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PARATYPHOID FEVER

19.

BY

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PARATYPHOID FEVER[1]

By R. D. KEITH, M.A., M.D.

Introductory.

ALTHOUGH the science of Bacteriology is as yet practically in its infancy, it is beyond question that with its birth and development many difficult problems in medicine have been solved, on many obscure points light is being from time to time shed, and new methods of diagnosis and treatment are being continually devised. It is only, however, by the combined labours of bacteriologists and clinicians that the full benefits of this science can be attained to, and the more closely the workers in the wards and in the laboratory combine, the more likely are these benefits to be speedily obtained and developed. The results found in the working out of the disease which I have chosen as my subject, bear out these statements to no small degree, and in my opinion tend further to show to the practitioner the importance of a sound working knowledge of bacteriology.

The subject is one of great interest, not only from the point of view of diagnosis and prognosis, but also from that of a probable line of treatment, especially when one considers the results of experiments with regard to the sera of animals immunised against this disease. Further, it throws some light on the agglutinative reaction and its value for diagnosis and prognosis. As time goes on the subject is becoming more fully investigated and its aspects are becoming daily widened, and therefore a review of the matter at the present time is not inopportune.

[1] Honours Thesis for M.D. Aberdeen.

Under the term typhoid fever there is no doubt that up to recent times many cases were included which were not really cases of this disease, but were cases of other febrile diseases of a somewhat indefinite kind. It is extremely probable, for example, that the great pandemic of influenza of 1899-90 revived in the minds of many the remembrance of a disease on the existence of which they had not counted, and many sporadic cases of which were probably called typhoid fever, at a time when the accurate means of diagnosis of the present day were not extant. The discovery of the typhoid bacillus by Eberth in 1880, combined with the discovery of the Gruber-Widal reaction in 1896, has at the present time, however, rendered the diagnosis of typhoid fever practically a certainty; and of late years the combined labours of clinicians and bacteriologists have proved, what was doubtless suspected by many, the existence of a disease resembling typhoid fever of a mild type, but caused by a different organism. Epidemics as well as isolated cases of this disease, which is now known as paratyphoid fever, have been described, in which the nature of the disease has been made manifest either by the isolation of the organism, by the serum reaction, or both in combination. In Germany, France, Holland, Roumania, America and in this country, cases have been described.

This paper is intended to give some indication of our knowledge of this disease, including its causation and mode of spreading and infection, and its bearing on the value of the serum agglutination reaction.

Chronologically, the first case was described by Achard and Bensaude (1) in 1896. It was that of a woman of 24, who was admitted to one of the Paris Hospitals, suffering from metrorrhagia with diarrhœa, general weakness and lassitude. After eight days' treatment the bleeding ceased, but the general symptoms did not subside. The febrile course, which had been present since admission, continued, with the exception of two sudden depressions. The stools were thin and frequent, and on several occasions blood was seen in them. The spleen was somewhat enlarged and the tongue coated. Typhoid fever was suspected. Widal's reaction was at first negative, but was more or less positive on several occasions, on which it was afterwards tested. With a paratyphoid organism (*i.e.* an organism which resembled the typhoid bacillus) with which the reaction was done, it was positive throughout. A bacillus which differed slightly from the typhoid bacillus was isolated from the urine on two occasions, but from the blood and spleen as well as from the stools they failed to isolate a bacillus corresponding

to that in the urine. The bacillus was found to react to the patient's serum throughout, and was suspected to be the cause of the illness.

These observers also isolated from the pus of a chondro-sternal abscess, in an infant of 7 months, an organism which was said by them to be a paratyphoid bacillus. The patient in this case was diagnosed as suffering from "mucous fever," and showed broncho-pneumonia with typhoidal spots, constipation and swelling of the abdomen.

In 1897, Widal and Nobécourt (2) described a paratyphoid bacillus isolated from the fœtid pus of a thyroid abscess following a disease whose course resembled typhoid fever.

It was found that the organism isolated reacted well with the patient's serum, but that the typhoid bacillus was not agglutinated. The bacillus resembled the typhoid bacillus in many respects and was pathogenic for the smaller animals. The serum of animals immunised by it reacted with it, but not with the typhoid bacillus. They considered the organism to be the cause of the abscess.

The first observer to take up this subject in Germany was Schottmüller of Hamburg (3). In the General Hospital of St George in Hamburg, from June to December 1899, fifty cases of typhoid fever were examined by cultivation from the blood. Of these, forty cases, *i.e.* 80 per cent., gave positive results. In one case of apparently fairly typical typhoid fever, it was found that the organism isolated differed from that of typhoid fever in that it produced gas in glucose broth, and further that the serum of the patient did not agglutinate the typhoid bacillus in dilutions as low as 1 : 12 while it agglutinated the bacillus isolated in dilutions as high as 1 : 50, and after the temperature fell as high as 1 : 100. The sera of a number of undoubted typhoid patients were tried, and while with the typhoid bacillus they gave a reaction of 1 : 100, with the bacillus isolated from the patient above mentioned only one gave a reaction as high as 1 : 20, while the rest were entirely negative. It was therefore concluded that the cause of the disease was not the typhoid bacillus, but that it was an organism of a similar kind, viz., the bacillus isolated. Pursuing his investigations, Schottmüller (4) in 1900, out of sixty-eight cases of clinical typhoid observed in the same hospital, found in five cases a bacillus different from the typhoid bacillus and in no way to be regarded as the typhoid bacillus. This opinion he based partly on the cultural differences and partly on the serum reactions which he obtained in these cases, and in that of a medical man who had been infected by the bacillus of one of them. On consideration he came to the conclusion that the bacilli isolated were the cause

of the disease, and that of six cases there were two groups, one of which contained two, and the other four bacilli. These two groups, subsequently described in the literature as type "A" and type "B," differ in degree both culturally and in their serum reactions. It was found that the serum reactions of the members of the first group corresponded with one another, but not with those of the second group, and that while the serum reactions of the members of second group corresponded with one another they differed from those of the first.

Schottmüller gave the disease the name "paratyphoid fever" from its close resemblance to typhoid fever, and called the organism isolated the paratyphoid bacillus. He calls attention to the fact that these cases of the disease constitute 8 per cent. of the typhoid-like cases in 1900, in the hospital of St George. He also commented on the mildness of the disease on the whole, and on the absence of complications.

The next observer in this field was Kurth (5) in Bremen. In this town in 1900 an outbreak of typhoid fever occurred during which careful examinations of the cases were made bacteriologically. Among many cases of undoubted typhoid fever admitted into the hospital, there occurred five in which, though the symptoms were undoubtedly those of typhoid fever, no Gruber-Widal reaction could be obtained with undoubted typhoid cultures. In one of these cases, by the finding of a bacillus in the stools and by the serum reaction in combination, in three by the serum reactions alone, and in one by the finding of the bacillus alone, it was demonstrated that the disease though resembling typhoid fever was caused by an organism which was not the typhoid bacillus.

Briefly the history of the outbreak is as follows:—In September 1900, two men, "Ahl" and "Pur," were admitted into the hospital at Bremen, showing marked symptoms of typhoid fever. They failed to give Widal's test for this disease. Later on there was a transitory suggestion of it in the case of "Pur," but "Ahl" throughout remained negative to it. After several vain attempts to isolate from the stools a bacillus which might be the cause of the disease, a bacillus was finally obtained from the patient "Ahl." Five weeks after the fall of temperature, serum from "Pur," the other doubtful patient, was found to give with the bacillus isolated from "Ahl" a marked positive reaction in a dilution of 1 : 500. A specimen of serum of "Ahl" had been kept since September and was found to give a positive reaction with the bacillus of 1 : 8000.

