

FLEXNER (S.) *With the author's compliments.*  
al

CERTAIN FORMS OF INFECTION IN TYPHOID FEVER.

BY

SIMON FLEXNER, M. D.

*presented by the author*

550.

[Reprinted from *The Johns Hopkins Hospital Reports*, Vol. V.]



CERTAIN FORMS OF INFECTION IN TYPHOID FEVER.

BY

SIMON FLEXNER, M. D.



JOHN MURPHY & CO., PRINTERS,  
BALTIMORE.

## V.—CERTAIN FORMS OF INFECTION IN TYPHOID FEVER.

By SIMON FLEXNER, M. D.

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

- A. Typhoid septicæmia associated with focal abscesses in the kidneys due to the typhoid bacillus.
- B. General Infection with the typhoid bacillus; perforative peritonitis caused by the streptococcus pyogenes.
- C. Typhoid Fever associated with miliary abscesses in the kidneys due to the typhoid bacillus. Non-transference of typhoid bacilli from mother to fetus.
- D. Typhoid Fever with perforation of the intestine; acute peritonitis with bacterial poly-infection.
- E. Typhoid Fever with perforation of the intestine (3rd week of the disease); acute streptococcus peritonitis and streptococcus septicæmia; absence of typhoid bacilli from cultures.
- F. Typhoid Fever; death from hæmorrhage (6th week of the disease). Disappearance of typhoid bacilli. Infection with bacillus coli communis.

The distribution of the typhoid bacilli in the body in typhoid fever must be considered as still presenting interesting features. That the bacilli may be present in the blood of these patients seems, in view of certain observations (Karlinski, Vincent), very probable, although the work of the earlier investigators (Rüttimeyer, Almquist, Pasquale, Guarnieri, Neuhaus), who claimed to have cultivated the organism from the general blood and that of the rose-spots during life, has, through later studies (Janowski, Stagnetto, Grawitz, Fränkel and Simmonds, Sittman), been discredited. It is, however, significant that the observations in which typhoid bacilli were believed to have been cultivated from the blood during life, and again at autopsy, as in the case of Karlinski, date from a time when the means of distinguishing between these organisms and certain other bacterial varieties, much resembling them, were not so complete as now.

It is a well-known fact that all cases of typhoid fever do not complete their course as a simple infection, by which is meant that the

morbid process, from its inception to its close, is due entirely to the action of the typhoid bacillus. The possibility of the interaction of other micro-organisms, secondary invaders, is now not to be doubted, although the effects of these subsidiary organisms may be comparatively slight, and entirely limited to the intestinal tract. It must always be a matter of importance—the question as to just what part of the intestinal lesions are caused by the typhoid bacillus acting alone, and how much of these are attributable to other micro-organisms, chief among which are the pathogenic staphylo- and streptococci. There are instances, however, in which the secondary micro-organisms come to play a more active part, as are seen in cases of metastatic abscess formation and inflammation due to the pyogenic bacteria (spleen, mesenteric glands, heart valves), the portal of entry into the system doubtless being the ulcerated intestinal tract; and in cases of perforative peritonitis the importance and significance of these organisms are hardly to be overestimated.

Among the fatal cases of typhoid fever which have come to autopsy in the Hospital, those here given have been chosen on account of their possession of features which lend interest to them in connection, first, with the distribution of the typhoid bacilli in the body and the unusual localized lesions directly attributable to them, and, second, the nature, distribution and effects of the secondarily invading bacteria.

CASE I.—*Typhoid Septicæmia associated with focal abscesses in the kidneys, due to the Typhoid bacillus.\**

In individuals who have died of typhoid fever, provided death has occurred not too late in the course of the disease, it is usually possible to cultivate the typhoid bacillus from various organs, among which the mesenteric glands, spleen, liver and kidneys (not to refer to the intestines) may be mentioned. The experience of this laboratory indicates that the bile is particularly rich in the typhoid organisms, and the autopsy records of the Hospital contain many instances in which they have been isolated from this fluid in pure culture. Now that Quincke and Stahlen have directed attention to it, the bone-marrow will doubtless be found to be a common habitat of the

\* This case, including plates and bibliography, appeared in the *Journal of Pathology and Bacteriology*, April, 1895.

organisms in the disease; and in several recent autopsies I have found them in considerable numbers in this situation. In cases of abortion they have been found in a conclusive number of cases to have passed through the placental barrier (Widal and Chantemesse, Hildebrand, Eberth, Ernst, Janizewski, Frascani), and to be present in the organs and even in the blood of the fœtus.

The bacillus of typhoid fever is, therefore, distributed in such a way as to indicate that it has, at some time during the disease, been present in the blood current. Yet it must be remembered that it is not, unless most exceptionally, found in the blood outside of organs, even at autopsies. The rarity of this condition is sufficient apology for recording cases in which a general typhoid infection of the body existed at autopsy.

This case presents, in addition, another feature which is perhaps of interest. The recent contributions to the study of the relation of the typhoid bacillus to local foci of suppuration have tended to show that in a variety of inflammatory processes this organism alone is concerned. This view, first advanced by A. Fraenkel, has, as is well known, been vigorously contested by Baumgarten and E. Fraenkel. The latter have contended that other bacteria, particularly the pyogenic cocci, were present, along with the typhoid bacillus, and were overlooked or had died out at the time of the examination. Now in the kidneys in this case a number of abscesses existed in which no other micro-organisms than the typhoid bacilli were demonstrable. Any assumption that other bacteria had been present is not to be reconciled with the short duration of the illness; and the numbers and relation of the typhoid bacilli to the foci of suppuration leave no doubt of their action.

The clinical course of the case was unusual. I am enabled, through the kindness of Dr. Osler, to whose ward the patient had been admitted, to give an abstract of the clinical history.

*CLINICAL SUMMARY.*—*Illness of two weeks' duration before admission; moderate fever; enlarged spleen; rigidity of muscles of neck and of right arm; mental dulness and delirium; cutaneous hyperæsthesia and increase of the reflexes; small amount of albumin, with red blood corpuscles in the urine; no diazo-reaction; for 3 days before death normal temperature; parotitis.*

Susan B., æt. 18, colored; admitted to the medical wards, 23rd April, 1894, complaining of headache, pains in the abdomen, and general weakness.

The patient is an only child; her father is living, her mother is dead, but from what disease could not be learned. There is a history of tuberculosis in the father's family.

She does not remember ever having had any of the diseases of childhood; was always strong and well; menstruated first at 17, and has been regular. Five weeks ago she began to have sick headaches, but without vomiting. She kept at work, though feeling wretched, until 2 weeks ago, when she began to have pains in different parts of the body, and weakness. She was restless and feverish, without appetite, slept very badly, and had diarrhœa. The patient was so dull and stupid that it was only with difficulty that a history could be obtained.

On admission at 5 p. m. her temperature was  $103.7^{\circ}$ ; the pulse 120, soft and regular. She vomited a dark greenish material. That night she was restless, but the temperature did not rise above  $103.5^{\circ}$ . She was sponged, and whisky was administered. The urine obtained and examined on the evening of admission was slightly brownish in color, acid; specific gravity, 1010; it contained a small amount of albumin, and microscopically showed leucocytes and red blood cells. No casts were seen; the diazo-reaction was not present.

24th April.—The patient is a small, thin, poorly nourished girl, and looks as if she had been ill some time. She lies on her back with the eyes half closed, and the face has a dull, typhoidal expression. The temperature was  $102.6^{\circ}$  at 8 o'clock; the pulse was 116, regular. The abdomen is not distended, but is held rather tense. The spleen is palpable, fully 4 cm. below the costal margin. During the examination the patient complains much of tenderness everywhere. The examination of the lungs and heart showed nothing abnormal. The first sound at the apex was a little prolonged and dull. The patient had one stool since admission, which was small, firm, and somewhat clay-colored.

25th April.—The patient had a better night; the temperature for the greater part of the last 24 hours has been below  $102^{\circ}$ . The urine is dark amber-colored, acid in reaction; specific gravity, 1010; no diazo-reaction; a small amount of albumin; contains leucocytes and

a small number of red blood corpuscles. The patient had one movement to-day, in which there was a small fæcal concretion, concentrically laminated. She had through the day a good deal of vomiting, and she took her nourishment—milk and albumen water—very badly.

26th April.—Patient has vomited less; temperature has not reached  $102^{\circ}$ ; no movement from the bowels; pulse is feeble, and ranges from 112 to 120. Only 400 cc. of urine was collected; she passed some involuntarily. Towards the afternoon of the 26th it was noticed that the head was much retracted, and held very stiffly, and the right arm was in a condition of extension, somewhat rigid, and any attempt to flex it caused pain.

27th April.—The temperature to-day was lower, and at 6 a. m. reached  $98.9^{\circ}$ , and the highest throughout the day was  $100.6^{\circ}$  at 6 p. m. She vomited repeatedly, talked incoherently, and moaned a great deal. She had one small stool at 10 p. m. She seemed very sensitive to the slightest touch. The retraction of the head and the rigidity of the arm persisted.

