TYPHOID AND PARATYPHOID FEVERS.
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There appears to be some tendency at the present day to assume that any doubtful febrile case which does not conform with the text-book description of enteric fever is an instance of the paratyphoid infection. We are first concerned in finding what grounds there are for this assumption, and we ask, Is it possible from clinical symptoms alone to discriminate between typhoid and paratyphoid fevers? Conradi,¹ who has studied fifty cases of paratyphoid fever, Chevreul² twenty-eight, Coleman³ twenty-three, answer, no! A survey of recent work on this subject will substantiate this negative conclusion.

A clear conception of the action of the Bacillus typhosus on the human body is essential for the discussion of the question. Our ideas have been much enlarged by the results of modern technique employed in the precise diagnosis of fevers, that is, by obtaining cultures of the invading microbe from the blood, or its isolation from dejecta, and by the quantitative estimation of the agglutinative power of the blood of the patient on these growths and on those of known origin.

It has been proved that the presence of Eberth's bacillus in the human organism may have very varying effects of every degree of severity. It may be a parasite long harmless to its host, or it may be the cause of a fatal malady. Beginning at the bottom of the scale we find that the enteric bacillus may be an inhabitant of the bile channels and intestinal canal of people who have been in perfect health for an indefinite period. Remlinger and Sneider⁴ were the first to discover the micro-organism in the alvine contents of healthy people. German observers have devoted much attention to these "bacillenträger" or "typhoid carriers," as they are rightly called. Thus Lentz⁵ has met with twenty-seven "typhoid carriers" and five "paratyphoid." Minelli⁶ last year published

⁴ Remlinger and Sneider, Annales de l'Inst. Pasteur, January, 1897.
a comprehensive paper on the subject. The importance of recognising such persons liable to endanger the community at large is shown by an example reported by Levy and Kayser. A woman, an inmate of a public institution, suffered from enteric fever three years previously. After this, sporadic cases occurred in the ward where she resided. Examinations of her faeces disclosed the presence of the enteric bacillus. Ultimately she herself succumbed to a second attack. The *B. typhosus* was obtained from her liver and spleen. They were very numerous in the bile and were found also in the interior of some gall-stones. Where Eberth's bacillus has been discovered in the dejecta of robust persons, the individuals concerned have mostly been in association with, or were liable to the same influences as, typhoid patients. Minelli, however, detected a "typhoid carrier" amongst 250 inmates of a prison where no enteric had occurred. It would not be rash, therefore, to conclude that there must be many soldiers who are harbouring the typhoid bacillus in every army which takes the field. This affords an explanation of outbreaks of enteric fever under circumstances which would otherwise compel us to believe it arose *de novo*. Moreover, these "typhoid carriers" live with the sword of Damocles hanging over them. If for any reason the defensive processes in their bodies be lessened, the bacillus, instead of being an innocent parasite, becomes an invading foe. It seems probable that the typhoid epidemics which so often arise immediately after the arrival of troops at a hill station in India are thus caused. The immunity of men who are fostering the bacillus in their bile channels and alimentary canals is lowered by the fatigue of the ascent. The microbe thereby gains a mastery signified by an attack of enteric fever. This is not an isolated incident in human pathology. Fraenkel's pneumococcus is an almost constant inhabitant of the normal mouth. The diphtheria bacillus may exist in the nasal passages and throats of persons in health. Cholera vibrios may be discharged in the evacuations of healthy people who have been in contact with cholera patients. The labours also of the Mediterranean Fever Commission have brought to light the fact that the *Micrococcus melitensis* may live in the bodies of men and animals for months or years without producing signs of illness.

Ascending the scale in the order of severity of the typhoid infection, cases of apyretic enteric have been recorded. An instance

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came under my own observation during the South African War. A typhoid-like tongue, diarrhoea, enlarged spleen, and typhoid spots were noted in a man who had no fever. West\(^1\) has reported a case of successful operation for perforating typhoid ulcer in a patient who had had no pyrexia or markedly impaired health until the rupture occurred. In 44 per cent. of 186 post-mortem examinations I have made on those who have succumbed to enteric fever, the lesions were found to be of much longer duration than the assigned period of illness. This would indicate that the invasion of the bacillus during the early stages was devoid of symptoms.

A little higher still on the scale we meet with cases of fever lasting one or two days. This class was well known to all those who had charge of fever cases in South Africa. The temperature would drop suddenly and in many convalescence would ensue, but in others, after an interval of some days apyrexia, the temperature would rise and pursue a typical enteric course.

Again, in those whose immunity is lower, though still great, the infection is marked by a few days' fever often ending in complete recovery, yet in others relapses will occur. I have in my possession fifty-nine charts of such short and mild febrile attacks, followed by relapses usually of greater severity than the primary illness. The diagnosis of these apparently insignificant febriculas may be confirmed in a more tragic manner by perforation taking place without warning. Velich\(^2\) states that such cases cause 2 per cent. of the sudden deaths occurring in France. Forman and Selby\(^3\) in the Journal of the Royal Army Medical Corps, January, 1905, record an eight day fever followed by a fatal relapse.

These mild cases figure largely in returns as "simple continued fever." I found\(^4\) that they were relatively more numerous amongst the inoculated than the uninoculated. The mortality of 947 cases of enteric fever amongst the uninoculated was 14·25 per cent., while that of 263 cases amongst the inoculated was 6·8 per cent. The average duration of pyrexia in the former class was twenty-eight days and in the latter fifteen days. Relapses were four times more frequent in the uninoculated.