On the 30th of June previous to this, a similar bacillus had been isolated from the urine of a servant girl, who had been in the hospital as a case of typhoid fever from May 23rd, but whose

serum gave only a trace of Widal's reaction in a dilution of 1 : 3 throughout. As many as twenty-six investigations were made with the sera from other doubtful cases and also from healthy people, but there was no trace of a reaction with these on the bacillus in dilutions of 1 : 1. In November of the same year two fresh cases appeared whose serum refused to give Widal's test, but which markedly reacted on the bacillus Kurth had isolated. Kurth unfortunately was prevented by death from carrying on his investigations, but those who subsequently took up the work found that his bacillus belonged to Schottmüller's second group. Kurth considered that the disease was essentially a mild one, that albuminuria when present occurred only at the height of the fever, and that convalescence commenced, in all cases, after the expiration of a week from the fall of the fever.

In October 1901, Brion and Kayser (6), while examining the blood of a young girl for the gonococcus, found instead of that organism a typhoid-like bacillus. The patient in addition to gonorrhœa suffered from irregular febrile attacks. The spleen was palpable, but varied from time to time in this respect, and a roseolar rash was present. From the urine and from a roseolar spot an organism was isolated which corresponded to that found in the blood and to the "A" group of Schottmüller.

In 1902 at Eibergen, in the Gelderland province of Holland, an outbreak of typhoid-like fever occurred, which was investigated by de Feyfer and Kayser (7). The first case came under their notice on the 27th of March 1902, and the last on the 10th of June 1902. All the cases showed similar symptoms, which clinically justified a diagnosis of mild typhoid fever. With the exception of case No. 13 of this series, which, from the serum reactions (1 : 1440 towards the bacillus paratyphoid "B." and 1 : 720 towards the bacillus typhosus) was regarded as a mixed infection by these observers, all the cases reacted strongly with the paratyphoid "B" bacillus, but failed to react with the paratyphoid "A" bacillus of Schottmüller. In a few only, and in those to a slight extent at most, with the exception of No. 13 as mentioned, did the serum react on the bacillus typhosus. The disease in these cases was described as having the following characters :—

(1) There was a short prodromal stage, which was characterised by an initial irregular rise of temperature to not above 38° C., with loss of appetite and pain in the head, back and limbs.

(2) The course was comparatively mild, convalescence was short, and there were no after effects.

(3) It had the character of an acute infectious disease and this depended on the surroundings. This was shown in the first house epidemic, where all the persons coming in close contact with the first patient were also attacked by the disease, while those of the household isolated from that patient escaped.

(4) In slight as well as in severe cases there was a remittent and an intermittent stage in the temperature and occasionally a somewhat critical fall. One was afebrile throughout.

(5) The frequency of the pulse was found to correspond on the whole with the temperature. It was regular, equal and weak, and occasionally, during the intermittent stage of the temperature, small.

(6) The gastro-intestinal tract was affected. There were vomiting and borborygmus in the initial stages. The tongue was always more or less coated. There was abdominal pain but no tenderness, and iliac gurgling was constant. The spleen was only occasionally palpable, but often enlarged on percussion. As a rule there was diarrhœa, which was often followed by constipation ; the stools during the stage of diarrhœa being thin, yellow, and often very fœtid. The urine contained as a rule no albumen, but showed a deposit of lithates. In many cases the indican reaction was present and also the "diazo" reaction.

(7) As a rule the sensorium was free, but some of the patients were somnolent and apathetic. Delirium was rare.

(8) Spots were present in half the cases.

(9) The blood serum agglutinated the paratyphoid "B" bacillus in all cases.

(10) Bronchitis was the most common complication.

(11) Sore throat was often present at the commencement of the disease.

(12) Only seldom was there slight hæmorrhage from the bowel. The disease was in all probability water-borne.

In February 1902 an epidemic broke out in one of the regiments stationed in the town of Saarbrück in Germany. This was investigated by Conradi, Drigalski and Jürgens (8). This at first showed the characters of an influenza epidemic. The patients were affected with sore throat, tonsilitis, fever and diarrhœa, and in several of the cases influenza bacilli were found in the sputum. At the same time, however, the suspicion which had existed from the first that it might be typhoid fever was further strengthened by a positive Widal's reaction in one of the cases. Rigorous bacteriological and sanitary measures were adopted. All the cases in which there was the slightest suspicion of disease were isolated ; and by the 19th of February,

50, and by the last of March, 90 cases were under observation. The suspicion was further supported by the finding in the stools of a patient a typhoid-like bacillus; and when this was found to react to the serum of a goat immunised to the typhoid bacillus, the diagnosis was considered to be undoubtedly typhoid fever. But it was found next that the bacillus isolated had produced gas in glucose media, unlike the typhoid bacillus, and now an extended bacteriological examination was made. The bacillus was isolated on Conradi and Drigalski's medium in all cases, from the stools, urine, or roseolar spots, and in some cases from more than one source.

The sera of the patients were tested with the bacillus isolated and also with cultures of the typhoid bacillus, and the results showed an agreement with the cultural differences. The sera of twenty-four out of thirty patients showed a positive reaction in 1 : 100 with the typhoid bacillus; but with the bacillus isolated much higher reactions were obtained, and it was found that the reaction of the serum on the homologous bacillus lasted many months, while that on the typhoid bacillus disappeared at a very early period. The results with the serum of animals immune to the typhoid and with that of others immune to the bacillus isolated, showed that the typhoid immune serum was much more powerful towards the bacillus typhosus than towards the bacillus isolated, and that the reverse was the case with the sera of animals immunised by the bacillus isolated.

The investigators remark that, considering the fact that they had been engaged for over two years on similar investigations on typhoid cases, this bacillus of Saarbrück, had it been present in other cases, could scarcely have been overlooked, and call attention to the fact that in other diseases of the intestine the organism was not found in the fæces, nor was it at any time found in the fæces of normal individuals. They also consider that, taking all facts into consideration, the disease was not a mixed infection, but that it was caused exclusively by the Saarbrück bacillus. They also refer to the fact that Hünermann (9), independently found and investigated the bacillus and that his results are in agreement with their own. It was further shown that the bacillus was similar to Kurth's bacillus, and also Schottmüller's "B" bacillus, but that it differed from Brion and Kayser's bacillus which belongs to the "A" paratyphoid group.

Conradi and his collaborators considered that the symptoms on the whole were those of abdominal typhoid. The appearance of diarrhœa, the presence of spots, the enlargement of the spleen, the comparative slowness of the pulse, and in two cases at least the marked typhoid appearance of the patients,

combined with a positive Widal's test, clinically led at first to a diagnosis of typhoid fever. The disease started with a chill or even a distinct rigor. So sudden, indeed, was the onset, that some of the patients who were at drill in the morning were severely affected by the disease within a few hours. The temperature rose rapidly, and by a step-like ascent reached its height in two or three days. This sharp rise was not, however, followed by a continuous illness, though the symptoms to begin with were severe and even markedly typhoid like. The disease often changed very unexpectedly by an abatement of the severe clinical symptoms and a quick progress to recovery. The temperature as mentioned rose rapidly, but in only a few did it keep continuously high even for a few days, and in most of these few it fell by lysis. Mostly, however, there was a lytical fall to normal after two or three days, and in some cases there was a totally irregular temperature curve. Throughout, the temperature was comparatively low. The axillary measurement seldom reached 40° C., and it was over 39° C. only in half the cases, and in these only for a very few days. The total duration of the fever lasted over a week only in one-fourth of all the cases. A few throughout had scarcely any rise of temperature at all.

