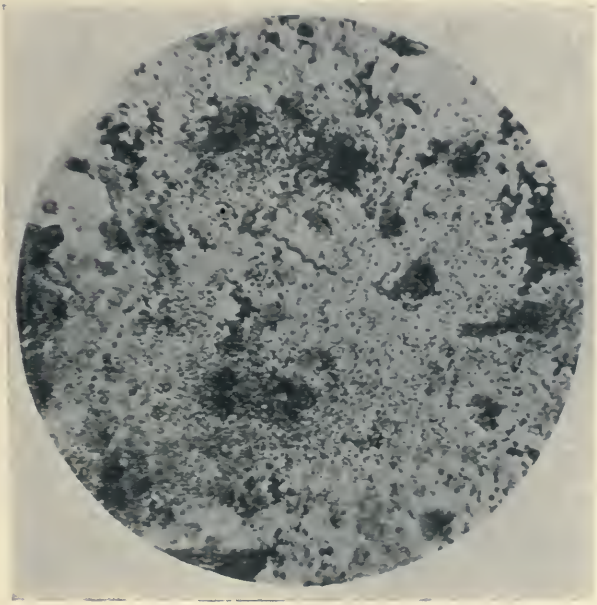

Fig. 3.—Spirocheta pallida, small atypical, by circa 1800 (silver).

pictures. In these forms the thick extremity is commonly well-marked. One of these is seen in about every ten individuals.

Besides these a shorter slightly thicker form (especially in the silver preparations) may be seen in the secondaries; they are depicted in Fig. 1 *C*, also Fig. 3. This form is usually quite regular and both ends have nearly the same

diameter, although one end may sometimes slightly exceed the other; in the photograph one extremity is a trifle clubbed.

It has been suggested that this clubbing is a coil of the terminal filament, but upon search through simple stains no such position of the fine end could be found. With the silver method both ends stain with the same intensity and with gentian violet both ends take the stain badly. The

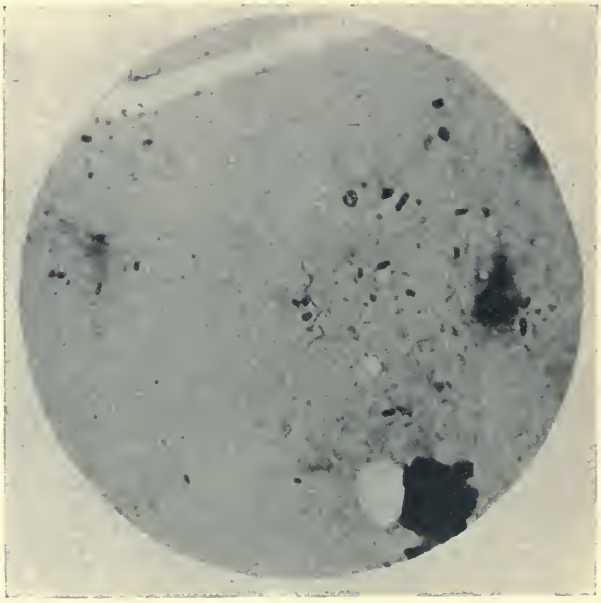

Fig. 4.—Spirocheta refrigens, by circa 1800 (gentian violet).

average length of this small form is 10.1 microns and the average number of windings is eight. These are met with about once among twenty spirals. They may be differentiated from the Sp. refringens by the fineness and apparent flexibility of the latter in the silver mounts, by the facts that the coils of this spiral form a small arc of a large circle and the ends are of the same thickness and take the stain with

equal intensity. The average length of the Sp. refringens is 12 microns and the number of curves averages six (Fig. 4).

The bulbous ends were not found on spirals in smears from Vincent's angina, the normal mouth, carious teeth and an ulcerated surface.

Although these forms were observed in the material at hand it should be emphasized that I lay no importance upon them as characters of sex, age, stage of development, involution, correspondence to the stage of the disease or nature of the lesions. They may assist in settling the nature of the spiral, however. Since none of the essentials of the protozoa have been found, the proper classification remains an open question. Zetnow has lately discovered that the flagella of the Sp. pallida, unlike those of the bacteria, will stain with methylene blue. The term "Sp. pallida" has been used in this paper, since we have no exact nomenclature at present. Realizing the differences from the bacteria and from the protozoa (flagellata) Schaudinn has suggested the name "Treponema." We will hope for further information to establish the identity of the Sp. pallida.