The true nature of these abortive fevers has long been known to Army medical officers. In the notes for the guidance of officers

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\(^1\) West, Journal of the Royal Army Medical Corps, December, 1904, p. 655.

\(^2\) Velich, Arch. f. Hyg., clx., 2, p. 118.


joining the Suakim Expeditionary Force, issued by the Medical Department, War Office, February 14th, 1885, the following occurs: "The events making up the medical history of an army in the field develop themselves with a regularity which is almost monotonous. Looseness of the bowels, under the name of camp diarrhoea, begins to come on almost as soon as the army takes the field. This is in a large number of cases compatible with good health. Soon cases of fever appear, some of very brief duration, which are classified as 'heat fever,' and some are attended with diarrhoea, marking the commencement of enteric fever. The disease embraces every variety from the mildest to the severest types, from the so-called ambulant to the most fatal forms. The disease occasionally runs so mild a course as to resemble febrile dyspepsia, and then the fever fails to be recognised at all or fails to be rightly designated. One thing is certain. The tabulated number of admissions falls very short of the number of cases that have really suffered from enteric fever. The high rate of mortality is mainly attributable to the fact that only the severe and more pronounced forms are diagnosed and returned as enteric fever. It must be borne in mind that this fever does not invariably conform to the temperature ranges which have been far too arbitrarily laid down by medical authors." Those who took part in that expedition know that this forecast was accurate to the letter. The prevalence of gastric derangements premonitory to an epidemic of typhoid has been noted in the Worthing, Maidstone and Lincoln epidemics. The statistics of the Spanish-American War are most illuminating: 15·3 per cent. of the troops who had not suffered from diarrhoea developed enteric fever, while only 6·8 per cent. of those who had had previous attacks of diarrhoea contracted enteric. Hence it must be inferred that a large proportion of such cases of looseness of the bowels was in reality enteric fever, which conferred on the subjects immunity against further attacks.

Still further proof from the epidemiological side that "simple continued fever" is enteric fever, is afforded by the masterly analysis of the statistics of the fevers of Pietermaritzburg by Lieutenant-Colonel R. J. Simpson, C.M.G., R.A.M.C. He showed that there is a strong positive correlation between simple continued and enteric fever. The curves of their respective seasonal prevalence closely correspond, implying a common factor in their causation. Major

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1 Simpson, Journal of the Royal Army Medical Corps, October, 1905, v., p. 503.
J. W. Cockerill\(^1\) has arrived at a similar conclusion from a careful study of the epidemiology of the continued fevers of Bermuda.

Finally, that such short febrile attacks are due to the enteric bacillus has been demonstrated by the cultivation of that microbe from the blood. Biffi and Galli\(^2\) obtained Eberth's bacillus from the blood of twenty-seven out of thirty cases of mild pyrexia examined. Perquis\(^3\) similarly has grown the microbe from the blood of those subject to only transitory fever. It must here be noted that the blood of "typhoid carriers" does not contain the bacillus.

At the top of the scale of severity of typhoid infection we have cases which present the picture of the disease as it is usually painted in text-books, concerning which there is no doubt clinically. Treupel\(^4\) observed a typical temperature curve in only 46 per cent. of his 60 cases.

We hope to have made plain the protean characters which infection with the enteric bacillus may assume. We now proceed to compare these with the syndrome presented by the invasion of the paratyphoid bacillus.

Paratyphoid fever is not a well-defined entity. It is impossible to find a diagnostic point by which it may be separated from enteric. Most of the published cases are described as resembling typhoid fever. The lassitude, head- and backache, ill-defined gastrointestinal symptoms at the outset, in no way differ from enteric. It may commence suddenly, but in about 10 per cent. of enteric attacks the symptoms begin abruptly. In four or five days the clinical picture is completed in the typhoid state and posture, flushed cheeks, perhaps herpes on the lips, typhoid spots, pain and gurgling in the right iliac fossa, enlarged liver and spleen, slight bronchitis, diarrhoea or constipation, pulse dicrotic and slow, epis-taxis. The temperature is rarely higher than 104\(^\circ\) F., and remains raised for ten or fifteen days in the severer cases. Defervescence takes place by lysis. Shorter attacks have also been recorded with sudden onset, vomit¿ting, diarrhoea and pyrexia, and thus resemble food poisoning. In these cases also typhoid spots have been seen. The complications are seldom serious. Intestinal hæmorrhage is rare, perforation has not been reported. Pleural effusion, phlebitis,

\(^1\) Cockerill, *Journal of the Royal Army Medical Corps*, June, 1905, iv., p. 796.
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meningitis, and neuritis may occur. Suppurations beneath the periosteum in the gall-bladder and testis have been noted. The urine is slightly albuminous in one-third cases. The changes in the formed elements of the blood are similar to those which take place in enteric fever, that is to say, leucopenia with a mononuclear increase in the earlier period, followed by an eosinophilia in the later, is observed. The incubation period, according to Prieffer1 and Sacquepée, is usually fifteen days. It may sometimes be curtailed to five or six days.