On the whole the temperature in this epidemic, which is the first large epidemic to be described, resembled closely that in Schottmüller's and Kurth's cases. The course of the disease throughout, even when the symptoms were threatening at first, was mild, and there were no fatal cases. Attention is called to the fact that the history of this epidemic shows the great value of a thorough bacteriological examination in such cases, both from the indication it gives as to the prognosis in the disease as well as from a hygienic point of view. The nature of the disease, by the finding of the bacillus, was early proved in most of the cases and in half of them it was proved within the first week. From the symptoms and physical signs it was evident that the gastro-intestinal tract was affected, but in the absence of fatal cases it was impossible to say what the exact nature of the disease was. The epidemic is one of great interest and especially from the resemblance of the cases to abortive and so-called mild attacks of typhoid fever.

Hünermann (9) independently investigated cases in the same outbreak as regards the serum reactions, and found that in 19 cases the sera reacted up to 1 : 1000 and even 1 : 2000 with the bacillus which he isolated, while at the same time the reaction with the typhoid bacillus varied from 1 : 30 to 1 : 100. Of all cases the reaction towards the typhoid

bacillus was positive in dilutions of 1 : 100 in 16 cases, in 1 : 60 in 8, in 1 : 30 in 7 cases, while 7 were negative to typhoid. He states that it was probable that the outbreak was spread through damage to the water-pipes in the barracks.[1] From the stools of the one patient coming under his personal experience Hünermann isolated a bacillus, and from the urine during a relapse the same bacillus was isolated. This organism was found to coincide with that isolated by Conradi, Drigalski and Jürgens during the same epidemic.

In 1902 Korte (10) observed two cases clinically like typhoid fever, one of medium severity, the other slight. In the first case Widal's reaction for typhoid fever was positive 1 : 320. On examining the blood, however, an organism was isolated which corresponded to bacillus paratyphoid "B." The serum of the case gave at one period with the bacillus isolated a reaction as high as 1 : 40,000. That the organism was the cause of the disease Korte concludes from the marked difference in the strengths of the respective reactions, and from the fact that a similarly marked reaction was given by two varieties of bacillus paratyphoid "B" viz.: Kurth's and Schottmüller's "B." He further showed that in animals inoculated with the bacillus isolated the serum reaction was at first 1 : 320 for typhoid, but 1 : 10,000 for paratyphoid "B," these strengths almost exactly corresponding to the reactions given by the patients' serum during the course of the fever, and he further showed that these sera reacted in the case of the bacillus isolated in a manner similar to the paratyphoid bacillus "B" of Schottmüller and Kurth. In addition he showed that an injection of this serum protected mice against subsequent fatal doses of the bacillus. In his second case no organism was isolated, but though not regarded as certainly paratyphoid fever it was considered as probably being so since Widal's test for typhoid fever was negative; while with three strains of paratyphoid "B," the serum reacted positively up to 1 : 2500, and further a certain amount of protection was shown in the case of mice by the serum against the paratyphoid "B" bacillus. The fact that the typhoid bacillus was agglutinated in the first case, he attributes to an interagglutination action. The bearing of this phenomenon will be considered later.

Jochmann (11) has described a case which he regarded as a mixed infection of paratyphoid and scarlet fevers. The case was apparently one of very severe scarlet fever. There were glazed white patches on the tonsils, otitis media, albuminuria

[1] Priefer (43) has recently published a very complete account of the sanitary arrangements in the barracks affected, demonstrating the infection of the water supply from a defective closet.

and hæmaturia. Cultures made from the blood showed streptococci and large numbers of paratyphoid bacilli. These bacilli fermented glucose but not lactose. The case is important in that it was fatal and that post-mortem there was no change in the follicles or Peyer's patches and no ulcers in the bowel, and that in the opinion of Jochmann it demonstrated the possibility of an infection with the paratyphoid bacillus being a mixed one.

In December 1902, a case came under the notice of Lucksch (12). The illness began with tiredness and weakness, diarrhœa, slight splenic enlargement and coated tongue. Spots were present. There was continuous fever. Conjunctivitis and bronchitis were present as complications. Taken in conjunction with a positive serum reaction, these facts gave rise to a diagnosis of typhoid fever. The case was very severe and death ensued about the 16th day. A bacillus was isolated from the blood the day before death, and it was found to correspond with bacillus paratyphoid "B." It gave, moreover, with the serum of the patient, a positive reaction of 1 : 10,000 microscopically, while the serum of the patient gave with the typhoid bacillus a reaction of only 1 : 200 microscopically, and then only doubtfully.

Post-mortem no appearances of typhoid were found. There was parenchymatous degeneration of the organs with reddening of the mucous membrane of the bowel, but the appearances of the bowels were altogether different from those of typhoid. The case is interesting as being one of the few fatal cases.

In July and August 1902, Kayser (13) met with three additional cases of the disease. All of these showed clinical symptoms of typhoid fever, and in all three it is to be noted that the fever showed a markedly remittent character and that the disease was mild, lasting in all scarcely three weeks. In one case the serum gave a positive reaction of 1 : 50 with the typhoid bacillus, but with paratyphoid "B" 1 : 1000, while with paratyphoid "A" it gave no reaction. In the second case with bacillus paratyphoid "B" there was an instantaneous reaction at 1 : 100, but with typhoid and paratyphoid "A" there was no reaction. In the third case the reaction with paratyphoid "A" and typhoid was negative, but with paratyphoid "B" it was positive at 1 : 200. Kayser thinks the only method of diagnosis is bacteriological, and that the disease is mild and the prognosis good. The mortality in his opinion is between 1 and 2 per cent.

An interesting account is given by Sion and Negel (14) of a house epidemic which they investigated in the town of Jassy in Roumania. This town has a very primitive water and sewage system, and typhoid fever is endemic all the year round. In the

autumn and winter months, however, exacerbations occur, during the course of one of which Sion and Negel observed the house epidemic in question. In the house, which consisted of two small rooms, six persons lived, three adults and three children. All of these contracted the disease, but with the exception of two, they were not brought under the notice of the observers till late in the course of the illness. The first of the patients, a man of 24, was admitted to the hospital suffering from what appeared to be an extremely severe attack of typhoid fever, and his sister, who lived in the same house, was also in hospital at the same time with a similar illness, but with the symptoms less marked. The other four patients were observed in their home. The first-mentioned patient died; the others recovered. The symptoms in all the cases were those of typhoid fever. From the blood of four of the patients during life, as well as from the tissues of the fatal case after death, a bacillus was isolated apparently resembling the typhoid bacillus. Culturally, however, it differed both from that organism and also from the bacillus coli communis, and resembled closely the bacillus paratyphoid "B."

From the mud of a polluted stream by which the water supply of the house was evidently contaminated, a bacillus of an identical nature was isolated. The serum reactions of all the patients were identical. Their sera reacted with their own bacillus, with the bacilli isolated from the other cases and with that isolated from the stream to the same degree; while both with the bacillus typhosus and a laboratory strain of bacillus coli communis, the sera reacted to exactly the same degree as with the bacilli isolated from the various cases in the house epidemic. Using immune serum the observers found that the bacilli of the epidemic were influenced by the sera of animals immunised by the different bacilli isolated to exactly the same degree. The homologous sera were not more potent towards their own bacilli than towards the others isolated. It was found, however, that though the typhoid and coli bacilli reacted to these sera equally to one another, they reacted much less markedly than did the various bacilli isolated. Again, it was found that bacillus coli immune serum had a much greater influence on these bacilli of the epidemic than had typhoid immune serum. Both from the cultural characteristics and the immune serum reaction, Sion and Negel concluded that the bacilli isolated by them were identical. They also concluded that the bacillus was the cause of the house epidemic and that it was much nearer the coli than the typhoid group. In the patient who died, the post-mortem appearances showed no resemblances to those of typhoid fever.