It did not seem possible to decide as to the nature of the case. Though it looked more like typhoid fever on her admission, the retraction of the head and rigidity of the neck muscles, the general sensitiveness and the rigid extension of the right arm suggested, very naturally, cerebro-spinal meningitis. The blood was carefully examined for malarial organisms, and cover-slips were stained for tubercle bacilli; the leucocytes numbered 6,000 to the cubic millimetre. The urine was yellow, acid, distinctly cloudy, with heat and nitric acid; no diazo-reaction. Microscopically there were many epithelial cells, chiefly from the bladder, some leucocytes, and a smaller number of blood cells. The sediment was collected and stained for tubercle bacilli with negative result.

28th April.—On account of the vomiting she has been fed, for the past 24 hours, by rectal injections. At the morning visit she was lying with the head thrown back, and resisted slightly any attempt to bend the neck. She replies to questions in a confused and hesitating manner. There is no photophobia; the pupils are equal and react to light. After being aroused, she lies with her eyes open, but with rather a staring expression. She moves the left arm readily, but the right is extended and motionless by her side. It is not so rigid to-day, though she winces and cries out when any attempts are

made to flex it. The deep reflexes in the left arm are active; in the right they cannot be tested. The knee jerks are a little exaggerated, and there is well-marked ankle clonus on both sides. The abdomen is not swollen; not especially tender. As satisfactory an examination as possible was made of the uterus, but nothing abnormal could be detected. The temperature fell to  $98.2^{\circ}$  this morning, and the highest registered through the day was  $100.1^{\circ}$ . The patient had one well-formed stool.

29th April.—The rigidity of the muscles of the neck is still marked, and the stiffness in the right arm persists. Mentally she seems somewhat clearer, says she has no headache, and puts out her tongue when asked. From 10 o'clock last night the temperature has been a little below  $99^{\circ}$ . She has been passing urine involuntarily.

30th April.—The temperature continues normal; was  $98.2^{\circ}$  at 8 p. m. and  $98.4^{\circ}$  at 8 this morning. The pulse is feebler, just 100, and not irregular. There is no strabismus. She moves the left arm about freely; the right arm shows slight clonic movements, and at intervals becomes quite rigid. The ankle clonus could not be obtained to-day. The abdomen is flat, and not more sensitive than in other parts.

May 1st.—Until 8 a. m. the temperature was about  $99^{\circ}$ . This morning it was noticed for the first time that there was a soft swelling in the left parotid region, which is not painful. The vomiting has been very obstinate. She retains the nutritive enemata. To-day the right arm is easily flexed, and can be moved in all directions. The heart sounds are, and have been, perfectly clear. There are few râles at the bases of the lungs, but there has been no diffuse bronchitis. The temperature rose a little through the day, and reached  $100.2^{\circ}$ ; the pulse became more rapid and feeble, and she died at 5.30.

Autopsy 17 hours after death.

ANATOMICAL DIAGNOSIS.—*Typhoid fever (ileo-typhus and colotyphus); hæmorrhagic enteritis; acute splenic tumor; multiple abscesses in the kidneys; parenchymatous degeneration of the liver and kidneys; purulent infiltration of the parotid gland; œdema of lungs and glottis.*

Body of a small, sparely-built negro girl. Subcutaneous fat in small amount. Muscles bright red in color.

Peritoneal cavity.—No excess of fluid. The intestines are distended.

Pleural cavities.—Both dry. The lungs are free from adhesions. Both are voluminous.

Pericardial cavity.—No excess of fluid, and both layers of the pericardium are smooth.

Heart.—Right auricle and ventricle contain dark and partly decolorized clots. In the left ventricle a small, partially decolorized clot. All the valves are normal.

Lungs (Right).—The upper and middle lobes are œdematous; the lower lobe is congested. The bronchi are filled with frothy serum. Vessels at base free. (Left).—Lower lobe congested; the upper lobe œdematous. Bronchi contain frothy serum; vessels at base free.

Liver.—Weight, 1700 grms. It is soft, swollen, and the sharp edges are rounded. On section it is fatty in appearance, the lobular markings being obscure. The bile is thin, light-colored, and contains a granular sediment.

Spleen.—Weight, 420 grms. The capsule is thin and distended. On section the substance is soft and pulpy; the follicles are visible and apparently not enlarged.

Mesenteric glands.—Swollen and congested.

Adrenal glands.—Apparently normal.

Kidneys.—They together weigh 320 grms. (Left).—Large and pale. The capsule strips off easily, and beneath it, imbedded in the cortex, a number of small white nodules, larger than miliary tubercles, can be seen. Others are visible in the cut sections of the kidney. (Right).—In general the same as the left. In this kidney there are several larger white areas, the largest of which is triangular in shape; the base of the triangle, measuring 4 mm., is situated at the surface. The capsule corresponding with this area contains small hæmorrhages.

Parotid gland.—On the left side it is swollen and infiltrated with pus.

Larynx.—The posterior epiglottic tissues and the aryteno-epiglottidean folds are infiltrated with serum, and present a gelatinous appearance.

Intestines.—The small intestine is bile-stained throughout. The mucous membrane is cloudy, and sticky mucus covers its surface. The patches of Peyer in the upper parts of the small intestine present the shaven-beard appearance. The first ulceration occurs in the ileum 200 cc. above the valve. It is round, about the size of a 1-cent piece,

and is superficial and clean. 160 cm. above the valve there is a large ulcer, involving the entire circumference of the gut; it is 10 cm. in width, is irregularly convoluted superficially, and the surface is necrotic and sloughy-looking. This ulceration apparently does not reach beneath the submucosa, but the whole thickness of the intestine is involved in the infiltration. On the serous surface small white points (lymphomata) can be seen. Between this ulceration and the ileo-cæcal valve there are several smaller losses of substance. The lower end of the ileum is, together with the valve, inclosed in one larger ulceration of the same general appearance as the larger ulcer already described. Some of the solitary follicles of the cæcum are ulcerated, others are swollen, the centres of these often being necrotic. The ascending, transverse, and in part the descending colon, show the same conditions as the cæcum.

Beginning at the larger ulcer, 160 cm. above the valve, and continuing downwards to the latter, the mucous membrane is infiltrated with blood, the surfaces of the valvulæ conniventes being more affected than other places, except immediately about the ulcers. The swollen and ulcerated follicles in the large intestine are surrounded by a zone of hæmorrhage.

Fresh frozen sections of the heart muscle show it to be free from fat; sections of the liver and kidneys show parenchymatous and fatty degeneration of the epithelial elements of these organs.

Bacteriological examination.—Cover-slip preparations made at the time of the autopsy from bile, spleen, and nodule in the kidneys, showed many bacilli having the form and staining properties of the typhoid bacillus. This organism was found alone in these cover-slips. From the pus of the parotid gland the cover-slip preparations showed many streptococci.

Cultures.—Agar-agar plates were made at the autopsy from the heart's blood (right auricle), lungs, kidneys, mesenteric glands, spleen, bile, liver, bone-marrow (femur), and parotid gland. These plates, kept at 37° C. for 48 hours, gave the following results:—

Bile.—Crowded with colonies, apparently all of the same kind. Proven to be a pure growth of the typhoid bacillus.

Spleen, mesenteric glands, and bone-marrow, all contained many colonies of the typhoid bacillus.

**Kidney.**—Two cultures were made from this organ. The first was taken from one of the white nodules, the second from the intervening kidney substance. From the nodule many colonies developed, and they consisted entirely of the typhoid bacillus. The other plate contained fewer colonies, from which two kinds of organisms were separated, one agreeing with the typhoid bacillus, the other with the *Bacillus coli communis*.

**Lungs.**—From the congested portion of the right lower lobe three organisms were isolated—(1) *Streptococcus pyogenes*; (2) Typhoid bacillus; (3) *Bacillus coli communis*.

The streptococcus colonies predominated.

**Heart's blood.**—On this plate 20 to 30 colonies, all having the same features and proving to be the typhoid bacillus, developed.

**Parotid gland.**—The agar-agar plate was crowded with minute colonies of the *Streptococcus pyogenes*. Sections of the gland hardened in alcohol showed a pure streptococcus invasion along the ducts into the gland acini, associated with an interstitial and parenchymatous infiltration of leucocytes, with polymorphous nuclei.