Cases of paratyphoid fever have been reported in the United Kingdom, France, Germany, Italy, Roumania, United States, Brazil, India, Ceylon, China, Japan, Philippines, Tunis, and Senegal. Two instances in South Africa came under my own observation. The disease is chiefly prevalent during the enteric season. Boycott2 met with three cases of paratyphoid fever and 176 of enteric. Foreign observers put the ratio higher. Wells states that 10 per cent. of typhoid-like fevers in Chicago are paratyphoid. Kolle3 estimates the proportion at the same figure. I myself have isolated the paratyphoid bacillus in two and the enteric in forty-six cases.

About 500 accounts of paratyphoid infection are to be found in medical literature.4 The mortality of these was about 2 per cent. Post-mortem appearances have been recorded in fifteen. In many of these necropsies the evidence of paratyphoid infection was not convincing. In Strong's5 case typhoid lesions were found in the intestine. The agglutinative power of the serum on the paratyphoid culture isolated was not tested. Berg and Libman6 observed typhoid ulceration of the bowel in their case. The action of blood was five times as great on the typhoid bacillus as on the growth isolated. Ascoli's7 description of the post-mortem appearances and of the micro-organism obtained in his instance are consistent with enteric fever. Schmidt's8 patient succumbed to pyaemia consequent on suppuration of the gall-bladder. He isolated a microbe like the typhoid bacillus, but considered it was a para-

typhoid, since strong typhoid serum did not clump it. Sacquepèè has grown, however, such non-clumping strains of Eberth's bacillus from a typhoid spleen. Bancel has met with similar cultures from three typhoid abscesses. Nicolle and Trenel and Batty Shaw have had a like experience. Tuttle also concluded that he was dealing with a paratyphoid bacillus because the culture failed to agglutinate with typhoid serum. Typhoid ulcers were found in the ileum. In the bowel of Jochman's patient there were no changes to be seen, but death was caused by scarlet fever. The paratyphoid bacillus was obtained only on the day preceding. Wells and Scott observed in their patient, who succumbed on the thirty-third day, several superficial confluent ulcers with greyish basis in the last two feet of the ileum, more closely resembling dysentery than enteric. The lymphatics were not infiltrated nor were the mesenteric glands swollen. The ulceration was limited to the ascending colon in Luksch's necropsy. Le Count and Kirby observed only slight swelling of Peyer's patches in an infant of four months, whom they thought died of a paratyphoid A infection, but as their microbe failed to ferment mannite, levulose and maltose, it differed from it. Sion and Negel have found congestion of the mucous membrane of the ileum and colon, but neither the follicles nor mesenteric glands were enlarged. Brion noted typhoid lesions in his case, Firth in his, Guerbet and Henry in theirs, Castellani in his also. In the South African instance described below enteric ulcers were present.

It is therefore clear that there are no definite post-mortem appearances by which paratyphoid fever can be recognised. Many examples of enteric fever have been recorded in which no changes have been discovered in the intestinal canal. With only a passing

7 Wells and Scott, Journ. of Infectious Diseases, i., p. 72, 1904.
10 Sion and Negel, Cent. f. Bakt. Orig., October 8th, 1902, xxxii., p. 482.
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reference to Chiari and Kraus, monograph on typhoid fever without ulceration, published before modern technique for the identification of the B. typhosus had been introduced, Weichardts, Guizetti, Michelazzi, and Chevrel, have all recorded cases in which the typhoid bacillus has been isolated from the blood, though no vestige of bowel ulceration was discovered at the post-mortem examination.

For the clinical observer, therefore, there is only one fever—enteric, and it is left to the bacteriologist to determine the actual infecting agent. Cockerill in his study of the prevalence of continued fevers in Bermuda takes up this point of view on epidemiological grounds.

The possibility of obtaining an exact diagnosis hinges on the fact that the fevers under discussion are bacteriæmas and not merely local infections of the intestinal tract. Consequently, if blood be withdrawn under conditions which preclude contamination and introduced into nutrient media, the bacillary growths obtained are the infecting agents, since blood in health is sterile even in "typhoid" and "paratyphoid carriers." Positive results are unequivocal. But fresh human blood exerts a lethal action on typhoid and paratyphoid bacilli. This bactericidal power is enormously increased in these fevers. On the authority of Korte and Sternberg it may sometimes be evident if the blood be diluted 4,000,000 times. Therefore it is necessary that the ratio of the medium to the blood inoculated should be large, or that the germicidal constituent be inhibited by means of bile—Conradi's method. In practice it is usual to draw 5 to 10 cc. of blood from the median basilic vein and distribute in four or five flasks each containing 300 cc. of broth. One of the latest contributions on blood culture with the aid of bile is Kayser's. He recommends that 2·5 cc. of blood should be mixed with 5 cc. of sterile ox bile. After fourteen to twenty hours incubation at 37° C. he plates on Endo's or Drigalski-Conradi's agar. He thus isolated Eberth's bacillus from 117 typhoid patients and paratyphoid bacilli from seven. In common with other observers he found that the earlier in the course of

1 Chiari and Kraus, Zeit. f. Heilkunde, 1897.
2 Guizetti, Polieclin. Roma, 1901, viii.
the illness he made the examination the greater success he attained. He recovered the typhoid bacillus from all the enterics in the first week, and the paratyphoid from 80 per cent. of the early paratyphoid fevers. He remarks that the latter micro-organisms disappear from the blood more quickly than the former. If he made use of a small quantity of blood, such as might be drawn from the finger-tip, his failures were increased. The literature of blood-culture in typhoid fever is now extensive. I have collected the results of thirty-seven investigators. Eberth's bacillus was isolated from the blood of 1,150 cases out of 1,303 examined, that is in 88.4 per cent. The number of times paratyphoid bacilli have been recovered from the blood is not very large. Chevrel records twenty positive results, Kayser seven, Conradi six, Korte two, Coleman and Buxton, Brion, Gwyn, Allen, Castellani, each one.