I wish to acknowledge my thanks to Dr. Lavenson for assistance in preparing the photomicrographs.

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A REPORT OF TWO CASES OF RELAPSING FEVER.[1]

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and

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The extreme rarity of relapsing fever in this country justifies the publication of these two isolated cases, which came under our observation in the wards of the University Hospital last fall. They were admitted to the service of Dr. James Tyson, to whom we are indebted for the privilege of making this report.

The earliest authentic accounts of the occurrence of relapsing fever came from Ireland and Scotland during the early part of the eighteenth century. Subsequent outbreaks occurred in those countries during the forties and sixties. The beginning of the nineteenth century found a coincidence of epidemics in Ireland and Scotland, and in 1847 and 1848 the disease made its appearance in London, Liverpool, Manchester, and many other towns of England. Another series of outbreaks was reported in Scotland and England from

[1] Read before the Association of American Physicians, Washington, D. C., May 11 and 12, 1908.

1868 to 1873, since when the British Isles have been free of the disease in epidemic form.[1]

Its presence in Russia was first reported from Odessa in 1833, from which time outbreaks have occurred throughout that country up until the present. Reitlinger says it has reached as far North as Archangel, and that in 1674 St. Petersburg was a great centre for the malady. The larger cities of the Muscovite Empire have been visited frequently. According to Tictin, Odessa is the seat of an epidemic every fifteen or twenty years. It appeared in Finland in 1865, Siberia in 1866, and in Poland in 1868.

Reports of the disease in Germany date from 1847. Widespread epidemics occurred in North and East Germany from 1868 to 1873, and again in 1878 and 1879. Outbreaks occurred in Bosnia and Herzegovinia in 1847, 1887, and 1890, and in 1903.

Few cases have been reported from Asia Minor and the North African States, while in Egypt the disease has been quite prevalent. East and West Africa are cursed with that form known as "tick fever."

Relapsing fever is epidemic in India, and numerous epidemics have been reported from China.

The disease was first introduced to the Western Hemisphere in 1844 by Irish immigrants who landed at Philadelphia. Under like circumstances, it was imported into New York in 1847. Flint discovered fifteen cases in Buffalo in 1850. It was epidemic in New York and Philadelphia during 1869, and from the latter place spread slightly through Pennsylvania during the two following years. This epidemic formed the basis of the extensive clinical studies made by Pepper and Rhoads. California was afflicted with an epidemic among the Chinese in 1874.

In South America the disease first appeared in Peru in 1854, and spread to Chili and Bolivia in 1856. A few cases

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[1] Hirsch's Handbook of Geographical and Historical Pathology, vol. i.

have been reported from Cuba, Mexico, and Panama in recent years.

Griesinger, in 1853, was the first to call attention to the relationship of relapsing fever to bilious typhoid, a clinical entity which was observed and described in many of the above-cited epidemics. He looked upon them as modifications of the same morbid process. After the discovery of the causal agent by Obermeier, in 1873, Moschutkowsky, by inoculation experiments, proved the communicability of the disease, and likewise the identity of bilious typhoid and relapsing fever.

Case I.—J. Y., aged twenty-three years, white, and a native of Turkey, was admitted to the hospital September 23, 1907.

Chief Complaints. Headache and general malaise.

Personal History. Patient was born in Turkey and went to a native school for seven years, after which he spent two years in St. Paul's College, working as a carpenter for his tuition. He came to this country from France on September 18, 1907; he had been in France about one month, going there from Turkey. Smokes moderately, but does not use alcohol; denies having had any venereal disease.

Family History. Father and mother are living in Turkey; five sisters and one brother living, and well. No history of renal, tuberculous, malignant, or cardiac disease.

Previous Medical History. Patient does not remember having had any of the diseases of childhood. He states that in recent years he has had several attacks of fever, accompanied by headaches. These attacks resembled his present illness. They usually occurred in the late summer and lasted anywhere from a few days to two weeks. During the attacks the abdomen became hard, there were severe headaches and general malaise, and the bowels, as a rule, were loose. Patient has had no illness for the past two years, except a slight rise of temperature while on the steamer coming from France.