In studying the bacilli isolated from this case, special attention was paid to distinguishing between the typhoid and the colon bacillus when they occurred together (lungs and kidneys), and to proving that the organisms found in the heart's blood, kidney nodules, as well as in the other organs mentioned, were really typhoid bacilli.\*

\*The recent writers on the means of distinguishing the typhoid and colon bacilli regard the fermentation (Smith, Chantemesse and Widal, Fuller, Dunbar, Welch, Valentini, Germano and Murea, Silvestrini), milk (Dunbar, Maloz, Valentini, Welch, Blachstein, Silvestrini), and indol (Péré, Ferrati), tests as sufficing to establish this distinction, and my own experience accords with that of these authors. Recently a new medium has been introduced by Wurtz for separating these two forms. It consists of lactose-gelatine colored with an alkaline litmus tincture. The colony growth in this medium can, through the change in the reaction produced in it, be used for this purpose. The colon bacillus colonies are said to become pink, whereas the typhoid remain blue. In several tests recently made with this medium, agar being used in place of gelatine, I found that the typhoid bacilli produced sufficient acid when acting upon lactose to turn the medium slightly pink; but the acid-reaction is less strongly marked than that caused by the colon bacillus. I have, moreover, had the opportunity of observing a variety of the typhoid organism which, when planted in litmus milk, gives at first a typical reaction; that is, after 24 to 48 hours at 37° C., it causes a faint pink color to appear. This color persists for some days (5 or 6 in the thermostat), when it changes back to blue, the blue gradually increasing in intensity until after 10 days or 2 weeks, the alkaline-reac-

The weight of opinion among bacteriologists at this time, is that the colon group of organisms can be sharply differentiated from the typhoid bacillus. However, it no longer suffices for distinguishing them to observe the colony growth upon agar and gelatine plates, or the growth upon potato; neither does the possession of motility and stainable flagella serve to distinguish the typhoid from the colon bacillus. On the other hand, the power of acid and indol-production, the property of setting up fermentative changes in sugar with the liberation of gas, and the coagulating influence upon milk, possessed by the colon group of organisms, separate it from the typhoid organism, which produces alkali, does not yield indol in cultures, is not capable of fermenting sugar, and has no coagulating effect upon milk.

The bacilli separated from this case were tested by these means, by observations of their growth upon different solid culture media, as well as by microscopical study; and it was found that in the heart's blood, spleen, bile, liver, mesenteric glands, bone-marrow, and abscesses of the kidneys, the typhoid bacillus was present in pure cultures.\*

The number of observations at the present time referring to the typhoid bacillus as the cause of post-typhoid inflammations is so large as to admit of little doubt of an etiological connection between the

tion is very prominent. This fact agrees with Wurtz's observations on the alkaline (ammonia) producing power of the typhoid bacillus, as opposed to the acid production of the colon bacillus. Pfeiffer has, moreover, just pointed out that animals rendered immune from the typhoid bacilli, contain an anti-toxine in their blood which is bactericidal to them, and not to the colon group of organisms, and other forms which seem to be even more closely related to the typhoid bacillus.

\*The typhoid bacillus has been found in local inflammations as follows:—In connection with bone giving rise to osteomyelitis and periostitis, by Ebermaier, Orlow, Valentini, Achalme, Chantemesse, Colzi, Melchoir, Dupraz, Buschke, Sultan; in abscesses of skin and muscle and periarticular abscesses, by Melchoir, Raymond, Rosin and Hirschel, and Swiezynski; in acute endocarditis, by Carbone, Vincent, Girode; in circumscribed peritonitis, by A. Fränkel, Lehman; in cerebro-spinal meningitis, by Kamen, Honl, Hintze, Stühler, Mensi and Carbone, Vincent; in abscesses in the spleen and mesenteric glands, by Roux and Vinay, Lehman, Flexner; in purulent cholecystitis, Gilbert and Girode Chiari; in sero-fibrinous pleurisy and empyema, by Ferret, Loriga and Pensuti, Valentini, Spirig, Weintraud; in purulent strumitis, by Colzi, Honl, Jeansalme; in suppurative epididymitis, by Gilbert and Girode; in suppurative orchitis, by Tavel; and in a suppurating lipoma of the knee, by Sittman.

organism and the pathological process. The length of time during which this organism can remain in the body is not a little surprising. Among the first of the observations bearing on this point, is that of Welch, who found in a rabbit which had been inoculated with typhoid bacilli 4 months previously, and had recovered, and which later succumbed to another experiment, that the typhoid bacilli which had disappeared from all other situations were still present in considerable numbers in the bile of the animal. The longest period yet recorded in which the typhoid bacillus had been found in the body after recovery from a typhoid fever, is that reported by D. Buschke, in which, in a rib-abscess, they were present seven years after. The list of cases in which this organism has been found in local foci of suppuration is now very large, and includes most situations in the body. In the study of some of these it is not improbable that the strict bacteriological requirements, concerning, in the first place, the identity of the bacillus, and in the second the absence of other organisms, may not have been carried out. But a few carefully studied cases, in which the typhoid bacillus is proven to have been present alone, renders the doubtful ones more probable. In the study of the abscesses in the kidneys\* in this case, this fact was kept in mind. Therefore, examinations were made—(1) of cover-slip preparations from the abscesses, (2) of cultures in agar-agar, etc., (3) sections from the kidney hardened in alcohol were stained in various ways, as will appear, for organisms, with the result that the typhoid bacillus was found alone in the lesions.

The abscesses can be separated into two groups, depending upon their sizes. The smaller ones are limited to the cortex of the kidney.

\*The typhoid bacillus has been found in the kidney by the culture method in many instances, in which no lesions have been detected, and in association with lymphomata by several authors, viz., Konjajeff, Spirig, Karlinski. Faulhaber was able to grow from an anæmic infarction of the kidney, in a case of typhoid fever associated with fresh vegetations on the mitral valve, a large number of typhoid colonies. The lymphomata are described as usually microscopic in size, but they may reach a size sufficiently large to be seen with the unaided eye. They are composed of accumulations of round cells with single nuclei. The bacilli are present, so far as they can be seen, in small masses and groups, lying amid the cellular infiltrations. Konjajeff saw them in both capillaries and tubules, while Spirig could not clearly ascertain their situation. Neither discovered them in the glomeruli. Von Wunschheim has just published a report of 2 cases, in which abscesses in the kidneys were produced by the typhoid bacillus.

Their shape, as found upon microscopical examination, is linear rather than round, the central zone richly infiltrated with pus cells, being surrounded by a wide but less thick, round-cell infiltration. Specimens stained for 2 hours in Loeffler's methylene blue, differentiated in 1-1000 acetic acid, dehydrated in absolute alcohol, and cleared in oil of cloves, show, under a low power,—objective No. 3, ocular No. 3,—large masses of bacteria; in a single section as many as six of these collections of bacteria may be visible. These masses of bacilli are entirely and promptly decolorized by Gram's method of staining, and no other organism could be found, after painstaking search, in specimens stained in this manner. The same result was obtained with Weigert's fibrin stain.

Towards the centre of such an area the cellular infiltration is so great as to obscure the structure of the tissues; and when the latter can be made out the staining is feeble, and in it many nuclear fragments are to be seen. The infiltrating cells vary in form, some of them possessing single and others compound (polymorphous) nuclei. At the edge of the infiltration it can be readily seen that many of the cells are intertubular. These partake as a rule, although not exclusively, of the character of small round cells. Some of the tubules are dilated and filled with polyform leucocytes. The masses of bacteria are often so surrounded by cells that their location is not always to be made out with certainty. But they appear at times to be intratubular; besides the large masses described, smaller foci of bacterial accumulation are to be seen among the cells.

The larger abscesses involve the medullary as well as the cortical part of the organ. From the surface the infiltration extends in somewhat irregular parallel lines for a considerable depth into the pyramids. In such an area the nuclei of the cells are to a large extent of the polyform (polynuclear) variety. However, between the tubules, at a little distance from the thickest infiltration, there are many small cells with spherical nuclei present. In the central foci of leucocytic infiltration the kidney tubules are dilated and filled with pus cells. Tubules of the convoluted type are often distended to more than twice their normal size, and the straight tubules of the medullary rays are equally affected. Following the tubules downward into the pyramid, the intratubular exudate is very common, while the intertubular is more scanty.

The bacteria are in large masses and in smaller aggregations, and may now be seen to be distinctly inside of the tubules and surrounded by pus cells. Indeed, some cells appear to have taken up the bacteria. The forms of the bacteria are readily made out in the smaller accumulations. They consist of short, plump rods, with rounded ends, which in the alkaline methylene-blue fluid show an irregularity of staining. The larger masses can be easily seen with a No. 3 objective (ocular No. 3), whereas the smaller groups require the aid of the one-twelfth in. oil immersion to bring them to light. A few small groups of bacteria were observed between the tubules, probably intravascular.

An interesting feature was observed in several glomeruli in infiltrated areas. Masses or thrombi of bacteria were seen in the afferent vessels, and similar bacilli were present in the glomerular capillaries, and had passed through these, as they were found again in numbers in the capillary space. The epithelium lining the capsule of Bowman was in such cases entirely degenerated.

The epithelium of the cortical tubules, particularly of the convoluted portions, is swollen, granular, and often degenerated. Those tubules, which are adjacent to, or within, the areas of cellular infiltration, show at times an absence of stainable nuclei in the lining cells. The form of epithelial degeneration, which is seen most frequently, is, however, of the hyaline variety, and the hyaline material, which is highly refractive, can be seen to run together to form actual tube casts. Those tubules, in which many pus cells occur, have no demonstrable epithelium, or are lined by low, compressed cells, often still possessing stainable nuclei.