In America also a considerable amount of work has been done on the subject. The descriptions of the cases are, however, in some instances incomplete and no epidemics have been observed. It will also be noted with interest that most of the bacilli isolated on that continent belong to the "A" type of paratyphoids, while on the contrary those isolated in Europe have been mostly "B" paratyphoids.

In connection with the subject an interesting series of seventeen cases was met with by Brill (15) in New York, during the months of July, August and September 1897. The symptoms were those of a disease clinically closely resembling mild cases of typhoid, but in none of the cases was Widal's reaction for typhoid fever positive. No bacillus was isolated.

In 1898, Gwyn (16) reported a case of a typhoid-like fever of a fairly typical nature. Widal's reaction was, however, negative throughout in dilutions above 1 : 5. From the blood a typhoid-like organism was isolated which differed somewhat from the typhoid bacillus in its cultural properties, especially in its growth on potato, and in producing gas in glucose. Further, it was agglutinated by the serum of the patient in high dilutions—up to 1 : 2000—but was not acted on by powerful typhoid sera of agglutinative strengths of 1·300 up to 1·1500. Gwyn therefore concluded that the bacillus isolated, whose characters we now know coincide with those of paratyphoid "A" bacilli, was the cause of the disease, a typhoid-like organism.

In 1900, Cushing (17) isolated, from the pus of a costochondral abscess, which developed during convalescence from a clinically typical attack of typhoid fever, and which burst spontaneously six months after recovery of the patient from the illness. It was found to ferment glucose and failed to coagulate milk. The patient's serum failed to give Widal's reaction but was potent towards the bacillus isolated in dilutions of 1 : 800. Typhoid sera of high potency had, moreover, no effect on the bacillus isolated. Cushing concluded that the organism isolated was the cause of the abscess, and from comparisons with other paratyphoid organisms he concluded that it also belonged to that group.

In 1902 Johnstone (18) described a series of four cases which he met with and which clinically represented mild cases of typhoid fever. In each of the cases an organism was isolated which belonged culturally to the paratyphoid "A" group. This fact, combined with the positive action of the sera of the patients on the organisms isolated and the want of reaction on the bacillus typhosus, the bacillus coli communis and on all bacilli other than paratyphoid organisms, led to the belief

that the organisms were the cause of the disease, which was concluded to be paratyphoid fever.

In 1901 Coleman and Buxton (19) described a case which was apparently typhoid fever. Widal's reaction was, however, negative on all occasions in dilutions above 1 : 20, and even at that dilution the reaction was very doubtful. With a bacillus which was isolated and which culturally showed the characters of a paratyphoid organism the agglutination during the first five or six days was hardly perceptible, but by the 27th day it was positive in high dilutions. Dried blood from the patient also agglutinated the bacilli of Gwyn and Cushing, but not in dilutions so high as the bacillus isolated. A rabbit immunised to the bacillus reacted strongly with it and also with Gwyn's bacillus (an "A" paratyphoid), but failed to react with the typhoid bacillus as well as with a "B" bacillus of Schottmüller. On these grounds they concluded that the organism was a paratyphoid bacillus of the type "A."

Hewlett (20) in 1902 described a case clinically like typhoid fever in which the serum agglutinated the typhoid bacillus in dilutions of 1 : 10, but not typically, on the 9th, 19th and 30th days of the disease, failing, however, to give the reaction at 1 : 50. On the other hand, it agglutinated a bacillus which was isolated from the patient and which culturally was a paratyphoid bacillus in dilutions of 1 : 100. The case is also interesting from the fact that a relapse occurred in it.

Early in 1902 Longcope (21) met with two cases clinically like typhoid fever, one of which proved fatal. In both cases an organism was isolated which somewhat resembled the typhoid bacillus, but which differed from it in important points. Culturally the organism from the fatal case belonged probably to the "B" group of paratyphoids, while that of the case which recovered belonged probably to the "A" type, and the serum reactions tend to strengthen this opinion. The reaction of the serum of case 2 was positive towards its own bacillus up to 1 : 200, to Cushing's bacillus up to 1 : 200, and Gwyn's up to 1 : 500. The serum of case 2 gave, however, a reaction with the paratyphoid "B" bacillus from case 1 of only 1 : 20. With the typhoid bacillus during the primary attack a positive reaction in case 2 was got only in dilutions of 1 : 12; but during convalescence a reaction of 1 : 20 developed, and this lasted throughout the course of a relapse which took place. In the fatal case no lesions of a definite kind or in any way pointing to typhoid fever were found in the intestine. A bacillus exactly like that isolated from the blood during life was isolated from the heart, blood, lungs, liver and spleen in large numbers post-mortem.

In 1902 a case was described by Hume of Liverpool (22)

in which the following were the chief clinical points of interest :—

(1) The presence of a typical typhoidal onset and typhoidal symptoms with spots, enlarged spleen, and a fairly typical temperature curve.

(2) Profuse and long continued diarrhœa with, for a time, bloody stools and for a week or more involuntary motions, and the continuance of the diarrhœa for more than a month after the temperature fell to normal.

(3) A well-marked relapse.

(4) The occurrence of cystitis during convalescence.

In this case a bacillus was isolated from the urine and stools. This bacillus was found to differ from the typhoid bacillus, and was found to resemble the paratyphoid "A" bacillus. Widal's reaction 75 days after the onset was found to be negative with the typhoid bacillus, but was positive with the bacillus isolated from the stools and urine up to 1 : 200. The bacillus may possibly belong to the "A" group of paratyphoids, but it must be regarded with suspicion since it produced indol. I have examined a bacillus isolated from the stools of a similar case and find it in all respects culturally identical with Hume's bacillus, but I do not consider the organism a paratyphoid bacillus, since it produced indol in glucose-free media.

Libman (23), Strong (24) and Pratt (25) have also described cases in which paratyphoid bacilli have been found either post-mortem or during life.

Clinical Characteristics.

Up to the present time, over 100 cases of paratyphoid fever have been published. For the purpose of a minute clinical analysis, however, only 46 of these are available. Conradi, Drigalski and Jürgens (8) gave a general description of the epidemic at Saarbrück, but of the 38 patients attacked in that epidemic a detailed report of only one case has been published—by Hünermann. Again, Zupnik and Posner (26) have published a series of 9 cases which were diagnosed by the serum reactions, but have given no detailed account of the symptoms, merely stating that the illness could not in these cases be distinguished from typhoid fever. Five of the cases published in America are of little value for clinical analysis, while three of the cases mentioned by Sion and Negel are described too shortly to be of use from that point of view.

The cases which remain of value for the present purpose are not uniformly described, some observers omitting points on

which others lay stress, so that from a detailed analysis of the available cases no really convincing statistics from a clinical point of view can be deduced, although they are interesting as far as they go.

Paratyphoid fever is an acute infectious process caused by a bacillus closely resembling in many particulars the typhoid bacillus, and the symptoms and course of the disease closely resemble those of typhoid fever.

The onset of the disease is marked by headache, lassitude, loss of energy, and general weakness. Occasionally there is epistaxis, and in some cases vomiting and pain in the abdomen. By the time the patient comes under observation he is feverish and may feel chilly, but regularly marked rigors are hardly ever met with. The temperature is said to rise gradually during the first two or three days by a step-like ascent. This was observed in the Saarbrück barracks epidemic, where careful observations could be made from the first. As a rule, the temperature does not rise above a moderate height (102° F. or thereby) except in the more severe cases, nor does it remain for more than a few days at this height continuously. In some of the more severe cases it may remain for a week or ten days at that height, but generally, even in cases which have a severe appearance at the commencement, the temperature after remaining for a few days continuously at the same height begins to sink and gradually, in the course of a few days, reaches the normal line.