History of Present Illness. The onset occurred during the afternoon of September 20, when patient was taken with severe headache and felt very tired. He went to bed, and toward the evening became feverish, and at times very dizzy. He took a cathartic, and in consequence his bowels were loose all of Saturday, previous to which time they had been regular. He was confined to bed all that day, and continued to suffer with headache and general malaise. He states that his head felt very heavy and that he was very weak. All of yesterday the symptoms continued. There was no nose-bleed, no abdominal pain, no nausea.

Physical Examination. Patient is a fairly well-nourished male, with fair muscular and bony development. There is no jaundice, cyanosis, or edema; no pallor of the visible mucous membranes. The skin has a bronze hue. The pupils are equal, and react to light and accommodation. The tongue is coated with a whitish fur; the breath is foul; the teeth are in fair condition. There are visible pulsations in the neck. The chest is fairly developed, and expansion on both sides is equal. There are no abnormal prominences. Tactile fremitus is about the same throughout; percussion gives a clear resonant note all over the chest, and there is a normal vesicular murmur on auscultation. The pulse is soft and remarkably dicrotic. The cardiac dulness extends from the third rib to the right border of the sternum to the midclavicular line. The apex beat is not palpable; the heart sounds are weak and distant; a faint systolic murmur is heard at the apex, and is not transmitted. The liver dulness extends from the upper border of the sixth rib to the costal margin; the splenic dulness extends from the eighth to the twelfth rib, between the anterior and posterior axillary lines. The spleen is not palpable. The abdomen is negative. The extremities are negative.

Urine analysis revealed a trace of albumin, numerous light and dark granular casts, mucus, and leukocytes.

Blood Count. Hemoglobin, 47 per cent.; erythrocytes, 3,550,000; leukocytes, 4700. The Widal reaction was nega-

tive. Examination for malarial parasites was negative. Blood smears stained by Wright's method revealed the presence of the spirochæte of Obermeier in small numbers. The spirochæte were found at 3 P.M. of September 24; at 4.30 P.M. numerous preparations of the patient's blood were made, but examination of these failed to discover any spirochæte. The patient's temperature at 3 P.M. was 105.2°; at 6 P.M. it was 103.2°. At this time the patient was tubbed, and at 6.30 P.M. his temperature was 99.3°; at 9 P.M. it was normal, and at 12 midnight it had dropped to 95°. The following day, September 25, the patient felt quite comfortable. The systolic murmur which was heard during the height of the fever had disappeared. The spleen remained about the same size.

On October 4, or ten days after his crisis, he felt more tired than usual, but otherwise was quite normal. There was no elevation of temperature, and examination of the blood proved negative. For nineteen days after his crisis he ran a subnormal temperature. In all other respects his convalescence was unnoteworthy, and he was discharged cured on October 19.

CASE II.—J. M., aged twenty-two years, white, and a native of Armenia, was admitted to the hospital on October 2, 1907.

Chief Complaints. Headache, general abdominal pain, and malaise.

Social History. Patient was born in Turkey, and went to a native school until he was sixteen years of age, when he entered St. Paul's College and worked as a tailor for his tuition. He came to this country about fourteen months ago, and has been working at his trade ever since; does not use alcohol or tobacco; denies any venereal history.

Family History. Father and mother have lived in this country for about one year; they are in good health; two brothers and one sister are living and well. No history of tuberculous, cardiac, or renal disease.

Previous Medical History. Patient states that he had several diseases during childhood, but cannot recall any of them

by name. He has always enjoyed fairly good health. Four years ago he had an attack of fever, which lasted for five weeks; this was accompanied by a spotted rash. Since then his health has been good.

History of Present Illness. On the arrival of J. Y. (Case I) in this country, September 18, 1907, he went to live with this patient, and slept with him from September 18 until his admission to the hospital on the twenty-third day of that month. On September 20 Case I was taken with his attack of fever, and Case II slept with him three nights after the onset of the disease. This patient's illness started rather suddenly on September 30, or ten days after first exposure. The attack was ushered in with a chill, after which the patient went to bed. He had no pain, but a general feeling of discomfort and more or less chilliness. On the following day he had quite a little general abdominal pain, accompanied by fever and rather severe headache. His bowels were constipated, and he was ordered a cathartic, which acted favorably the next day. On October 2 the headache and fever continued, and, in addition, he had severe attacks of abdominal pain. There were no prodromal symptoms of typhoid.