So far as these foci are concerned, the process is not distinguishable from acute suppuration, although the tissues show no particular tendency to soften and break down.

It should be mentioned that in a few places there are considerable masses of bacteria inside of tubules, showing less reaction around them, on the part of the tissues, than that described. Such appearances are uncommon in the cortex, but in the pyramids, in the collecting tubules, masses of bacilli are embedded in pus cells, with little or no surrounding intertubular infiltration.

There can be no doubt that the bacilli gained entrance into the tubules through the glomerular capillaries. This is shown not only by the appearances already described, but also by the almost complete

absence of the bacilli in the intertubular tissue. It would appear that most of the pus cells seen in the pyramidal tubules also come from places higher up in the kidney.

The size of the masses of bacteria in some of the pyramidal tubules suggests that an increase must have taken place after these parts were reached. In a few instances a tubule, usually in the papillary portion of the pyramid, has been completely filled by a growth of the bacilli, and around these there may be no reaction whatever, so that a post-mortem increase is not to be excluded.\*

In considering the features presented by this case in the light of the literature bearing on the typhoid bacillus, it would seem as if it were necessary to regard this organism as being concerned in a variety of pathological conditions. Just as a larger and fuller acquaintance with the properties of the diplococcus pneumoniæ has shown it to be at one time able to cause as definite a pathological process as acute lobar pneumonia, at another abscess formation, and at still another a general infection of the body, so the typhoid bacillus seems capable of producing on the one hand the typical lesions and classical features

\* A few cases of especial interest have been reported in which the typhoid bacillus has been widely distributed in the body in association with definite lesions, or in which this organism has been isolated from the organs at autopsy with very slight or even entire absence of lesions in the intestine indicative of typhoid fever. It is at this time becoming to be very circumspect in the interpretation placed upon these cases, unless the most rigid requirements as to the identity of the organism are carried out. Hence in the cases reported by Banti and Karlinski of a typical typhoid fever, where no definite lesions of typhoid fever existed, and yet the organisms were obtained from the blood during life, and the organs after death, it may be questioned whether they are to be accepted as conclusive. But the same is not true of the case reported by Du Cazal in which, upon the closest inspection, no lesion could be found in the intestine. Yet typhoid bacilli which behaved in a typical manner upon various culture media, and did not ferment lactose nor redden Wurtz's agar, were isolated from the much enlarged spleen. The symptoms during life were those of typhoid fever, and at the autopsy the mesenteric glands, spleen and kidneys were swollen and congested. The case of Vincent contained a number of superficial ulcers in the ileum, and a deeper one just at the valve. The spleen was swollen, and in it was an abscess the size of a walnut, containing thick, viscous, white pus; the mitral valve contained several fresh vegetations; there was a hæmorrhagic infiltrated plaque, the size of a 5-cent piece, at the summit of the left ascending parietal convolution, and from all these typhoid bacilli in numbers were obtained in pure culture. They were also grown from other organs and the heart's blood. The bacilli were decolorized by Gram's method, and grew like typical typhoid bacilli in bouillon, Vincent's (carbolic acid) bouillon, and upon agar-agar.

of typhoid fever, and on the other of localized foci of inflammation and suppuration, and finally a genuine typhoid septicæmia.

It would be interesting if not profitable to inquire into the peculiar conditions which permit at one time the invasion of the blood by this organism, whereas, as a rule, it does not find in it a suitable medium for development. The fact is too well known to need repetition, that normal human blood serum quickly kills many typhoid bacilli. It is not improbable, therefore, that in such instances the germicidal power of the blood has been either annihilated or diminished, and it may be well to ask whether, as in the experiments of Vincent and Chantemesse and Widal with the streptococcus and its soluble products, or of Sanarelli with the products of the bacillus coli communis and the bacillus proteus, the general infection might not be explained by the development of a concomitant infection, in this case a streptococcus parotitis. Vincent has shown, moreover, that in human beings a streptococcus invasion of the body makes the prognosis very grave, even when it occurs towards the close of the disease, and after the typhoid bacilli have almost disappeared from the system. Among his cases is one that was complicated by an otitis media of streptococcus origin, in which on the fifteenth day there was augmentation of the fever, and an inverse type of temperature. Seven days later death occurred. The autopsy showed a general streptococcus and typhoid infection, the former organisms predominating in the heart's blood. But as opposed to such a supposition as the above, are the many instances of suppuration due to the pyogenic cocci, in the course of typhoid fever, in which there is an absence of evidence pointing to an invasion of the blood by the typhoid organisms. However, it may be well to study more particularly the relation of the typhoid bacillus to the blood in human beings in this class of cases.

CASE II.—*General infection with the typhoid bacillus; perforative peritonitis caused by the streptococcus pyogenes.*

Barbara W., aged 21, admitted to the medical wards (Dr. Osler) September 5th, 1893, complaining of pain in the neck, chest and abdomen, and great weakness.

Two of her brothers are ill with typhoid fever in ward F, and several other members of the family have had the disease this summer, and she has recently been nursing a brother who died of the disease.

With the exception of pneumonia at thirteen, she has been very healthy.

Present illness began about two weeks ago, with headache and loss of appetite; bowels were constipated, and she had at times slight pain in the abdomen. She had also cough and pains in the chest. She has been keeping up in order to help her mother do the nursing at home.

On admission the temperature was  $102.5^{\circ}$ , and rose in the evening to  $104^{\circ}$ . She had retention of urine and was catheterized.

Patient was a healthy looking, well nourished girl; face a little flushed; tongue swollen and furred. The abdomen was everywhere soft; there were no rose-spots; the spleen was not palpable. The examination of the lungs and heart was negative. The temperature range was not high, and during the first three days in the hospital she had only six baths. At first the bowels were constipated; then on the eighth she had four stools.

On the 9th and 10th the temperature was higher and more persistent. The pulse was regular, of good volume, and not dicrotic. The abdomen was not distended; spleen was not palpable, and there were no rose-spots to be seen. She had two or three soft movements a day.

On the 11th and 12th the temperature kept between  $103^{\circ}$  and  $104^{\circ}$ . The abdomen was soft, not distended, not painful. The tongue was furred, not dry.

On the 13th she was not so well; pulse was more rapid, reached 130; temperature was nearly  $105^{\circ}$ . She complained of pain in the abdomen, but there was no special swelling. She had three movements on the 13th.

On the 14th the temperature was almost constantly above  $104^{\circ}$ , and at 2 a. m. reached  $105.2^{\circ}$ . The abdomen was slightly distended. The diarrhoea had increased very much; the respirations were short and costal. The hands and feet were cold and clammy. The gravity of the general condition contrasted with the comparatively slight local features. The abdomen was not much distended, and only on deep pressure painful. There was foetal heart rhythm. Throughout the night of the 14th she became much worse; movements were frequent, and the collapsed condition was marked. She was given subcutaneous injections of salt solution. The pulse was

very rapid, and almost uncountable. The patient took her nourishment well. The abdomen became more distended, tympanitic, and tender. There was 3 cm. of liver dulness in the right nipple line. The patient became much worse throughout the day and died at 2 p. m. in the afternoon of the tenth day after her admission to hospital, and about the 21st day of the disease.

Autopsy seventeen hours after death.

*ANATOMICAL DIAGNOSIS.*—*Typhoid fever; perforation of the appendix vermiformis, with peritonitis due to the streptococcus pyogenes; general infection with the typhoid bacillus.*

Body of a well nourished girl, 162 cm. long; rigor mortis present in the extremities. Abdomen much distended, the tympany extending upwards over the liver.

The peritoneal cavity on incision permits an escape of gas and contains a considerable amount of yellowish brown fluid.

The intestines are matted together by fresh fibrino-purulent exudate, most abundant in the right iliac region. Coils of the small intestine have a dry glazed appearance, and are much distended by gas; the serosa is intensely injected. On separating the ileum from the cæcum, to which it was attached by fresh adhesions, the enlarged and swollen appendix was brought to view. This runs over the right brim of the pelvis. In the appendix, almost at its extremity, there is a perforation leading into its lumen. There is no attempt at localization of the abscess. The diaphragm on the right side is at the third space; on the left side, at the fourth rib.

*Intestines.*—Throughout the entire ileum and the lower part of the jejunum the solitary glands and the Peyer's patches are uniformly enlarged. As the ileo-cæcal valve is approached the patches of Peyer become much more prominent, and many of these are capped with small yellow sloughs. Beginning about 40 cm. above the valve there are actual ulcerations, none of them, however, being clean. The mucous membrane of the cæcum and the ascending colon is much swollen and congested, the solitary follicles being enlarged, the apices of some capped with sloughs. The vermiform appendix is 9 cm. in length; its mucosa is swollen, and varies from 4 to 5 mm. in thickness. There are large areas of necrosis of the mucous membrane

present, and 2 cm. from its tip a perforation occurs, whose diameter is 5 mm.

The mesenteric glands are greatly swollen and congested.

The spleen weighs 280 grammes; the capsule is free from adhesions; on section it presents a purplish-brown color, and it is of very friable consistence.