Occasionally a critical fall is observed, and it has been observed by most investigators that even at its height the temperature has as a rule a remittent or intermittent character. This remittency or intermittency is certainly always marked towards the latter part of the febrile period. In one case, the fatal one described by Longcope, the temperature rose just before death to 108° F., while one of the cases described by De Feyfer and Kayser was afebrile throughout. During the febrile period the face is as a rule rather pale and the cheeks flushed, and in severe cases the lips are cracked and dry and covered with sordes. The patients, too, are somnolent and apathetic, and there is in many a clouding of the sensorium, but delirium of a marked nature is not common, and is only found in somewhat severe cases. The pulse is as a rule quite regular but somewhat small. Its frequency, according to some, is not increased at the commencement of the disease to an extent corresponding with the height of the fever.

A roseolar eruption resembling that of typhoid fever was present in 32 out of 46 cases. It was described in some cases as occurring not only on the skin of the abdomen and chest but

also on the back and limbs, and in one case even on the face. It is not mentioned by any of the observers whether or not the spots come out in crops.

The tongue is as a rule covered with a moist white coating, but occasionally it is dry and furred.

Diarrhœa is more prominent than constipation and is occasionally present at the commencement of the disease. In four cases blood has been observed in a medium quantity in the stools. The abdomen is not as a rule very markedly distended, nor is tenderness a prominent feature, but occasionally pain is present, and iliac gurgling is an almost invariable accompaniment of the disease.

The spleen is enlarged in the majority of cases. In 15 out of 41 cases it was palpable at some stage of the disease, in 13 it was found enlarged on percussion, while in the remaining 13 it was not enlarged.

The liver is not affected as far as one can make out during life.

The urine during the course of the disease shows a deposit of lithates. Albuminuria where present is as a rule not marked and is found during the height of the fever. Hyaline and granular casts have been observed and in one case blood was found to be present. In 19 out of 46 cases the urine was found to give the diazo reaction, and in 8 the test for indican was positive.

The heart is practically always unaffected. In only three cases was any abnormality in the sounds detected and in these it consisted of a faint systolic murmur at the apex.

With regard to the lungs, bronchitis is comparatively common, being present in about one-third of the cases.

Karl Gütig (27) found that in six patients examined by him the neutrophile leucocytes sank during the febrile period to a low percentage and during convalescence gradually began to rise again. During the period of fever the lymphocytes were also diminished in amount, but later on an increase in their number took place, so that in the period of convalescence in some of the cases they formed half the number of the total white cells present. The eosinophile cells almost entirely disappeared from the blood during the rise of temperature. Shortly before or after the fall, however, they returned again in increased numbers.

As a rule emaciation is not so marked in this disease as in typhoid fever.

Complications. These are not uncommon, though as a rule they are not serious. Bronchitis is the most common. Pharyngitis is not uncommon, and next in frequency to it comes broncho-pneumonia. Thrombosis of the femoral veins, pleurisy

phlebitis of the veins of the leg, endocarditis (14) and cystitis have also been observed. Sequelæ have not definitely been proved to occur.

The diagnosis can be made only by bacteriological methods.

The prognosis is good. At present only five fatal cases have been recorded. The disease is of short duration, lasting in most cases not more than 14-28 days in all.

The treatment is the same as in typhoid fever, but in this disease, since as a rule convalescence is quickly established, solid food may be allowed somewhat earlier than in enteric.

In all probability the mode of conveyance of the infectious agent is the same as in typhoid fever. De Feyfer and Kayser (7), Conradi (8), Hünermann (9) and Sion and Negel (14) believed that in the epidemics described by them the disease was conveyed by water. It is certainly not markedly infectious, since Schottmüller (4), Kurth (5) and others mention that among the persons living in the same houses as their patients none had contracted a similar disease, nor indeed were cases of a similar nature known to exist at the time in the same locality. Evidently, however, the same precautions as regards hygienic measures should be employed as in cases of typhoid fever. Indeed a case is recorded of a medical man who was apparently accidently infected with the disease during the course of experiments with a paratyphoid bacillus.

In the Saarbrück epidemic it was definitely determined that the incubation period was about 14 days, the spots appearing from the 20th to 26th day (Priefer, *loc. cit.*).

Synopsis.

In	6	out of	46	cases epistaxis occurred at the start of the illness.
„	„	„	„	„ the pulse became dicrotic.
„	28	„	41	„ the spleen was enlarged.
„	15	„	28	„ it was palpable.
„	13	„	28	„ it was enlarged to percussion but not palpable.
„	13	„	41	„ it was not enlarged.
„	36	„	48	„ diarrhœa was prominent.
„	10	„	„	„ constipation.
„	2	„	„	„ the bowels were normal.
„	4	„	„	„ blood was observed in the stools.
„	12	„	46	„ the urine contained albumin.
„	19	„	„	„ the diazo reaction was positive.
„	8	„	„	„ the indican test was positive.
„	6	„	„	„ casts, hyalin and granular, were present.

In 1 out of 46 cases blood was found.
„ 32 „ „ „ roseolar spots appeared.
„ 14 „ 47 „ the patients were females.
„ 33 „ „ „ „ „ „ males.
„ 3 „ 46 „ a systolic murmur at the apex of the heart was found.
„ 10 „ 37 „ the abdomen was distended.
„ 2 „ „ „ „ „ „ tender.
„ 9 „ „ „ „ „ „ painful.
„ 27 „ 48 „ complications were present.
In 14 bronchitis.
„ 6 broncho-pneumonia.
„ 9 pharyngitis.
„ 2 cystitis.
„ 1 thrombosis of femoral veins.
„ 1 phlebitis of veins of leg.
„ 1 endocarditis.
„ 1 paresis of left deltoid.
„ 11 „ 48 „ delirium was present.
„ 32 „ 41 „ termination was by lysis.
„ 5 „ „ „ „ „ „ crisis.
„ 3 „ „ „ „ „ „ death.
One case was afebrile throughout.

Post-mortem Appearances.

Up to the present only three authentic fatal cases have been described, viz.: by Longcope (21), Lucksch (12), Sion and Negel (14), Wells and Scott (44), and Tuttle (45). In all of these paratyphoid bacilli have been isolated from the organs after death, and in each the organism isolated corresponded to a bacillus isolated from the same patient during life, but in no case was any characteristic lesion found. The appearances were in most cases those of an acute general infection. In the case of Wells and Scott, at the lower end of the ileum a few ulcerations were found, but no enlargement of the Peyer's patches. In Tuttle's case there were five small ulcers reaching almost to the serosa, and the lower part of the ileum and the large intestine were filled with blood.

The Morphology, Cultural Characteristics, and Behaviour towards Various Media of the Bacillus of Paratyphoid Fever.

The bacillus of paratyphoid fever was first mentioned as causing a typhoid-like illness by Achard and Bensaude (1) in

Paris in 1896. Since then it has been stated to have been found in America, Germany, Holland, Roumania and England.[1] That the bacillus is the cause of a typhoid-like disease has probably been conclusively proved. It has been found in the blood, stools, urine, and roseolar spots during the course of the disease, while the typhoid bacillus was not found to be present, and it has also been isolated from the gall-bladder, and from abscesses in various situations following illnesses which were apparently typhoid fever.

Conradi, Drigalski and Jürgens (8) also showed that in small animals killed by the inoculation of a paratyphoid bacillus the same organism could be isolated from the intestine in pure culture, and further that at the height of the disease in the epidemic described by them it was found in the fæces almost to the entire exclusion of other organisms. It has been shown by all the observers who have investigated the disease that the serum of the patients suffering from the disease has a much more potent agglutinative action on paratyphoid bacilli than on the bacillus typhosus or any other organism.