Paratyphoid bacilli belong to the typhocoli group of bacteria. They occur as short motile rods with rounded ends, 3 to 4 μ long, and 0.6 μ wide. In broth cultures their length may be much increased. They possess two to six flagella and are non spore bearing. They do not retain the stain with Gram. Bipolar colouration is frequent. It is usual to subdivide paratyphoid bacilli into A and B varieties, though this division is somewhat arbitrary and does not embrace all the strains hitherto described.

<table>
<thead>
<tr>
<th><strong>Paratyphoid A.</strong></th>
<th><strong>Paratyphoid B.</strong></th>
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<tbody>
<tr>
<td><strong>Broth.</strong></td>
<td><strong>Broth.</strong></td>
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<tr>
<td>Freer multiplication, with pellicle formation at times.</td>
<td>Freer multiplication, with pellicle formation at times.</td>
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<tr>
<td>No indol in four days.</td>
<td>No indol in four days.</td>
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<tr>
<td>Proteinochrome reaction in 2 days.</td>
<td>Proteinochrome reaction in 2 days.</td>
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<tr>
<td><strong>Gelatine slope.</strong></td>
<td><strong>Gelatine slope.</strong></td>
</tr>
<tr>
<td>Colonies somewhat thin and translucent, less furrowed than typhoid.</td>
<td>Thick, opaque, white abundant growth.</td>
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<tr>
<td>No liquefaction.</td>
<td>No liquefaction.</td>
</tr>
<tr>
<td><strong>Agar slope.</strong></td>
<td><strong>Agar slope.</strong></td>
</tr>
<tr>
<td>Like typhoid.</td>
<td>Like B. coli.</td>
</tr>
<tr>
<td><strong>Potato.</strong></td>
<td><strong>Potato.</strong></td>
</tr>
<tr>
<td>Like typhoid.</td>
<td>Like B. coli.</td>
</tr>
<tr>
<td><strong>Milk.</strong></td>
<td><strong>Milk.</strong></td>
</tr>
<tr>
<td>Unchanged.</td>
<td>Unchanged first ten days, then thinning and brownish colouration.</td>
</tr>
<tr>
<td><strong>Litmus milk.</strong></td>
<td><strong>Litmus milk.</strong></td>
</tr>
<tr>
<td>Slight permanent acidity.</td>
<td>Early faint acidity, followed by permanent alkalinity.</td>
</tr>
<tr>
<td><strong>Lactose media.</strong></td>
<td><strong>Lactose media.</strong></td>
</tr>
<tr>
<td>No gas, slight acidity.</td>
<td>No gas, slight acidity.</td>
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</tbody>
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1 Castellani, Lancet, February 2nd, 1907, p. 284.
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**Paratyphoid A.**

- Glucose media.
  - All reactions negative.
  - Mannite, Dulcite, Glycerine.
  - Acid.
  - Lfoxulose, Maltose, Galactose.
  - Acid and gas.
  - Saccharose and Raffinose.
  - Unaffected.

**Paratyphoid B.**

- Glucose media.
  - Acid and gas.
  - Mannite, Dulcite, Glycerine.
  - Acid.
  - Lfoxulose, Maltose, Galactose.
  - Acid and gas.
  - Saccharose and Raffinose.
  - Unaffected.

- Glucose neutral-red media.
  - Acid and gas.

- Drigalski-Conradi's agar, or Firth's litmus-lactose-agar.
  - Blue, like typhoid.

- Endo's agar.
  - Colourless colonies like typhoid.

- Proskauer and Capaldi No. 1.
  - Slow production of acidity.

- Proskauer and Capaldi No. 2.
  - Marked acidity, followed by alkalinity.

- Malachite green agar.
  - As dewdrops, like typhoid, destroying colour and forming clear zone.

There are several dyes sold under the name of malachite green, some of which are useless for the purpose. Loeffler, who introduced the method, employs tetramethyl-diamidophenylcarbinol zinc chloride double salt in the proportion of 0.006 to 0.007 per cent. With this the growth of the B. coli communis is inhibited.

Vaccinated media.—Paratyphoid A does not grow on agar which has served as a medium for paratyphoid A, paratyphoid B, B. coli communis or B. typhosus.

Paratyphoid B thrives on agar from which growths of paratyphoid A and B. typhosus have been removed, feebly on B. coli media, and very scantily or not at all on agar slopes from which cultures of paratyphoid B have been washed away.

Virulence.—The paratyphoid bacilli are very virulent. Feeding animals with paratyphoid B usually causes death. Their pathogenic action on man is sometimes highly marked. The number of meat-poisoning epidemics which have had their origin in paratyphoid B infections is large. Keyscher records an extensive outbreak in Berlin caused by meat infected with paratyphoid B, and refers to similar epidemics previously reported. Fromme and Heller have published similar infections this year.