The liver weighs 1350 grammes; the capsule is smooth; on section the organ is of uniformly yellowish-brown color and friable. The gall bladder contains a very little turbid yellowish-brown bile.

The kidneys are essentially alike. They are somewhat swollen; the surface is smooth; on section it is moist; the cortex is opaque. The glomeruli are visible and red.

The heart weighs 185 grammes; is free from valvular lesions; its muscle is soft, pale, and relaxed.

The lungs are bound by old adhesions to the costal wall. On section they are quite uniformly congested.

The other organs apparently are normal.

Cultures in this case were made from the peritoneal cavity, the heart's blood, the bile, and all organs upon agar-agar. From all the sources, including the heart's blood, a growth was obtained which was proven to be the typhoid bacillus. In the peritoneal cavity, cultures of which were made from the purulent exudate, the only *other* organism found was the streptococcus pyogenes.

CASE III.—*Typhoid fever associated with miliary abscesses in the kidneys due to the typhoid bacillus. Non-transference of typhoid bacilli from mother to fetus.*

Clinical history.—Anne M., æt. 23, white, admitted to the medical wards (Dr. Osler) 14th of January, 1892, complaining of fever and general malaise.

The patient stated that her father, mother, brothers and sisters were all drowned. Previous to the drowning she had lost neither brother nor sister; they had always been healthy.

She has always been healthy, this being her first illness. Catamenia began at 15; married at 18. She had one child, now 2 years old, which is healthy.

Her present illness began five days ago with "quickenings movements." Her catamenia have been absent five months. For the last

five days she has complained of fever; appetite poor; bowels constipated. She suffered at times from pain in the back.

At the time of admission she was very feverish, skin hot and dry, pulse 120. The spleen was just palpable, and several rose-spots were present over the abdomen. The uterus reached nearly to the umbilicus. The temperature was 105° F. on entrance, and on January 15th it fluctuated between 101.6° and 104.3° F. The patient has been sponged every three hours since her admission, and to-day (January 15th) she looks distinctly brighter.

January 15th.—Patient is well nourished, lips and mucous membranes of good color, tongue dry and brown. Sordes on the lips. Pulse, 24 to the quarter, of distinctly better quality than on entrance, though the tension is rather low. There is a marked dulness of both corneæ, and the upper incisors show the Hutchinsonian nicking distinctly. Thorax.—Respiration and resonance clear in front; in the back an occasional moist, hoarse râle is heard. Heart.—Apex in 4th space, outside nipple. Dulness does not pass 3rd interspace. At the apex the 1st sound is followed by a soft, blowing murmur which is heard a short distance into axilla, over the whole cardiac area, and loudest in the pulmonic region. Heart's action regular. The 2nd pulmonic rather sharp. The mammæ are enlarged, areolæ of nipples dark in color, follicles prominent. Hepatic flatness at 6th rib in mammary line reaches to costal margin; border of liver not palpable. Splenic dulness markedly increased, beginning at 7th rib and reaching nearly to costal margin. The border, which could be just felt yesterday, not palpable to-day, owing to abdominal resistance. Abdomen evenly distended over the lower portion. There is pigmentation about the umbilicus and linea alba. A smooth, rounded, fluctuating mass can be felt extending from the pelvis within one inch of the umbilicus. This tumor is regarded as the pregnant uterus. There are typical rose-spots over the abdomen and chest. On the left ulna, near the elbow-joint, there is a slight prominence. The right tibia is fairly smooth; the left shows a slight prominence at about the junction of the lower and middle third. Urine.—Amber, hazy, reaction amphoteric; sp. gr. 1010; no albumen; distinct diazo-reaction; no sugar. Microscopical examination.—Triple and amorphous phosphates, leucocytes and epithelial cells.

January 19th.—Urine dark brownish-red in color; flocculent deposit; sp. gr. 1018; distinct diazo-reaction; distinct trace of albumen; epithelial cells and leucocytes in sediment; no casts seen.

January 21st.—From the 15th to the 19th the temperature of the patient remained very high, touching every day points above 104° F. Yesterday the highest point reached was 102° F.; this morning it is 101.7° F. Mental condition clear; tendency to constipation rather than to diarrhoea. The pulse is regular, 26 to the quarter and of fairly good quality.

January 22nd.—Urine—no albumen, no casts, distinct diazo-reaction.

January 27th.—Diazo-reaction still present. Color of the urine reddish-brown; neither albumen nor casts present.

January 30th.—Temperature from 21st to 24th remained about the same—touching 104° F. every day; from 24th to 27th the temperature was somewhat lower and the patient seemed rather easier. Yesterday at 10 a. m. temperature reached 105° F. Pulse more rapid and the patient complains of pain in the right breast where a slight caking can be felt in the middle of the gland. This morning the temperature fluctuated between 100° and 100.4° F. a fall of 4.6° F. having occurred between 2 p. m. yesterday and 2 a. m. this morning. The rose-spots are fading, tongue still dry and coated, and emaciation is beginning to become evident. The pulse is 28 to  $\frac{1}{4}$  and of distinctly better quality than for the last two days.

February 4th.—In the last five days the temperature has varied between 98° and 104.6° F. The quality of the pulse seems no worse; this morning it is 29 to the quarter. The urine was examined several times since the last report, the diazo-reaction having gradually grown fainter at each examination, to be missed on the 4th inst.

February 9th.—Since the 4th the temperature has ranged between 99.8° and 104.6° F. The pulse has been more rapid and rather smaller in volume. Wednesday a fresh crop of rose-spots appeared on the abdomen.

February 11 and 12.—The diazo-reaction began to appear again in the urine.

February 13th.—For the last four days the temperature has touched a point above 104° F. daily; pulse 120–140, perfectly regu-

lar, though the volume is low. The rose-spots, which lately appeared, are now almost gone. The foetal movements are lively.

February 15th, 16th and 18th.—The condition of the patient remains about the same. The temperature continues to rise to 104° and over. On the 16th a fresh crop of rose-spots appeared. Pulse on the 15th ranged from 132 to 150.

February 19th.—A number of small boils, quite superficial, appeared on the arm, axilla and back. The patient has been wandering slightly in her mind.

February 22nd.—The foetal heart was for the first time audible.

February 23rd.—Since 10 p. m., the 21st, the temperature has not touched a point beyond 100.8° F.; the pulse has been slower, and the general appearance of the patient is better. Last night she was quite restless. Urine dark in color, turbid, acid, sp. gr. 1012, considerable albumen, hyaline casts covered with leucocytes, some red blood corpuscles and many leucocytes.

February 25th.—Yesterday morning the patient became considerably hoarser, she could not speak above a whisper, and at noon there was considerable interference with respiration. A considerable degree of oedema was made out about the glottis. Dr. Halsted saw the patient at 8 p. m., and tracheotomy was performed with temporary relief; during the night the patient failed and died at 5.05 this morning.

Autopsy 5 hours post-mortem.

*ANATOMICAL DIAGNOSIS.*—*Typhoid fever of late date with nearly healed and healing ulcers; ulceration of mucous membrane of the gall bladder; multiple miliary abscesses of kidney due to the typhoid bacillus; furnuculosis of arm and suppuration of axillary gland due to the staphylococcus cereus flavus; cedema glottidis; tracheotomy; bronchitis and broncho-pneumonia. Pregnancy of 6th month; cerebral hæmorrhage and general cedema of fetus.*

Body of a medium sized, slightly built, somewhat emaciated woman. Surface pale. A tracheotomy wound extends from the thyroid cartilage to within 4 cm. of the sternal notch. On the right arm, near the shoulder several small swellings occur, two or three of which present small external openings which lead into small abscess cavities, containing creamy pus. The corresponding *axillary glands* are en-

larged and on incision contain pus. Lymphatic glands of the body generally, not swollen.

Peritoneal Cavity.—Both layers of the serosa are smooth, glistening and moist. The peritoneum covering the small intestine shows a few reddish patches, corresponding to which the serosa is thickened. The mesenteric glands are swollen, dark-red in color and softened.

Small Intestines.—Show many ulcers. These extend from the cæcum to within 2 metres of the pylorus. Commencing at the upper portion of the gut, the ulcers are in general small and superficial, with unclean bases and irregular margins. The large ulcers are circular in outline and their edges are low and covered over with granulation tissue. At the edges of some of these there are smaller areas in which either a new ulceration has taken place, or a part of the old ulcer is left uncovered. Not infrequently a number of ulcers occur close together, these presenting about the same characters. They have clean centres which extend to the muscular coat, the edges being covered over by irregular granulations, or even at times being overlaid by the undermined mucosa (overhanging ulcers). At the ileo-cæcal valve the area of ulceration is very large, the circular muscle is exposed in the base of the ulcers, many of which have overhanging edges. Those in the higher parts are for the most part nearly healed or rapidly healing, in a few instances, entirely healed, while lower down the healing is far less advanced and fresh ulceration is occasionally met with.