Physical Examination. Patient is a fairly well-nourished male, with fair bony and muscular development; no edema, cyanosis, or jaundice. The skin is of a dark hue, with slight cutaneous eruptions at different parts of the body. There is no enlargement of the superficial lymphatics. The pupils are equal and react to light and accommodation. The tongue is coated with a whitish fur, the breath rather foul, and the teeth in good condition. There is visible pulsation in the vessels of the neck. The chest is fairly well developed. Respirations are somewhat rapid and shallow, and expansion on both sides is equal. Percussion gives a clear note posteriorly and anteriorly on the right side; on the left side resonance is slightly impaired from the clavicle to the fourth rib, over which area the breath sounds are somewhat harsh and prolonged, although there is harsh breathing, especially

anteriorly, throughout both lungs. Tactile fremitus is about the same throughout. A few fine moist rales can be heard scattered over both sides. The cardiac dulness extends from the third rib to the midsternal line, to the midclavicular line. At each heart beat a precordial wave can be seen. The apex is visible and palpable in the fifth interspace just within the midclavicular line. The heart sounds are rapid but strong. There is no murmur. The second pulmonic sound is accentuated. The pulse is poor and markedly dicrotic. The liver dulness extends from the lower border of the fifth rib to the costal margin. The speen is enlarged to percussion, but is not distinctly palpable. On admission yesterday, however, the spleen was palpable. The abdomen is slightly tympanitic; otherwise it is negative. The extremities are negative.

Blood Count. Hemoglobin, 85 per cent.; erythrocytes, 5,820,000; leukocytes, 15,600; Widal reaction was negative; preparation of the blood stained by Wright's method revealed the presence of the spirochæte of Obermeier in moderate numbers.

Urine Analysis. This revealed a trace of albumin, some mucus, leukocytes, and epithelial cells, but no casts.

The temperature ranged from 101° to 105°, with a proportionate pulse rate and a disproportionately rapid respiration rate until October 6, which was seven days after the onset. On this day the temperature began to fall rapidly at 6 P.M., and at midnight had reached 97°. Patient did not feel greatly improved in spite of this drop in the temperature. He vomited once, and nausea was noted throughout the evening. The skin was quite moist. From October 6 until October 13 the patient gained rapidly, and on October 12, except for a little weakness which was rapidly disappearing, he felt entirely normal. His appetite was good. On this date the spleen was decidedly palpable. On October 13 his temperature rose from 98° at noon until it reached 103° at 9 P.M. This temperature rise was accompanied by malaise, and the

patient went to bed. The face and conjunctivæ were quite flushed; the tongue was coated, the skin hot and dry, and the spleen rapidly increased in size until it reached one-third the distance from the costal margin to the umbilicus; his subjective symptoms, however, were much less than his high temperature would lead one to expect. No backache or headache were complained of. The heart sounds were rapid but clear. The adomen was tympanitic. Calomel was prescribed. Careful examination of the blood for spirochæte failed to discover them. The temperature ranged between 100° and 104.6°, with a proportionate pulse and a disproportionately rapid respiration rate, from October 31 until October 16, when it fell by rapid crisis from 104.6° at 12 noon to normal at 6 P.M., and to 95° at three o'clock the following morning. There was a concomitant but not proportionate drop in the pulse and respiration. On the following day, October 17, the spleen had markedly decreased in size. Examination of the blood proved the presence of spirochæte, but in rather scant numbers, on October 14, 15, and 16, the three days of the attack. From the date of his crisis, October 16, until the date of his discharge, October 27, the patient went through an unnoteworthy convalescence.

Kolle and Wasserman give the incubation period of relapsing fever as seven days. In the first case it was quite impossible to judge of the length of the incubation period, but the second case, having slept with the first case while in fever on the nights of September 20, 21, and 22, and having developed the disease suddenly on September 30, shows quite clearly that here the incubation period was confined to an interval of from seven to ten days in length.

Oks averaged the statistics of twelve observers, and found that one febrile period occurs in 37.7 per cent. of the cases, two febrile attacks occur in 54.3 per cent., and three in 14.2 per cent. Our first case had no relapse, and our second case had but one.