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Vaccination.—It is possible to protect animals against several lethal doses of paratyphoid A and B by injection of killed cultures. Their resistance against \textit{B. typhosus} is also thereby increased. The serum possesses bactericidal, agglutinative and immune bodies. The latter are fixed by the specific bacillus. Thus paratyphoid B bacillus fixes the paratyphoid B immune body, the paratyphoid A the A immune body. Neither are fixed by Eberth's bacillus, except to a limited extent. These experimental sera are of great value in the identification of the groups. The blood of animals immunised with the "A" variety of paratyphoid bacilli, clumps other A strains in approximately as high dilutions, but only influences paratyphoid B when much less diluted. Paratyphoid B sera do not of necessity agglutinate all strains of paratyphoid B in the same ratio. They have no great action on paratyphoid A. As a general rule neither A nor B experimental sera agglutinate the enteric bacillus.

The vitality of members of the paratyphoid group is higher than that of the coli, typhoid and dysentery bacilli. They are also more resistant to heat than the latter, but exposure at 60° C. for five minutes destroys them.

Paratyphoid A infections in man are of infrequent occurrence. Only about twenty cases have been recorded. Unlike the typhoid bacillus the paratyphoid group is widely diffused in nature. Morgan has discovered paratyphoid A in the intestinal canal of healthy animals. Boycott isolated paratyphoid A from the urine and faeces of a patient whose blood reacted to paratyphoid B. Smallman\textsuperscript{1} found paratyphoid B in the tissues of 10 per cent. of 200 guinea pigs, treated with living or dead typhoid bacilli or their toxins. MacConkey\textsuperscript{2} met with the same experience.

Bacteriological examination of dejecta.—Boycott urges the preliminary incubation of faeces in dulcite bile-salt broth twenty hours at 37° C. The paratyphoid organisms ferment dulcite freely and tend to outgrow most of the coli. Plates of MacConkey's bile-salt-neutral-red-lactose-agar are streaked with the above. Dysentery, typhoid and paratyphoid bacilli leave the medium unchanged, while the colon bacillus decolourises it. Dulcite is at present unobtainable. Loeffler's malachite green broth may be substituted for the elimination of the colon bacillus, and Firth's lactose-litmus-agar for MacConkey's agar. The blue colonies on the latter are inoculated into glucose broth. If acid and gas are produced, enteric bacilli are excluded, and the presence of paratyphoid bacilli rendered prob-

\textsuperscript{1} Smallman, \textit{Journal of the Royal Army Medical Corps}, July, 1905, p. 137.
\textsuperscript{2} MacConkey, \textit{Journal of Hygiene}, 1905, p. 343.
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able. They are also introduced into mannite-nutrose-litmus water, which remains unchanged if they are dysentery bacilli, Shiga type. Subcultures are made into litmus milk, in which paratyphoid A causes permanent acidity, and paratyphoid B acidity followed by alkalinity in ten days or a fortnight. In neither case curdling occurs. The clumping reactions of normal serum and of the blood of the patient on the micro-organism isolated is then ascertained. But it must be noted that paratyphoid bacilli obtained from dejecta are not so agglutinable as those grown from the blood. If in the course of an epidemic a paratyphoid bacillus having the same characteristics is repeatedly recovered from the dejecta to the exclusion of every other pathogenic agent, this microbe very probably represents the cause of the epidemic. But this cannot be maintained in sporadic cases. Then the only criterion of certainty is blood culture. Paratyphoid bacilli have been discovered not infrequently in the stools of persons suffering from enteric fever. (Kayser). The diagnosis of paratyphoid fever has been made, in the great majority of instances reported, on account of the isolation of a paratyphoid bacillus from the dejecta, or of agglutinative reactions, on which too great confidence cannot always be reposed, as will be seen later. It is, therefore, not improbable that some of these cases should not have fallen under that heading. Like the typhoid bacilli, paratyphoid may appear in the urine and feces for weeks after convalescence. Lentz states the latter continue from six to fifteen months in 4 per cent. of the cases.

A few reports of short febrile attacks have been published in which the \textit{B. coli communis} has been grown from the blood. Canon \textsuperscript{1} has collected the accounts of five examples of this infection. Coleman and Buxton relate two. Castellani \textsuperscript{2} describes a short fever occurring in Ceylon. In one case he isolated the \textit{B. coli communis} from the blood. Moutier \textsuperscript{3} reports a \textit{B. coli} fever.

THE DIAGNOSIS OF TYPHOID AND PARATYPHOID FEVERS BY AGGLUTINATION TESTS.

Some normal human bloods will agglutinate completely the typhoid bacillus in a ten-fold dilution. The serum obtained from 2 per cent. of healthy people will produce traces of clumping when diluted 30 times. Also a normal blood diluted 50 to 150 times may clump certain paratyphoid strains. Several cases of meningitis have been reported in which the blood has agglutinated the \textit{B.