Spleen.—Large, weight 250 grams. The capsule is slightly roughened by small connective tissue outgrowths. Consistence of the organ moderately firm. On section the cut surface is intensely hyperæmic; the Malpighian bodies are visible but not enlarged.

Liver.—Enlarged; weight, 2300 grams. The surface is smooth. On section it is pale, homogeneous and cloudy in appearance. Beneath the capsule of the right lobe there are several small ecchymoses.

Gall bladder.—Distended with bile. The mucous membrane contains several small superficial ulcers and erosions. The ulcers have sharp edges, and they extend apparently no deeper than the mucous membrane. In some the mucosa appears to be advancing over the edge of the ulcers. No concretions present.

Kidneys.—They are both of the same size and general appearance. Together they weigh 400 grams. The capsule strips off readily; the

general surface is pale. Imbedded in the kidney substance, just beneath the capsule, numerous greyish foci which can be seen to be composed of light-colored points closely crowded together occur. In addition to these larger single ones are scattered through the cortex. On section the larger collections present somewhat the appearance of infarctions extending into the pyramids. The centres of these are of a greyish color, the periphery being surrounded by a zone of hyperæmia. The cortex of the kidneys is pale, the markings obscure, the regions of the convoluted tubules appearing more opaque than other parts.

*Larynx.*—The tissues of the epiglottis are infiltrated with serum and present a gelatinous appearance.

*Heart.*—Weight, 276 grams. All the valves normal. The myocardium pale and easily torn.

*Lungs.*—In the posterior portion of the lower lobe of the right lung several broncho-pneumonic areas are present, surrounded by œdema. In the left lung there are fewer such foci.

*Uterus.*—Enlarged. It extends 7 cm. above the symphysis pubis and contains a fœtus and fœtal structures. The fœtus apparently is of the 6th month. It measures 32 cm. in length. No malformation in it was observed. The subcutaneous tissues contain much fluid, and they are pale in color. The serous cavities are filled with clear fluid. The brain substance of the fœtus is softened, and into the left cerebral hemisphere a hæmorrhage has taken place which has much lacerated its substance and extended into the lateral ventricle on that side. The other organs present no noticeable abnormal appearance. They are, however, very soft and œdematous.

*Frozen sections.*—Sections from the liver, kidney and heart muscle of the mother showed them to be quite fatty. In addition, in the liver, there were many typical "lymphomatous" nodules. The fat in the kidney was situated in the epithelium of the convoluted tubules, but was not present in very large quantity. The secreting cells generally presented a swollen and coarsely granular appearance. The heart on the other hand was very fatty, the fat being distributed diffusely throughout the myocardium.

*Bacteriological examination.*—This examination consisted in the study of cover-slips and the preparation of Esmareck roll-cultures from all the organs. In addition, in the case of the kidneys, the

lesions there were studied in sections of the alcohol-hardened tissues as will appear. *Furthermore a set of Esmarck roll-cultures (in agar-agar) was made from all the organs and the meconium of the foetus with the uniform result of finding them completely sterile.* Only the results of the bacteriological study will be given here, it being understood that the same methods for the differentiation were used as in the previous case.

Heart's blood and spleen, no growth.

Mesenteric and cæcal lymph glands, liver, bile and kidney, pure cultures of the bacillus of typhoid fever.

Lung (broncho-pneumonic area), pure culture of a streptococcus growing in conglomerate masses without clouding the bouillon.

Pus in axillary gland, pure culture of the staphylococcus cereus flavus.

In the case of the kidney two roll tubes (agar-agar) were made, one from the kidney substance and the other from the greyish-white nodules. In both cases the same organism were obtained, which were shown to be the bacillus typhoideus.

**Histological Examination of the Kidneys.**—The small foci described are found to be caused by a purulent infiltration of the tissues. The pus cells are present in the interstitial tissue and within the tubules. They are absent from the capsular spaces of glomeruli, even when the surrounding tissue is intensely infiltrated with them and they extend into the pyramidal part of the organ. The tubules in the infiltrated areas show necrosis of their epithelia which at times form consolidated masses within their lumina, the adjacent tubules presenting a hyaline degeneration of their lining cells. The affected cells are filled with hyaline droplets of various sizes which stain with Weigert's fibrin stain. Fibrin filaments are by this method shown to exist in some of the tubules and to be intimately associated with the necrotic cells. The suppuration seems to differ from ordinary suppuration by the less extent of necrosis and the greater amount of hyaline degenerative changes, the tissues, at the same time, not tending to soften and break down. Typhoid bacilli\* in considerable

\* In addition to the method given for the demonstration of typhoid bacilli in tissues the following has been employed with excellent results. With it groups of typhoid bacilli, as small as 3 or 4 may be clearly shown among the pus cells, and the fact of their occurrence within pus cells was in this case established. Stain for

numbers are found among the pus cells in the tubules. Other microorganisms could not be demonstrated.

CASE IV.—*Typhoid fever with perforation of the intestine; acute peritonitis with bacterial polyinfection.*

Clinical History.—Matthias G., æt. 26, white; admitted to the medical wards (Dr. Osler) August 28, 1891, complaining of headache accompanied by chilly sensations and fever. His present illness began eight days ago.

The patient (German) has been in this country for 9 months; his occupation is that of a carpenter. His father died at 53 probably of pneumonia; mother living. He has two brothers and three sisters living—none dead. He does not know of having had any sickness as a child.

On admission it is noted that he was of large build, that his face was flushed, the tongue thinly furred, the skin dry and hot. Thorax well-formed; clear on percussion and auscultation. Heart sounds clear. Abdomen shows a diffuse erythematous eruption which extends upwards to the lower portion of the chest. A few bright red papules also present which fade on pressure. General tenderness is present over the abdomen, growing more acute in the left iliac fossa. Spleen not palpable. Temperature ranges from 99 to 102.5° F., pulse 88, respiration 24. Blood examination negative.

August 30th.—The spleen is palpable to-day; the urine is of a dark amber color, fairly clear, of acid reaction, does not contain albumen or sugar, and does not give the diazo-reaction. The sediment contains granular casts.

September 2nd.—The temperature has not ranged above 103° F.; the pulse has varied from 90 to 108; respiration 20–24. Fluid clear, abdomen not distended. A few rose-spots over abdomen. Heart and lungs clear.

September 5th.—The spleen is palpable below the ribs; the range of temperature between 99 and 103° F., pulse from 99 to 102.

10 minutes in Stirling's Gentian-violet (Gentian-violet 5 grms., Alcohol 10 cc., Aniline Oil 2 cc., water 88 cc.; filter), place in 1:1000 acetic acid solution for some minutes, dehydrate quickly in 95 per cent. alcohol, transfer to the slide, blot, add oil of cloves to clear and differentiate. Change the oil several times until the desired differentiation is obtained.

September 9th.—Yesterday at 4 p. m. the temperature rose to 104.6° F.; the falls are marked after the bath. Patient was delirious and restless last night. The pulse, in the last twenty-four hours, has been much more rapid; this morning the temperature is 98.2° F., the pulse 118, the respiration 32. At present the patient lies on his back with knees drawn up, his eyes are bright, and pupils dilated. He is delirious and restless. The abdomen is uniformly distended, rather tense and tympanitic. The skin is dry and harsh. Urine turbid, alkaline, pale-yellow in color, gives a faint diazo-reaction, contains many hyaline and granular casts, urates and phosphate crystals.

September 10th.—During the afternoon, yesterday, the pulse became much more rapid (142) and dicrotic. The patient lies in a state of muttering delirium. The urine contains albumen and many casts and red blood corpuscles. The sp. gr. is 1022. The temperature has ranged between 104.2° F. at 8 last night to 95° F. at 6 this morning. The abdomen is considerably distended, very tense and tympanitic; on pressure the patient flinches.

Death at 6.20 a. m. September 11th.

Autopsy five hours post-mortem.

ANATOMICAL DIAGNOSIS.—*Typhoid fever, with clean and deep ulceration; perforation; fibrino-purulent peritonitis. Acute splenic tumor; swelling and softening of mesenteric glands; ulceration of epiglottis; lung emphysema and congestion (hypostatic). Polyinfection with bacteria.*

Body 164 cm. long, strongly built and well nourished. At different points on the body congested areas are apparent and a few darker and smaller injected points. The abdomen is distended, the blood vessels of the neck turgid and contain with fluid blood. Muscles well developed and deep red in color.

Peritoneal cavity.—On incision there is a free escape of gas. The upper portion of the small intestine is greatly distended. The blood vessels of the serosa over the whole peritoneum are injected; the serosa itself is cloudy, and coagula of fibrin, loosely adherent, are scattered over it. In the dependent parts of the cavity about 200 cc. of turbid, yellow fluid are contained. *A perforation 2 mm. in diameter is found, located in a loop of intestine, situated in the left iliac fossa.*

Intestines.—The large intestine is firmly contracted; its mucous membrane is pale, and it contains tolerably firm, yellow faecal masses. The vermiform appendix is somewhat dilated, and in the swollen mucous membrane several superficial small ulcerations are apparent. The largest number of losses of substance is found in the ileum; the most advanced ones are situated at the ileo-caecal valve. The mucosa of the valve itself is ulcerated. The ulcers are surrounded by swollen edges which are undermined, and in their clean bases the circular muscular tunic is visible. A small quantity of necrotic material is found still adherent to a very few of the ulcers. Between the ulcers are swollen solitary and agminated follicles. Situated 22 cm. from the valve there is an ulcer 2 cm. in diameter, the clean base of which is formed by the circular muscular coat, whose edges are necrotic and in the centre of which there is a perforation 2 mm. in diameter. The first losses of substance are found in the upper part of the jejunum.