Hünermann (9) and de Feyfer and Kayser (7) have shown in two epidemics that the disease was water-borne, and there is no evidence to show that it spreads in a manner different from that in which typhoid fever is propagated. These observers have shown that probably the disease as far as yet known is infectious only through the dejecta.

Between the typhoid bacillus on the one hand and the bacillus coli communis on the other, exist a large number of bacteria which belong to neither group, and which have certain resemblances to both. All these, including the coli and typhoid bacilli are often referred to as one large group, the coli-typhoid group. Among the organisms which lie between the typhoid bacillus and the bacillus coli communis, there exist some which have not yet been properly worked out and classified, such as the paracolon bacilli. But there does exist a group whose characters have now been definitely decided. It is composed of a large number of bacilli, which vary greatly in their morbific effects, but the most important and the one most frequently made reference to is the bacillus enteritidis of Gärtner. To the group to which this bacillus belongs, various names have been applied, but at the present time it is generally known as the "intermediate group," or as the group of "Gärtner and its allies" (28). In 1893 Gilbert proposed to call this group the paratyphoid group, but this name has been rejected owing to the fact that a bacillus or group of bacilli has been isolated

[1] Since this was written descriptions of nine additional cases of the disease have been published in Japan (41).

causing symptoms almost exactly like those of typhoid fever, and to this bacillus or group of bacilli the name paratyphoid is much more applicable.

This group, then, may be said to consist of two sub-groups, the first, paratyphoid bacilli "A," and the second, paratyphoid bacilli "B." This designation arose from the description of Schottmüller, who found that two of the bacilli described by him differed from the other four culturally and also with regard to the serum reactions, although the symptoms caused by them were similar. His description has been found to be correct by all subsequent observers. The chief points of difference between these two classes briefly are:—

1. The growth on gelatine of "B" paratyphoids is more luxuriant than that of "A" paratyphoids.

2. The growth on potato is also more vigorous in "B" than in "A" paratyphoids.

3. Milk is curdled by neither, but while it remains unchanged by "A" bacilli, it is almost completely cleared after 14 days by "B" organisms. This action may possibly be due to a saponification.

4. In litmus whey, both forms produce a preliminary acidity but soon, after fifty hours or thereby, the "B" paratyphoid bacilli begin to turn it alkaline, and it remains so finally, the medium becoming blue, while it is unchanged by "A" bacilli after the preliminary acidity and reddening.

5. Further, it is found that they are distinguished by their serum reactions.

The chief points of difference between these two sub-groups having been noted, it will be convenient to describe the bacillus itself and its general cultural and chemical behaviour.

The bacillus is a short rod, very similar to the typhoid bacillus, but on the whole, somewhat shorter, and possessing 6-10 cilia, which impart to the bacillus a lively darting or rolling movement, especially in young cultures. It is almost as actively motile as the typhoid bacillus in cultures of the same age. It is certainly, in cultures I have examined, shorter than the bacillus coli communis, and its motility is much greater. It is decolourised by Gram's method and is stained rather lightly by the ordinary dyes. Preparations from cultures, especially on potato, show polar staining. It grows best at 37° C. and also, but not so quickly, at 22° C.

The cultural characters are the following:—

On gelatine plates after forty-eight hours the surface colonies are small, about the size of a pin's head, translucent and colourless. Later, after three or four days, they became more opaque. The margin is sharply marked, showing no sulci, and the colonies

are as a rule circular. They do not normally show radiate streaks on their surface such as are seen in colonies of the bacillus typhosus, nor do they show the vine leaf pattern of the latter. They are as a rule less luxuriant than those of the bacillus coli communis, but rather more so than those of the typhoid bacillus, especially in the case of the "B" sub-group.

In a gelatine stab culture a growth takes place both on the surface and along the track of the needle. The surface growth spreads as a whitish film slowly outwards in a circular manner.

On gelatine slope cultures there is nothing characteristic about its growth, except that it is perhaps more luxuriant than that of the typhoid bacillus. The growth in the case of "B" paratyphoids is more luxuriant than that of the "A" sub-group. The gelatine is never liquefied.

On agar plates the colonies are very similar to those of the typhoid bacillus but develop more speedily, while on agar slopes the growth develops as a moist, greyish white, somewhat diffuse layer. At first it is translucent and occasionally the growth is iridescent. Later on, in 24-36 hours, the film becomes opaque and slightly yellowish. The "B" paratyphoid growth is much more marked than that of the "A" group, which, indeed, very closely resembles that of the typhoid bacillus.

In bouillon there is a general turbidity and occasionally, though seldom, a membrane forms on the surface.

As a medium for the growth of these organisms potato is unsatisfactory. The growth is as a rule more luxuriant than that of the typhoid bacillus, and less so than that of the bacillus coli communis. Occasionally in the case of "B" bacilli the growth after some days assumes a brownish hue. "B" paratyphoids give a more luxuriant growth than the "A" group, but the medium as a means of differentiation is unsatisfactory, and the results are found to depend to a great extent on the initial reaction of the potato.

In neutral red agar, which contains glucose, gas is produced and the medium changes in colour, becoming in 24 hours decolourised. In 48 hours the medium is completely changed and comes to have a fluorescent yellowish green appearance. The upper layer of the medium in shake cultures is the last to change. This is perhaps due to the more aërobic conditions prevailing in that region.

On Conradi and Drigalski's medium, which contains lactose, nutrose, peptone, agar, and crystal violet with litmus added as an indicator, the colonies are blue and resemble typhoid colonies in every way, but differ from those of the bacillus coli communis in that the latter are red and turn the medium red.

On MacConkey's taurocholate lactose medium (22) the

colonies are greyish blue, and there is no surrounding haze, since the bile salts are not precipitated.

In Piorkowski's urine gelatine (4) the colonies are as a rule rounded and yellowish. They are seldom oval and as a rule do not show processes extending into the medium.

Schottmüller (4) found that, in a medium consisting of 5 c.c. of agar and 3 c.c. of blood, after 40 hours the deep colonies showed a dark green colour and were the size of a pin's head, while the surface colonies were moist and grey and the size of a lentil.

In sulpho-indigodate of soda, the colour of the medium is changed to yellow and gas is formed.

In acid fuchsin medium (14) typhoid colonies show no surrounding ring, while those of the bacillus coli communis show a marked red ring. Sion and Negel (14) found that their bacillus produced a slight appearance of a ring, but not to such a marked degree as is found in the case of the bacillus coli communis.

Actions on carbohydrates.

Glucose. In glucose-containing media gas is produced by both classes of paratyphoid bacilli, and the media become acid. Libman gives 1.5 per cent. as the amount of acidity produced. Kurth estimated that at 37° C. for 24 hours, 30 c.c. of normal acid was produced in a litre of 1 per cent. glucose broth. Schottmüller found that about one-third of a fermentation tube was filled with gas.

In saccharose no gas is produced.

In lactose no gas is produced.

In dextrose, Cushing (17) found that gas was produced, but only about half the amount compared with that formed by members of the intermediate group.

Formation of Indol.

In sugar-free media indol is not formed by paratyphoid bacilli as a rule. In only one case has it been definitely stated to have been formed. This was found by Hume. Libman found it present in one of his cases in slight amount after 8 days, while Cushing found slight traces of it after 8, 9 and 10 days, in dextrose free broth, but none in Dunham's medium.

In litmus whey, as stated previously, "A" paratyphoids do not produce a terminal alkalinity, while those belonging to the "B" class do.