\textsuperscript{1} Canon, \textit{Die Bakteriologie des Blutes bei Infektionskrankheiten}, 1905.
\textsuperscript{2} Castellani, \textit{Journal of Hygiene}, January, 1907.
\textsuperscript{3} Moutier, \textit{Arch. de Med. exp. et d'anat. path.}, xvi., 5, p. 649.
typhosus in 30-or 40-fold dilutions. In streptococcic, pneumococcic, proteus and coli infections a positive reaction up to 1 in 40 has been observed. By inoculating a rabbit with proteus and staphylococcus Jochmann\(^1\) obtained a serum capable of clumping the enteric bacillus when diluted 640 times. Lüdke\(^2\) and Netter\(^3\) found a reaction from 1 in 20 to 1 in 1,000 in various diseases of the liver. Kaemmerer\(^4\), however, in investigating fifty cases of jaundice, noted that the blood of two only clumped the enteric bacillus. My own observations on the blood of cases of epidemic jaundice, hepatic abscess and kala-azar infection of the liver have yielded negative results. I have not observed clumping of the enteric bacillus with a 20-fold dilution of the blood examined macroscopically at the end of twenty-four hours. Nevertheless it is clear that a positive Widal reaction with the typhoid bacillus is not always indicative of enteric fever. On the other hand, it cannot be too strongly emphasised that the absence of the agglutination of the enteric bacillus in a febrile case does not exclude infection by that microbe. Coleman and Buxton state that in 10 per cent. of 604 cases the serum reaction on B. typhosus was negative, although that organism was grown from the blood. Warfield\(^5\) isolated the enteric bacillus from the blood of thirty-seven patients. In twelve of them the clumping reaction failed. Seeman\(^6\) records a negative Widal reaction in eight out of thirty-two cases the blood of which gave the typhoid bacillus. Perquis in twelve out of thirty-three. Rolly\(^7\) in sixteen out of fifty. Ruata\(^8\) in two out of twelve. Castellani\(^9\) in four. Hewlett\(^10\) in three. Kayser grew typhoid or paratyphoid bacilli from the blood of nineteen cases which failed to clump the respective cultures. His cases were examined mostly in the second week of the fever. I myself failed to obtain agglutination in a 20-fold dilution in twenty-eight febrile attacks which were afterwards proved to be enteric fever. The importance of repeating the blood test is recognised by all. Lentz relates a case in which the serum reaction was negative till the

\(^{7}\) Busquet, Thèse de Paris, 237, 1903-1904.  
\(^{10}\) Castellani, Cent. f. Bakt., April 16th, 1902.  
twenty-eighth day of the fever, and Coleman one till the seventy-first
day. In a recent typhoid epidemic in South Wales in which there
were between eighty and ninety simple continued fever or "influenza" cases to about a dozen of typical enteric, positive serum reactions
were observed only on a second or third examination of the milder
cases. In the seventeenth annual report of the Medical Officer of
Health, West Riding of Yorkshire, reference is made to an outbreak
of fever in 1890. Many of the cases were typical enteric, while
many others were not, and were called under another name. In
1905 another epidemic occurred presenting a similar feature of the
mixed type of illness, but now Widal's reaction repeated on several
occasions demonstrated that the whole outbreak was enteric pure
and simple. S. Monckton Copeman in his report on the prevalence
of enteric fever at Fulbourn Asylum, Cambridge, states that owing
to the mild symptoms presented by many of the patients earliest
attacked the disease was called "influenza," but the results of serum
testing, more than once if necessary, showed the true nature of the
fever.

In paratyphoid A infections in man the index is usually low, 100
to 200. In paratyphoid B infections the reverse is the case, and
the blood of patients from whom this microbe has been isolated
may clump it when diluted 140,000 times (Zupnik2). Human
paratyphoid sera most often have only a feeble effect on the
typhoid bacillus, yet Schottmüller, Drigalski-Conradi, Jurgens,
Hunermann, have reported exceptions.

The sera of typhoid patients, on the other hand, may agglutinate
the paratyphoid group in as high as, or in higher dilutions than,
they clump Eberth's bacillus. Fox, Graf, and Jurgens each
record instances in which the serum derived from a patient
proved to be infected with Eberth's bacillus by blood culture has
clumped the paratyphoid in higher dilutions than the typhoid.
This fact is of great importance to remember. When a human
serum agglutinates the typhoid bacillus in higher dilutions than
the paratyphoid, then the infection is probably typhoid. But
when a human serum acts more energetically on the paratyphoid
than on the typhoid, we must not conclude on that account that

the fever is paratyphoid. We may in such a case gain some aid by making use of Castellani's test.\textsuperscript{1} He immunised a rabbit against Eberth's bacillus, and found that its serum not only clumped that micro-organism but would likewise agglutinate the \textit{B. coli communis}. Treatment of the serum with an excess of typhoid bacilli removed both the coli and typhoid agglutinins. He then inoculated an animal with both coli and typhoid cultures. The serum in this instance, after saturation with Eberth's bacillus, still retained its activity on the colon bacillus; and when saturated with the colon still agglutinated the enteric bacillus. Therefore, if we are called upon to investigate a serum which clumps both the typhoid and paratyphoid emulsions and surmise that it arises from a true typhoid infection, we first find the limits at which it clumps the paratyphoid bacillus. Then we treat a portion of it diluted ten times with an excess of typhoid agar emulsion. After a stay of two or three hours in the 37° C. chamber, we redetermine the agglutination index. If this serum be derived from a patient suffering from typhoid fever the paratyphoid agglutinins will have fallen to zero. If, on the other hand, the blood was obtained from a paratyphoid patient, the paratyphoid index will remain the same as on the first determination. This test has been extensively used. Rieux and Sacquepée,\textsuperscript{2} who have devoted much attention to the method, conclude that it usually indicates the infecting organism. That is to say, the bacillus which deprives the serum of all the agglutinins is the cause of the fever. The rule, however, is not absolute, and anomalous results are not infrequent.