The stomach contains dark-brown contents. Its mucous membrane is apparently normal.

Mesenteric glands.—Enlarged, congested and softened.

Spleen.—Bound to diaphragm by old adhesions, which cannot be broken down without lacerating the organ. It weighs 510 grams; the capsule is covered in part with fibrinous coagula; the consistence is moderately firm. On section it presents a dark brown color, and the Malpighian bodies are prominent.

Liver.—Capsule covered with fibrinous masses; otherwise it is smooth. On section it is pale, the lobules fairly distinct; no increase in fibrous tissue. Weight 1870 grams.

Kidneys.—Both of approximately the same size and general appearance. Together they weigh 510 grams. The surface is smooth; the capsules stripping off readily, and the stellate veins are injected. On section the striæ are visible; the glomeruli are easily seen; the cortex generally is pale and varies in thickness from 5 to 7 mm.

Adrenal glands and pancreas apparently normal.

Heart.—No valvular lesion; coronary arteries smooth; myocardium pale and soft. Weight 240 grams.

Lungs.—Free from adhesions; a small amount of fluid in each pleural cavity; the posterior borders of the lower lobes are intensely congested. The upper lobes are moderately emphysematous. The bronchi are intensely congested.

This case derives especial interest from the bacteriological examination. It illustrates to what extent a mixed infection with bacteria may occur in human beings. Of course the infection atrium was the intestine, the perforation found there opening the way for the escape into the peritoneal cavity of a considerable variety of microorganisms which happened to be present in its lumen. Soon the several kinds, although perhaps not equally, made their way into other parts and organs, and this very difference between those bacteria present in the peritoneum and those found elsewhere in the body is not without its instructive side. I cannot help holding up as an example the present case in comparison with the first two of our series in support of the fact that the conditions which enable the typhoid bacillus to flourish, if not to exist at all in the blood, must be very peculiar. As will be seen shortly in this case the typhoid bacillus found its way with other bacteria into the peritoneal cavity, and there seems to be no reason why it should not have been spread with the same facility through the body as its associates; and yet its distribution at autopsy was by no means so universal as some of the other forms.

The close association of the typhoid bacillus and the colon bacillus in this case will be remarked. With respect to the means used to separate them I would again refer to the remarks on this subject in the first case. In the course of the study of this case it was necessary to make many plate, roll and other cultures, and to keep the organisms under observation for considerable periods of time; and yet after certain colonies, existing side by side perhaps, in the original plates, had been isolated, and through their properties determined to be colon or typhoid, no transition of one to the other could be detected in the subsequent study of these forms.

The method pursued in the isolation of the several bacterial species was the use of various media and plate and roll cultures. Many hundred colonies were examined microscopically and grown upon all sorts of culture media with the result of separating the following forms from the different situations mentioned.

*a.* Bacilli, varying in length, short forms 2 to 3 times as long as broad; larger forms several times as long as broad. Colony growth upon agar-agar and gelatine resembles colonies of typhoid bacilli. They do not coagulate milk after several weeks; on potato the growth

is either invisible or slight, moist, showing little tendency to spread, and of yellowish-brown color. Drop cultures 24 hours old show active motility. No indol production. Does not ferment sugar. *Bacillus typhoideus*.

b. Bacilli, a little coarser than the preceding, all or nearly all are of the short form. Colony growth on agar more opaque than last; on gelatine it forms thin filmy surface colonies which show a blue translucence. Visible luxuriant growth upon potato of brownish-yellow color. Drop cultures 24 hours show no perceptible motility. Produces indol; ferments sugar. *Bacillus coli communis*.

c. Cocci, growing readily on all the culture-media, in the form of grape-like clusters. On potato an abundant yellow growth; in gelatine stick culture rapid liquefaction. *Staphylococcus pyogenes aureus*.

d. Minute white colonies showing no tendency to spread, but a little larger when on the surface than in the depth of the culture media; cover-slips show them to be composed of chains of cocci. *Streptococcus pyogenes*.

e. Bacilli, variable in length, motile, rapidly coagulate milk, quickly liquefy gelatine; colonies spreading (migrating). *Proteus vulgaris*.

These organisms were distributed in the following manner:

Peritoneal cavity.—Bacilli typhi abdominale, coli communis, proteus vulgaris. *Staphylococcus aureus*; streptococcus.

Mesenteric glands.—Pure culture of the typhoid bacillus.

Iliac lymph glands.—Typhoid and colon bacilli.

Retro-peritoneal lymph glands.—Typhoid and colon bacilli.

Spleen.—Pure culture of the typhoid bacillus.

Liver.—Typhoid bacillus and streptococcus.

Bile.—Pure culture of the typhoid bacillus.

Kidneys.—*Bacillus coli communis* and streptococcus.

Lungs.—Pure culture of the bacillus coli communis.

Blood.—Taken from the azygos vein. *Bacillus coli communis* and streptococcus.

Thoracic duct.—*Bacillus coli communis* and streptococcus.

Ulcer of intestine.—*Bacillus typhoideus*; bacillus coli communis; bacillus proteus vulgaris, and streptococcus. The colon colonies predominated.

CASE V.—*Typhoid fever with perforation (3rd week of disease); acute peritonitis; general streptococcus infection. Absence of typhoid bacilli from the cultures.*

This case is included as illustrating the importance of the secondary micro-organisms in typhoid fever, even after the disappearance from the body of the typhoid bacilli. Although the disease was yet at its height, the evidence of the cultures in this case is to the effect that the typhoid organisms themselves had either entirely disappeared or were so few in number that they were not transplanted with the tissue juices to the culture media.

Henry R., æt. 35, white, admitted to the medical wards (Dr. Osler) November 1st, 1892, complaining of chilly sensations and fever.

The patient's father is living and well; the mother died of pneumonia (?). One brother and one sister living; none dead.

He had measles when a child, but since that time he claims to have been healthy up to the present illness.

The present illness began about one week ago with pain in the back of the neck, stiffness of knees and a sense of fatigue. Four days ago he felt giddy and generally badly. No cough or expectoration. For the past five days he had been in bed constantly. Examination of the blood showed no malarial organisms.

November 2nd.—Temperature 104°, pulse 120, respiration 32. Yesterday afternoon the skin was flushed, hot and dry, and over the trunk a well-marked, but faint roseola could be seen. Spleen palpable; tongue dry and coated. This morning the pulse is 112, and slightly dirotic. Thorax clear throughout. Heart.—Point of maximal impulse not to be distinctly localized; cardiac flatness entirely obliterated by pulmonary resonance. Sounds are heard loudest in about normal position in 5th space, and appear of normal relative intensity. Liver border not palpable; abdomen not distended. There is slight tenderness in the ileo-cæcal region; some gurgling; no distinct rose-spots; urine brownish-yellow, clear, acid, specific gravity 1026, distinct trace of albumen, diazo-reaction present, epithelial cells, leucocytes and granular casts seen; no sugar. Blood.—Leucocytes 8,500.

November 8th.—The temperature between the 4th and 8th ranged between 100.6° F. and 104.2° F. Last night, during the bath, the

patient had an involuntary movement and the pulse became very weak. Since midnight the temperature has not been below 103.6° F. This morning the patient is rational, but the pulse is rapid; at the time of the visit, it was 144. Tension and volume not bad. The abdomen is not especially distended, but it is held very tense, and is generally tender. A number of typical rose-spots are present. Later note. For the past 18 hours the temperature has reached 104° F. The patient is less bright than he was, but there is no delirium. Pulse 130, tension low. The abdomen is much distended, especially in the epigastric region, which is very prominent. The patient sank during the evening and died at midnight. Note by Dr. Osler: "When I saw the man at 12 o'clock, noon, there were no marked symptoms of collapse. The pulse was rapid, but not small; face not pinched or anxious, and he answered questions readily. There was no pain in the lower abdomen. The tympany was higher than I have ever seen."

Autopsy 10 hours post mortem.

*ANATOMICAL DIAGNOSIS.*—*Typhoid fever (early and late ulcers) and swelling of follicles; perforation; fibrino-purulent peritonitis; acute splenic tumor; parenchymatous degeneration of viscera. General infection with streptococci.*

Body 160 cm. long; well-nourished; subcutaneous fat in moderate amount; muscles deep brownish-red in color.