According to Meschede, the average length of the febrile and afebrile periods, from observation of 360 cases, was as follows:

	I.	II.	III.	IV.	V.
Febrile . .	7—6	5— 4	4— 3	3—1	1—0
Afebrile . .	7—8	9—10	11—12		

The only febrile period in our first case lasted five days. In the second case the first febrile period had a duration of seven days in length, and the second febrile period was three days in duration. Mocszutkowski[1] states that the maximum duration of the apyretic periods is twelve days, and that if, after a period of this duration has passed, there occurs another febrile attack, it should be attributed to re-infection.

The first case ran a subnormal temperature for nineteen days after its crisis; the second case, during the afebrile interval, ran a slightly subnormal temperature; and for sixteen days after his second crisis the temperature was markedly subnormal.

Heydenreich and Ouskow[2] state that there is a considerable leukocytosis during the febrile periods. Brown,[3] on the other hand, noted a slight leukocytosis during the afebrile periods and a drop to normal during the febrile periods. Our first case showed a normal leukocyte count just before his crisis. The second case showed a leukocytosis of 15,900 on the fourth day of his first febrile period.

Unfortunately, a case of smallpox developed in the ward where these patients were confined on October 5. The ward was strictly quarantined, and our observation of the cases was thereby greatly handicapped.

Enlargement of the spleen is usual during febrile periods, with a diminution toward normal during afebrile periods, and a gradual decrease after convalescence sets in to normal. In the first case there was no palpable enlargement of the

[1] Kolle and Wasserman, Band iii.
[2] Ibid.
[3] Presbyterian Hospital Reports, 1906.

spleen, while in the second case, during the first febrile period, although the spleen was large, it was definitely palpable only at times; but in the afebrile period, six days after his crisis, the spleen could be readily felt. At the onset of the relapse the spleen rapidly increased in size until it had reached one-third the distance from the costal margin to the umbilicus, and on the day after the second crisis the spleen showed rapid decrease in size.

At present the principal distribution of the disease is East and West Africa, Europe, and India. Dutton and Todd considered the European and African fevers to be identical, and this view was more or less shared by Koch, who, however, recognized minor differences. On the other hand, Novy and Knapp, according to the morphology of the spirochæte, and through differences in animal reactions, differentiate the African variety from the European, and both of these from the Indian variety described by Turnbull, Walker, Powell, and others. These different forms they look upon as constituting a group of recurrent fevers. Some writers recognize a fourth variety, the American, to the cause of which Schellack[1] gives the name Spirochæte novyi.

There has been considerable argument as to what place in Nature the spirochæte occupy. Schaudinn, Prowazek, Keysillitz, Herxheimer, and others regard them as belonging to the protozoa, and nearly related to the trypanosoma. Koch, Borrel, Laveran, Zettnow, Novy and Knapp, Norris, Pappenheimer and Flournoy, Thesing, and many others look upon them as true bacteria, and in no way related to the trypanosomes. Kolle and Hetsch place them as a special class of microörganisms standing midway between the bacteria and the protozoa.

The arguments for and against their animal or vegetable character have been based on the following attributes: first, presence or absence of a nucleus, micronucleus (centrosome,

[1] Arb. a. d. k. Gesundtsamte, xxvii, No. 2.

or blepharoblast), and undulating membrane; second, the character and distribution of cilia; third, their behavior in the presence of certain chemical substances—and here might be included the phenomenon of plasmolysis; fourth, their artificial cultivation; and fifth, the means of their transmission. Nearly all of the evidence today seems to be in favor of their belonging to the Bacteria, and from our limited observation this is the view we are inclined to take. In our specimens we could not make out any cell structure whatever, such as nucleus, micronucleus, or undulating membrane.

Vladimirff[1] describes the spirochæte of Obermeier as a fine, spirally wound thread, somewhat pointed at the ends, whose greatest thickness is about 1 mu, and whose length varies from 10 to 20 to 40 mus, and even more. The number of spiral turns is variable (6 to 20), and in general is more or less proportional to the length of the individual. The radius of the spirals varies so widely that it is hardly possible to give an average length for the same. Norris[2] says the spirochæte in his case varied considerably in length and in the number of spiral turns. Numerous transitions existed in the closeness of these turns. Many of the longer forms showed an attenuated or unstained portion in the centre, suggesting fragmentation or fission. The spirochæte from our cases did not vary greatly in length or in the number of turns. Most of those we observed were about 20 to 30 mus in length, and showed from seven to ten spiral turns. Long forms were seen, and at times in these could be made out the unstained breaks referred to by Norris, which truly suggested transverse division of the cell.