In conclusion, it may be added that to gain the fullest information possible by means of serum reactions, it is necessary to find the limits of dilution at which the blood acts on the micro-organisms, and by repeated examinations to trace out the agglutination curve. It is essential also to control the cultures used by means of experiments with the blood of normal individuals.

The following are the only two examples of paratyphoid infection which have come under my notice. Both occurred in Pretoria:

(1) Fever with typhoid-like course and lesions. Paratyphoid A bacillus from spleen.

A native youth gave a history of an illness which resembled enteric fever of some weeks' duration. On admission to hospital he presented the usual signs and symptoms of that disease.\textsuperscript{3} Shortly

\textsuperscript{1} Castellani, \textit{Zeit. f. Hyg. u. Inf.}, 1902, xl., p. 1.
\textsuperscript{2} Rieux and Sacquepée, \textit{C. R. Soc. Biol.}, December 16th, 1905, lix., p. 663.
afterwards he developed lobar pneumonia, from which he succumbed. Typical healed and healing enteric ulcers were found in the lower part of the ileum, which was much congested. Somewhat higher the Peyer’s patches were greatly thickened. Small central ulcers were observed in a few of them. The mesenteric glands were slightly enlarged and congested. The upper lobe of his left lung was in a state of pneumatic consolidation. The paratyphoid bacillus was isolated from his spleen, which weighed 8 ounces, but Eberth’s bacillus was not detected. Fraenkel’s pneumococcus was recovered from the pneumatic lung. His serum did not agglutinate the typhoid bacillus in a 50-fold dilution, but reacted with the culture from his spleen. This growth resembles the enteric bacillus in being a motile rod which does not retain the stain with Gram. Unlike Eberth’s bacillus, it has two flagella at each end only; and it produces acid and gas in glucose broth. It does not ferment lactose nor does it curdle milk, and thus differs from the colon bacillus. Litmus milk is rendered permanently acid. This identifies it as a paratyphoid A strain. Further resemblances to paratyphoid A are found in its behaviour in broth, gelatine, agar, potato, Proskauer and Capaldi’s, Drigalski-Conradi’s, Firth’s litmus-lactose, neutral-red, caffeine, malachite-green, orcein, tartarated iron, nutrose-litmus, and sanatogen-litmus media, the latter two combined with lactose, glucose, saccharose, maltose, mannite, salicin. The identification by cultural tests is, therefore, complete, and is confirmed by means of serum reactions. Antityphoid serum (titre 600) in a 50-fold dilution does not clump it. The blood of a rabbit immunised with paratyphoid A (Brion and Kayser) agglutinates the splenic culture in as high dilutions as paratyphoid A. Moreover, treatment of the serum with an emulsion of the above, described bacillus removes all the agglutinins for paratyphoid A (Castellani’s test). Also the blood of a rabbit inoculated with this South African bacillus is as effective on paratyphoid A as on it. Paratyphoid A, too, deprives this serum of all the agglutinins capable of acting on the growth. Experimental paratyphoid B serum in a 50-fold dilution fails to clump it. The bacillus does not grow on agar which has served as a medium for B. coli, typhosus, paratyphoid A, paratyphoid B.

(2) Enteric-like fever.—Paratyphoid bacillus (new type) from subperiosteal abscess of tibia.

S. S. C. had contracted enteric fever in Egypt fourteen years previously. The illness for which he was admitted had a sudden onset marked by rigors, headache, pain in epigastrium and vomiting. He attributed his ailment to some salad he had eaten some
days before, which might have been contaminated with sewage. His temperature curve pursued an enteric-like course and had declined to normal limits in twenty-one days. His blood, tested in the third week of the disease, gave a positive reaction with the enteric bacillus in a 50-fold dilution. No sooner had the fever abated than he complained of pain in his left tibia of marked severity at night. A fortnight later a free incision was made over the painful area which had now become swollen and inflamed. About 7 cc. of yellow pus were evacuated which contained in pure culture the paratyphoid bacillus. This was agglutinated by his serum in a 50-fold dilution, but not in a 200-fold. Normal blood was without action on it. Strict precautions were taken to prevent contamination at the time of the operation and subsequently. Consequently, after an interval of a fortnight, agar slopes streaked with a glass filament which had been introduced into the bottom of the sinus again gave the micro-organism in pure culture. The wound healed in a month. After a time, however, the scar broke down, but the sinus thus exposed proved sterile. A sequestrum was ultimately removed.

The microbe isolated is a feebly motile rod, possessed of three long flagella at either end, which stain with difficulty. It is Gram negative and non-spore bearing. In broth it grows rapidly with even turbidity during the first twenty-four hours. Later a pellicle forms. Not a trace of indol is observed in a week, though marked in three weeks. On gelatine the colonies resemble those of paratyphoid A. There is no liquefaction. On agar there is thick growth, almost B. coli-like. On potato it produces a creamy layer in twenty-four hours without any gas bubbles. In litmus milk it produces strong acidity and reduces the colour. No curdling takes place. Nevertheless, on boiling these milk cultures immediate clotting occurs, a characteristic which Biffi has observed in the close allies of B. coli commutis, though not in paratyphoid A. In lactose media no gas is generated but only slight acidity. On the other hand, in glucose media its action is very energetic, acid and gas being abundantly formed. Maltose, cane sugar and salicin are also rapidly fermented with production of acid, while mannite is but feebly changed. Glucose-neutral-red media become fluorescent. On Drigalski-Conradi's and Firth's litmus-lactose-agar the colonies are blue. Acidity is produced in twenty-four hours in Proskauer and Capaldi's No. 1 medium, which then becomes alkaline. In Proskauer and Capaldi No. 2 there is faint acidity in