Peritoneal cavity.—On incising this cavity there is an escape of foul smelling gas. The surface of the intestines are much injected. In the cavity there are about 1000 cc. of turbid fluid. Covering the loops of the intestine occupying the right iliac region are flakes of fibrin. A small perforation occurs in one of the loops of intestine in this situation from which a yellowish semi-solid faecal mass protrudes into the peritoneal cavity. The diaphragm on the right side is at the 3d intercostal space; on the left side at the 4th rib.

Intestines.—Beginning with the ileum, the patches of Peyer are swollen. At a distance of 80 cm. above the valve an ulcer measuring 5 x 2 mm. is situated which passes through all the coats of the intestine in its midportion, the perforation being 1-5 mm. in diameter. The edges of this ulcer are undermined and its base quite clean. From this point downwards the solitary follicles are all swollen, and

in the centres of some of these small losses of substance have occurred. The ulcers are very few in number until the valve is reached; here they are quite numerous, larger and extend to the circular muscular coat. Some of these have undermined edges, and while in some the slough has been completely removed, to others dirty necrotic material still adheres. Neither the vermiform appendix nor the large intestine contains any ulcers.

Mesenteric and retro-peritoneal glands swollen and congested.

Spleen.—Enlarged; it weighs 750 grams; its capsule is wrinkled, and on section it is soft, of a brownish-red color, the pulp is abundant, and the Malpighian bodies are easily visible.

Liver.—Weighs 2400 grams. The surface is smooth, except over the right lobe, where there are several depressed spots which on section present a dark hæmorrhagic appearance. On section it is opaque, of a yellowish color; the lobules are invisible.

Kidneys.—Together they weigh 450 grams. Surface smooth and pale; stellate veins prominent. On section striæ obscure, cortex pale, its average thickness being 8 mm.; the glomeruli are visible and red in color.

Heart.—Weight 300 grams. All the valves normal; myocardium of a brownish-red color and firm consistence.

Lungs.—Free from adhesions, except a few light ones over the right lobe. On section they are moderately congested and œdematous. Mucous membrane of bronchi congested.

The pancreas, adrenal glands, stomach, testicles and bladder apparently are normal.

Frozen sections.—Kidneys.—No increase of the connective tissue. The epithelium of the convoluted tubules is swollen and granular, and a few of these tubules are quite fatty. A very small amount of fine fat can be made out in the glomeruli.

Liver.—The liver cells are swollen and granular; the Kuppfer's cells are fatty. No connective tissue increase. Many so-called "lymphomata" are present. These latter vary in size and appearance. The larger show, in addition to the necrotic cells, much detritus; the smaller show only hyaline liver cells. Surrounding these foci the liver cells are very fatty.

Bacteriological examination.—Cover-slips from the peritoneum show many streptococcus chains which were usually short, and bacilli of apparently only one species. Cover-slips from the spleen negative.

Cultures.—Agar-agar Esmarck rolls were made from the fluids and viscera.

Peritoneum.—Colonies of the streptococcus and the bacillus coli communis.

Retro-peritoneal lymph glands.—Streptococcus colonies.

Spleen.—Two streptococcus colonies only.

Bile.—One colony of the streptococcus.

Kidneys.—Streptococcus and bacillus coli communis. Former predominate.

Lungs.—Many colonies each of streptococcus and bacillus coli communis.

Heart's blood.—The roll is thickly studded with streptococcus colonies. No other kind of micro-organism present.

There can, we think, be little doubt but that the perforation of the intestine, the peritonitis and subsequent death were in this case directly attributable to secondary infectious agents, especially with the streptococcus pyogenes.

CASE VI.—*Typhoid fever; death from hæmorrhage (sixth week of the disease). Disappearance of the typhoid bacilli. Infection with bacillus coli commune.*

Wallace H., colored, aged 23, admitted to the medical wards (Dr. Osler) July 1st, 1895, complaining of pain in the head, stomach and shoulders.

The patient states that his father died of dropsy. His mother is living and well; the same is true of four brothers and four sisters, with the exception of one brother, who has rheumatism. Two brothers died in infancy.

He states that as a child he had measles, mumps, whooping-cough, chicken-pox, but has not been ill since that time.

His present illness dates two weeks prior to his entrance, and was ushered in with a violent headache over the frontal and occipital regions. Soon afterwards he complained of pain in his stomach, which has continued up to the present time. He has vomited several times. About one week ago he had profuse epistaxis. For ten or twelve days he has had diarrhoea.

July 1st.—The patient is found to be a large, well-made, well-nourished man. Dorsal decubitus is present. The skin is dry and

smooth; eyes dull; color of mucous membranes good. The tongue is coated. There is marked abdominal tenderness on pressure, particularly in the lower parts. The spleen is palpable. The thorax is clear. The heart's impulse is seen at the fifth space in the nipple line. On auscultation the first sound is replaced by a rumbling, soft systolic murmur, which is transmitted to the axilla. The second sound is clear and loud. The second pulmonic is accentuated; the second aortic fairly loud and clear.

July 2nd.—Pulse is 22 to the quarter, markedly dicrotic. On the back of the arms there are a number of slightly raised papules. Respiration is clear; the splenic flatness is practically obliterated by abdominal tympany.

July 4th.—The splenic flatness is increased, beginning at the eighth rib and extending to the eleventh costal margin. The border is not palpable. Patient appears drowsy.

July 11th.—Temperature is still elevated, but falls after baths. General condition appears somewhat better.

July 17th.—The stool to-day was semi-fluid, of a bright yellow color, containing a small quantity of bloody mucus and a few milk curds.

July 22nd.—Since the last note the condition of the patient has remained about the same. The temperature on the 18th and 19th ranged a little lower, the registered pulse having been for three days below 100. At about 7.40 a. m. on the 23rd the patient had a stool of bright, fresh blood, appearing to be about a quart in quantity. Fifteen minutes later he had another stool of about one pint of clots; fifteen minutes after this a third stool of a pinkish fluid character. The temperature at 8 a. m. was 98.2°. Almost immediately after the hæmorrhage the patient became almost pulseless, and rapidly sank in spite of all stimulation, dying about 8.30.

Autopsy five and a half hours post-mortem.

ANATOMICAL DIAGNOSIS.—*Typhoid fever (ileo-typhus and colotyphus); death from hæmorrhage; acute splenic tumor; parenchymatous degeneration of the organs.*

Body of a well nourished man, 169 cm. long; rigor mortis in the extremities; the surface and mucous membranes very pale; muscle dark red in color.

Peritoneal cavity contains a small amount of clear fluid. The mesenteric and retro-peritoneal glands are swollen and slightly congested.

Intestines.—Beginning 280 cm. above the valve there is a series of ulcers, the first being discrete and superficial, the lower ones larger, confluent, deeper, in many instances exposing the muscular coat of the intestine. Just above the valve there is a large mass of ulcerations involving nearly the whole of the intestine at this part. For the most part the ulcers are clean; a few of the superficial ones still contain the remains of the necrotic mucous membrane. The colon and rectum show superficial ulcerations similar to those found in the small intestine. These are quite numerous. The large intestine contains in its lumen a considerable amount of fluid blood. The eroded blood vessel was not found.

The spleen weighs 350 grams; the capsule is smooth; consistence is soft; on section it is dark red in color, and almost diffluent. The Malpighian bodies are very indistinct.

The liver weighs 2130 grams; the surface is smooth; on section the organ is homogeneous, of a yellowish color; the lobules being very indistinct.

The kidneys are the same in size and general appearance, and together they weight 320 grams. The surface is pale; on section the cortex is pale, swollen, averaging 9 mm. in thickness; the striæ are indistinct, and the glomeruli are pale. The other organs present no especially remarkable condition.

Cultures were made from the heart's blood, and the various organs upon agar-agar. The plates from the liver, kidneys, bile and blood remained sterile. Those from the lungs and spleen contained numerous greyish-white colonies which were composed of short, plump bacilli, giving all of the reactions distinctive of the bacillus coli communis. Numerous attempts to isolate the typhoid bacillus, involving the examination and study of a large number of colonies from these plates, were entirely unsuccessful.

It is not an uncommon observation in cases of typhoid fever which have terminated fatally, late in the course of the disease, at a time when the ulcers in the intestine have become entirely, or for the most part clean, and healing has already begun, to find that the typhoid

bacillus refuses to be cultivated from the tissues including the peritoneal lymphatic glands. The bacteriology of these cases may lead to some confusion concerning the fixity of the typhoid species of organism if it should so happen that in place of the typhoid bacillus forms with the properties of the bacillus coli communis are met with, unless it be borne in mind that the colon group of organisms finds the lesions existing in the intestinal wall very favorable for their emigration. At least the cultivation from these cases of colon bacilli should never awaken the suspicion that the two species are transmutable. For we now know, thanks to the observations upon the bacillus coli communis by Dr. Welch, that lesions of far less severity than are present in these cases suffice for their escape from the intestinal canal and their dissemination throughout the body. The present case is cited as an example in which, after the entire disappearance of the typhoid bacilli from the body, so far as failure to demonstrate them in cultures can be taken to exclude their presence, the colon bacilli were found in the tissues at autopsy.