The movements of the spirochæte are of three distinct kinds: the first, and perhaps the most important, is a rapid revolution around the long axis of the organism, first in one direction and then in the other; this might be compared to the motion of a corkscrew. The second variety of movement is a "fore-

[1] Kolle and Wasserman, Band iii.

[2] Proceedings of the New York Pathological Society, 1905 and 1906.

and-aft" shooting motion, whereby the organism darts ahead and as rapidly back; the third form observed is a slightly bending, or waving motion. It might very well be that the darting "fore and aft" shown by the organism when moving fairly rapidly is due to a driving effect of the screw-like motion around the long axis.

In fresh preparations of the blood from our two cases their movements were so rapid that no sign of the spirochæte could be seen, and it was only after they had quieted down at the end of twenty-four to thirty-six hours that the organisms could be observed at all. We succeeded in slowing their movements by placing the preparation on ice for about half an hour. In addition to those already noted, we could see running over the parasite a wave that suggested the movements of numerous cilia. When the organism had quieted down considerably, so that the revolutions around its long axis were quite slow, there was no "fore-and-aft" motion or darting to be observed.

Novy and Knapp noted a more or less continuous change of place in the movements of the spirochæte they studied. Koch, on the other hand, thought that this change of place did not occur, but that the organisms occupied approximately the same field for quite a time. According to our observations, we are inclined to agree with both of these observers. It is quite true that the organism remains in approximately the same field for a longer or shorter period of time; but, on the other hand, it is true that it does move from one field to another.

Zettnow,[1] in the Spirochæte duttoni, was able, through a special staining method, to demonstrate numerous cilia and flagella on the sides and ends of the organism. Fraenkel,[2] using the same staining procedure, showed their presence on the organism of American recurrent fever. Novy and Knapp

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[1] Kolle and Wasserman, Band iii.

[2] Hygienische Rundschau, vol. xvii, No. 5.

speak of an end cilium, or flagellum, on the variety which they studied. In the organisms we observed, at times we could make out what we thought to be a short, thick cilium at either end of the individual. This cilium was brought out by Wright's method of staining, but not at all distinctly. Otherwise, in the stained preparations no cilia were seen.

Norris succeeded in cultivating the spirochæte on fresh blood to which sodium citrate had been added. They grew in the first transplant slightly, but not in the second. Levaditi obtained successful cultures of the organism by inoculating collodion sacs filled with 2 c.c. of monkey serum heated to 70°, and placing the sealed sac in the peritoneal cavity of a rabbit. He carried through eight transplants in thirty-six days. If these same sacs were put into the peritoneal cavity of a rat degeneration forms of the organism appeared.[1] Novy and Knapp have been able to keep the organism alive and growing in their laboratories for over a year. Their method is a modification of Levaditi's idea. They inoculated collodion sacs filled with 2 or 3 c.c. of defibrinated rat's blood, and, after sealing, placed the sac in the peritoneal cavity of a white rat. The organisms in this method retained their form and multiplied very considerably. Transplants are made from one sac to another every three or four days.

We endeavored to cultivate the organism by ordinary methods, including aërobic and anaërobic, and also by the method of Novy and Knapp. None of our efforts, however, were successful. During two trials with the Novy-Knapp method we found at the end of three days that the sacs showed the presence of an extremely varied flora, evidently due to a slip somewhere in our technique. Some forms of spirilla were observed, but these organisms were all short and did not show more than two, or possibly three, spiral turns.

The staining methods made use of by us were Wright's and carbol fuchsin. The former method brought out the organism clearly, but revealed no particular internal structure.

It is now definitely established that the tick Ornithodorus

[1] Kolle and Wasserman, Band iv.

moubata carries the infection of African relapsing fever. Koch found on his expedition to Africa that if Europeans avoided the caravan routes where the infected ticks abound, they would escape the disease.

The mode of transmission of the spirochæte of Obermeier so far remains a problem, but in this connection it is interesting to note the work of Tictin[1] and Karlinski.[2] The former found that after bedbugs had sucked relapsing fever blood, if within forty-eight hours they were crushed and the obtained blood injected into monkeys, the latter were infected with the disease; but after forty-eight hours the results were negative, and at this time the spirochæte had lost their motility. Karbinski found that the spirochæte resisted the action of the digestive juices of the bedbug and still infected the insect thirty days after it had sucked the blood of a relapsing fever patient. We endeavored to carry out some experiments with bedbugs, but the scruples of the hospital authorities would not give this wingless pest a chance.