the first day, followed by increasing alkalinity. In hydrocele serum litmus water a pellicle forms and clotting takes place. In 1 per cent. sanatogen or nutrose, litmus water media combined with various sugars, pink milky turbidity is produced in the glucose, cane sugar, maltose, salicin tubes. The action is much less marked in those containing lactose and mannite. Slight growth is observed on agar, from which the Eberth's bacillus and paratyphoid A have been removed, but none on old paratyphoid B and B. coli tubes. Anti-typhoid serum (value 600) does not clump it in a fifty-fold dilution. Paratyphoid A, paratyphoid B, Gaertner and Aertryck sera, in dilutions above ten, do not agglutinate it. The blood of the rabbit immunised with the paratyphoid bacillus of the previous case in a ten-fold dilution, had no action on it. In short, while this bacillus differs from B. coli communis in not fermenting lactose, and in its feeble action on mannite, it claims relationship to the paratyphoid group by its marked action in generating acid and gas in glucose media. Nevertheless, it is separated from the more common types of paratyphoid A and B, through its splitting action on cane sugar and salicin. Its production of permanent acidity in milk would tend to connect it with paratyphoid A, but its more vigorous growth on agar, and its strong reducing power on litmus-neutral-red, malachite-green and orcein, distinguish it from the cultures of paratyphoid A in my possession. It may have some affinity to Strong's paratyphoid bacillus which fermented cane sugar. The low agglutinability of the bacillus by the patient's blood (50) is rather remarkable, but both Bancel and Batty Shaw have noticed this phenomenon in typhoid cultures isolated from post-typhoid abscesses. Paratyphoid bacilli from the dejecta frequently present the same peculiarity.

It is probable that the patient passed through an attack of enteric fever, since his serum reacted with typhoid emulsion in the third week in a 50-fold dilution, and in no higher dilution with the paratyphoid bacillus isolated from the abscess. It is only in exceptional instances of paratyphoid infection in man that the enteric bacillus is clumped in as high dilutions as the paratyphoid. Moreover, a month after the abscess had been evacuated, his blood agglutinated the typhoid bacillus in a 60-fold dilution, but failed to clump the paratyphoid in a twenty. Libman relates a paratyphoid infection secondary to enteric fever. But the list of cases reported of suppuration arising from paratyphoid bacilli is not long. Widal and Nobécourt obtained paratyphoid B from a thyroid abscess. Achard

1 Libman, Journ. of Medical Research, 1902, viii., p. 168.
and Bensaude\textsuperscript{1} from a case of osteomyelitis. Kranepuhl\textsuperscript{2} also from an abscess. B. Fischer\textsuperscript{3} from a subcostal abscess. Cushing recovered paratyphoid A from a chondrosternal suppuration. Pratt\textsuperscript{4} found paratyphoid B in an inflamed testis.

With regard to the specific treatment of these fevers, the theory and results of therapeutic inoculations of killed cultures of the invading microbe in the course of infections, were discussed in the number of our Journal for September last.\textsuperscript{5} Attention was drawn to Fraenkel’s series of typhoid cases treated by hypodermic injection of typhoid vaccine. More recently M. W. Richardson\textsuperscript{6} has recorded twenty-two cases of enteric fever benefited by typhoid toxin inoculations.

We are now required to isolate the infecting agent from the blood of febrile cases as soon as they come under our observation, not only for diagnostic and prognostic, but for therapeutic purposes, since recent researches show that the early specific treatment of a fever with a vaccine prepared with the actual invading microbe, offers a more hopeful prospect of success than the use of empirical remedies.

The main conclusions of this paper may be now summarised.

(1) The typhoid bacillus may be an inhabitant of the bile passages or alimentary canal without producing illness.

(2) When the typhoid bacillus invades the blood it may cause trivial symptoms with short pyrexia only.

(3) Paratyphoid infections cannot be distinguished clinically from enteric.

(4) Paratyphoid infections are less common than typhoid.

(5) A negative serum reaction with the enteric bacillus, or a positive reaction with a paratyphoid bacillus, is not sufficient to justify a diagnosis of paratyphoid fever.

(6) In every febrile case blood cultures should be made at once for diagnostic, prognostic and therapeutic purposes.

I am greatly indebted to Dr. A. E. Boycott of the Lister Institute, for the paratyphoid A, paratyphoid B, Gaertner and Aertryck rabbit sera, and to Professor Leishman for the paratyphoid A (South Africa) rabbit serum.

\textsuperscript{1} Achard and Bensaude, Bull. et mem. de la Soc. med. des Hop. de Paris, xiii., 220.
\textsuperscript{3} Fischer, R. Koch’s Festchrift, pp. 271-296.
\textsuperscript{5} Birt, Journal of the Royal Army Medical Corps, September, 1906, vii., p. 279.
\textsuperscript{6} Richardson, Journ. of Med. Research, February, 1905, xiii., p. 3.