Schottmüller found that in the case of his two "A" bacilli the amount of acidity produced after 48 hours was 1.6 and 1.4 per cent. respectively, while in the case of the four "B" bacilli the amount of alkalinity produced was respectively 2.8, 2.4, 1.8 and 2.4 per cent. after 10 days.

In milk the "B" bacilli produce both a terminal alkalinity and a clearing of the medium so that it becomes transparent, while the "A" group do not produce this clearing, or only to a very slight extent. The medium is finally acid or neutral or very slightly, if at all, alkaline in the case of "A" bacilli. Milk is never curdled by either group.

	Bacillus typhosus.	Paratyphoid "B" and Gärtner and its allies.	Paratyphoid "A."	Bac. coli com.
Glucose.	No gas.	Gas.	Gas.	Gas.
Lactose.	No gas.	No gas.	No gas.	Gas.
Taurocholate lactose agar.	Surface colonies, semi-transparent, bluish white. *Deep*, more opaque. No haze.	As with bacillus typhosus.	As with bacillus typhosus	Surface colonies, yellowish with orange centre. Surrounding haze.
Conradi and Drigalski's medium.	Blue colonies.	Blue colonies.	Blue colonies.	Red colonies.
Neutral red agar.	No changes.	Yellow green and fluorescent, gas produced.	As in para "B."	As in para "B" but more quickly complete.
Indol.	—	—	—	—
Litmus whey.	Acid.	Transient acidity. Terminal alkalinity.	Acid.	Acid.
Milk.	Acid, no clot.	Finally alkaline and opalescent. No clot.	Acid or neutral or faintly if at all alkaline. No clot. No clearing.	Clot. Acid.

The above table is intended to show more clearly the characteristics distinctive of these allied organisms. From this table it will be seen—

(1) That there is a distinction between "A" and "B" paratyphoid bacilli.

(2) That as regards the characteristics here alluded to paratyphoid "A" organisms are on the whole nearer bacillus coli than the "B" group.

(3) That bacillus paratyphoid "B" is identical as regards its cultural characteristics with Gärtner's bacillus.

(4) That "A" and "B" paratyphoid bacilli are distinct both from the bacillus coli communis and the bacillus typhosus.

The inferences which one might draw from these facts are that while it is possible to distinguish both classes of paratyphoid bacilli from each other, as well as from the bacillus coli communis and the bacillus typhosus, it is impossible to distinguish paratyphoid "B" bacilli from Gärtner's bacillus and its

allied intermediates without taking the serum test into account.[1] For diagnostic purposes the serum test should be combined with a bacteriological examination of the blood, urine or stools, wherever it is possible.

Pathogenicity.

When injected into the smaller animals such as mice, guinea-pigs and rabbits, the paratyphoid organisms are fatal in varying doses.

Brion and Kayser found that $\frac{1}{3}$ c.c. of a 24-hour broth culture killed white mice at the latest after 24 hours, while a dose of 4 c.c. of the same kind of culture injected subcutaneously was fatal for guinea-pigs of 200 grammes weight and under. They also found that an injection subcutaneously of 5 c.c., followed after an interval of several days by a second dose of 10 c.c. of a culture killed by heat, killed a rabbit of 1545 grammes weight after 5 weeks.

Kurth found that $\frac{1}{200}$ of a loop of an 18-hour agar culture of his bacillus killed a guinea-pig weighing 300 grammes within 24 hours. A single loop of an agar culture of Korte's bacillus was fatal for guinea-pigs weighing 200 grammes.

All observers have found similar effects to ensue from the injection of small amounts of various strains of paratyphoid bacilli either subcutaneously, intravenously, or intraperitoneally injected. Libman, Cushing, Pratt, Achard and Bensaude, Widal and Nobécourt, Conradi, Drigalski and Jürgens, Hünermann and Hume among others, have found the organisms isolated by them to be pathogenic for the smaller laboratory animals.

When injected subcutaneously the organism is found, both in fatal cases and in animals which recover, to produce subcutaneous abscesses in many cases, and from these abscesses the organisms have been isolated.

In fatal cases in animals the post-mortem appearances are peritonitis and enteritis with enlargement of the mesenteric glands and spleen. The liver sometimes shows focal necroses and both that organ and the kidneys are found to undergo parenchymatous degeneration. Occasionally abscesses have been found in the spleen. Evidently, then, the bacillus is

[1] Whilst going to press, Trautmann (39) and Schottmüller (42) have independently come to the conclusion that whilst ordinarily causing acute gastro-enteritis, B. enteritidis (Gaertner) may cause a typhoid-like disease, the difference apparently depending on whether the toxines, or toxines and bacilli, or bacilli alone are ingested (Schottmüller). There is a noteworthy resemblance between Gaertner's bacillus and the paratyphoid B., in so far that in each the toxines are thermostable.

pyogenic. The lungs also have been found to be congested. In nearly all cases the organisms have been recovered from the organs after death, more especially from the heart blood, and Conradi, Drigalski and Jürgens found that in guinea-pigs killed by their bacillus, the organism could be recovered from the fluid contents of the bowel in pure culture.

Hume fed two rabbits with cabbage or bread soaked with his bacillus. Both died, one on the fifth, the other on the ninth day after the feeding commenced. The abnormal post-mortem appearances were the same in both cases. The ileum showed swelling of Peyer's patches and of the solitary follicles. The large gland at the ileo-cæcal valve was much swollen and showed hæmorrhagic points on its surface. The spleen was not swollen. From the ileum the bacillus was recovered in abundance and from the mesenteric glands and bladder in pure culture. All the other organs gave sterile cultures. On the whole, however, feeding experiments have been non-conclusive with regard to the relation of the disease produced in animals to that produced in man by the bacillus.

The Serum Reactions in cases of Paratyphoid Infections and their Bearing on the Serum Test in Typhoid Fever.

One of the most interesting problems in the sphere of medicine in recent years both to clinicians and also to bacteriologists has been the nature and value of the serum agglutination reaction, not only in cases of typhoid fever but also in certain other infections. The history of the phenomenon need not be entered into here, it is well known. The exact nature, however, of the phenomenon is still obscure, and though working theories have been formulated with regard to it, none of them can be said to have been definitely established. Gruber and Durham considered that it might be due to some change in the outer part of the bacteria when they were brought into relation with the sera of certain patients, notably when typhoid bacilli were brought into contact with the sera of patients suffering from that disease. This change he thought might result in the production of a sticky substance which caused the bacteria to adhere to each other. Another conception is that the presence of certain bacteria in the organism gives rise to certain indefinite chemical substances which give to the serum of the patient, when it is brought into contact with bacteria of the same nature as those present in the organism, the power of rendering these non-motile and of forming them into larger or smaller groups. Not only, however, are these agglutinating substances produced, but other

chemical substances are formed at the same time which may have different attributes and which may produce various results.

Joos (38) has shown that the presence of salts is necessary for agglutination to take place, and a theory has been put forward that the electrical discharges passing between its ions cause agglutination or sedimentation to take place (Wright).

Anderson Craw (36) supposes that surface tension plays an important part in the phenomenon.

A culture of a bacillus when introduced into an organism, whether that of an animal or of a human being, by methods such as intravenous or subcutaneous injection, is not a simple substance. The bacilli and their toxins form not one but many complex chemical bodies, each of which may stimulate the organism to produce a corresponding chemical substance.

The toxins may induce certain of the cells of the organism to produce an antitoxin in the body or may cause the production of anti-bacterial bodies, while another of the complex substances contained in the culture may cause the formation of a chemical substance which gives to the serum, when that is brought into relation with bacilli such as were injected, the power of producing the agglutination reaction. These substances are termed agglutinins. The same processes may occur when the bacilli enter the body by natural channels. This, then, is an extremely brief statement of the working theories held with regard to the reaction.