Monkeys, white mice, rats, and guinea-pigs are susceptible to infection with both Spirochæte duttoni and Spirochæte obermeieri. Rabbits, dogs, and ponies have been infected with the African variety. Fraenkel was able to infect three starved mice with Spirochæte duttoni by feeding to them the cadaver of an infected mouse. We succeeded in transferring the infection from the second case to white rats during both the initial attack and the relapse.

Undoubted cases have been reported where the mother has transmitted the Obermeier spirochæte to the fetus through the placenta.

The organisms appear in the blood usually with the onset of the fever. Some authorities have noted their first appearance in the circulation as long as three days after the initial rise of temperature, while others have discovered them some hours before the paroxysm. They are found in the circulating blood and in the spleen during the febrile periods, but

[1] Jour. Trop. Med., vol. v.
[2] Zentralbl. f. Bakt., 1902.

as yet it is a question what becomes of them during the afebrile periods. As a rule, they disappear shortly before the crisis, but many observers have found them at varying times up until three days afterward. Naunyn related a case in which the organisms became very sparse after the crisis, but had not entirely disappeared fourteen days thereafter.

In our first case the diagnosis of the disease was made through examination of a stained blood specimen at 3 P.M. At 4.30 P.M. numerous blood preparations, both stained and fresh, were made, but persistent and careful examination failed to discover any organisms. The hour of 3.30 marked the beginning of the crisis in his case, and nine o'clock that evening found the patient's temperature normal. In the second case the organisms disappeared with both the first and second crises, and were not to be found during the afebrile periods. In this case, a short time after the onset of the relapse, examination of the blood for spirochæte proved negative, but was positive on the following morning.

Spirochæte live for variable lengths of time outside of the organism. If the blood be taken during the early part of the initial attack, the parasites will live, and be actively motile for a long period. In our second case they were quite active after seventy-two hours in an ordinary sealed wet preparation at room temperature. Toward the end of the febrile period it will be found that the organisms soon lose their motility and die quite rapidly. This would seem to speak for the formation of antibodies in the serum.

Koch,[1] as well as Dutton and Todd, concluded from their observations that an attack of tick fever conferred immunity. Natives of tick-infected districts are not susceptible to the disease, whereas Europeans are. That this is not a natural race immunity is proved by the fact that natives who live at some distance from the infected caravan routes when first exposed are just as susceptible as Europeans. Koch[2] and Kudicke, through experiments with the African spirochæte,

[1] Deut. med. Woch., 1905.
[2] Berlin. klin. Woch., 1906

showed that this acquired immunity occurs in monkeys. Norris and Novy demonstrated its occurrence in rats infected with Spirochæte obermeieri, and Breinl,[1] working with both the African and European forms in monkeys and rats, observed that infection with one form did not confer immunity for the other. This fact he interpreted as strongly favoring their distinction.

Gabritchewsky,[2] in an interesting series of experiments, was able to confer immunity to mice through vaccination. He found that vaccination with a species of spirochæte found in the chicken would not confer immunity to infection with Spirochæte obermeieri. He demonstrated that the injection of antispirochæte horse serum conferred immunity to infection for at least twenty-four hours. How much longer such immunity lasted was not determined.

The immune serum of rats has been proved to possess bactericidal and agglutinating properties by both Norris[3] and Novy[4] and their co-workers. These properties have been demonstrated in human serum by Karlinski,[5] and Hoedlmoser,[6] and the latter endeavored to make use of them in diagnosis. These bactericidal and agglutinating powers fade after four to six months.

Novy and Knapp[7] have noted a pronounced curative action on the part of immune blood in white rats. If a rat whose blood shows the presence of numerous spirochæte to the field be injected with 2 c.c. of immune blood, the spirochæte disappear entirely within an hour.

Gabritchewski[8] injected patients with 40 to 60 c.c. of serum from an immunized mule, and found that the number, duration, and severity of the febrile attacks were beneficently influenced.

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[1] Lancet, 1906.
[2] Centralbl. f. Bakt., etc., vol. xxxviii.
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