The value of the agglutination test has been much discussed. It has been asserted by some that in cases which were undoubtedly from a clinical point of view typhoid fever, the test has been negative. In this relation the disease now known as paratyphoid fever is of great importance. During the course of the investigations which have been conducted with regard to this disease, it has been shown that in many cases which were clinically typhoid fever, some of them at first apparently of a severe type, the sera of the patients have failed to give or have given only to a slight degree the characteristic reaction. With organisms, however, to which the name paratyphoid bacilli has been applied, and which have been isolated from these same patients or from other cases apparently of typhoid fever, the sera have given marked positive reactions. In some cases not only has the patient's serum reacted to the bacillus isolated from that patient, but has also given a positive reaction with other paratyphoid bacilli to a marked degree, and in many cases indeed these sera have been found to react on other paratyphoid bacilli to as high an extent as on their own bacilli, and in some cases even to a higher degree. It has been shown that in cases in which the serum gives a positive

reaction with the typhoid bacillus, it is produced in much lower dilutions with that bacillus than with the paratyphoid organisms, unless the case is one in which there exists a mixed infection; and that the sera of patients infected by the paratyphoid "A" bacillus do not give a positive reaction with paratyphoid "B" bacilli or only to a very slight degree; and further, that on the whole, the serum reaction of the paratyphoid "B" bacillus is more closely related to the bacillus typhosus than is the paratyphoid "A." The sera of certain of the cases have also given positive reactions in very low dilutions with other allied organisms, notably with the bacillus of Gärtner and the bacillus psittacosis and also with the bacillus coli communis; but from a practical point of view, in carrying out the test clinically, the only bacilli to be taken into account are the typhoid bacillus and the paratyphoid bacilli "A" and "B."

Is then this test invalidated by the facts which have been brought out by this enquiry? The opposite is the case, but in order that the test may be valid certain precautions must be adopted.

In the first place it ought to be noted whether the test is done macroscopically or microscopically, the macroscopic method being preferably performed by means of Wright's sedimentation tubes.

Secondly, a definite minimal dilution which shall be regarded as a positive standard must be adopted. In the early days of the test, Widal considered that a positive reaction in dilutions of 1 : 10 was an absolute proof of the existence of typhoid fever. This limit was soon found to be insufficient, and the minimum dilution was considered to be 1 : 30, and now it is considered by many that 1 : 50 is the lowest limit of dilution at which a positive reaction should be considered proof of the existence of typhoid fever. Some are inclined to place it even at a higher limit, Bruns and Kayser (29) putting it at 1 : 75. With the sera of patients the macroscopic method probably gives positive results in dilutions of nearly the same degree as the microscopic. With immune sera, as will be noted in the next part, the results given by the two methods are somewhat different.

In the third place, a definite time limit should be allowed for the reaction to take place. With the microscopic method the most serviceable limit is probably 30 minutes, while in the sedimentation method two hours should be allowed for the reaction to take place.

A positive reaction should be considered to be present when all the bacilli have entirely lost their motility, and when clumping is distinct with the microscopic, and when there is a distinct deposit with the macroscopic method.

The serum should be tested not only with the typhoid bacillus but also with the bacilli paratyphoid "A" and "B," and the upper limit of the potent dilutions should be ascertained in each case. Should the dilutions with two of the bacilli come very close to each other, the case must be suspected to be a mixed infection, and Castellani's test (30) should be carried out when sufficient serum can be obtained. This test consists in mixing with the serum, in an appropriate small tube, bacilli belonging to one of the types giving the positive reaction. The tube should then be placed in the ice chamber and allowed to stand till these bacilli have been acted on by their appropriate agglutinins and have sunk to the bottom, leaving the upper part of the fluid clear. This clear upper layer of serum must then be pipetted off and again tested with the first tried bacillus. If it gives no longer a positive reaction the serum is then tested with the other suspected bacillus, and if the reaction is positive to nearly the same degree as it was originally the case must be regarded as a mixed infection. If, however, the serum does not give a positive reaction with the second bacillus the original proximity of the reactions with the two bacilli must be regarded as being due to a group inter-agglutination. This phenomenon will be referred to further on. Castellani's test is still *sub judice*, and has to undergo the trial of application to practical bacteriology. The precise proximity in the degree of dilution which must lead to a suspicion of a mixed infection is still undecided.

With regard to the serum test, the personal equation plays a great part, and the variety of opinion as to what exactly constitutes a positive reaction leads to some difficulty when one attempts to compare the results obtained by different observers. There is no doubt, however, that with due precautions the test, though not absolutely infallible, is of the greatest possible significance and importance, and in cases which are proved to be paratyphoid fever, of the greatest value from a prognostic point of view.

Reference has already been made to the fact that when certain organisms are introduced into the bodies of animals certain substances are produced, some of which give to the serum of the animals the power of neutralising toxins, others that of dissolving and killing the bacteria, and others the faculty of producing an agglutination of bacilli such as were introduced, and if the bacilli are motile, the power of checking their motion. Such a serum is termed an immune serum. For example, by repeated injections of either killed or living cultures of the typhoid bacillus into an animal, such a serum can be produced. It has, when injected along with one lethal dose, or even in

some cases a considerable number of fatal doses, of the typhoid bacillus into the peritoneum of a guinea-pig, for example, even in small quantities, the power of protecting the animal against the typhoid bacillus by virtue of its antibacterial and also, but in this case to a less extent, of its antitoxic properties. Even when injected a short time previous to the introduction of the fatal dose of typhoid bacteria, the serum has still the power of attacking these organisms and of protecting the animal against their action. Not only has such a serum this power, but it can also agglutinate typhoid bacilli when brought into contact with these. The same conditions hold with regard to paratyphoid bacilli and also with regard to organisms such as the bacillus of Gärtner and several others which are not, however, of so much immediate importance in connection with the present subject. The precise relationship of the agglutinative and protective powers is an undecided but interesting point. It cannot, however, be entered upon here.

Sera of this nature can be produced by repeated and graduated doses of killed or living cultures, or even of the liquid products of cultures, obtained by autolysation and filtration, which have very strong agglutinating powers on organisms such as were used in the process of immunisation. Not only do sera of such a nature agglutinate their homologous organisms, but they may also, though to a markedly less degree, agglutinate related bacteria. For example, Korte (10) produced in a rabbit by the injection of a paratyphoid "B" bacillus which he termed the bacillus "Sch," an immune serum which agglutinated the homologous bacillus as well as other paratyphoid "B" bacilli in dilutions of 1 : 20,000, and which, moreover, also agglutinated the bacillus typhosus in dilutions of 1 : 320 and paratyphoid "A" bacilli and the bacillus coli communis in dilutions of 1 : 40. Many similar examples could be cited. This phenomenon is known as an interagglutination reaction or as a family or group agglutination, since it is caused by the action of sera produced by members of one group or family upon one another. In general the more nearly members of one group or family are related, the more marked will be the action of immune sera produced by them on one another. Durham (28) has given a simple explanation of this phenomenon. He considers that neither the bacillus nor the agglutinine is a simple substance, but that each probably is made up of a number of substances. Each of the component parts of the agglutinine may have an agglutinative affinity for a corresponding constituent of the bacillus, and the more closely the component parts of the two agents in the reaction correspond the greater affinity will there be between them and the more pronounced will be the reaction.

If we take A, B, C, D, E, etc., to represent possible component parts of the bacillus, and let a, b, c, d, e, etc., represent parts of the agglutinine having corresponding affinities to these components, then the greatest agglutinative affinity will exist between a bacillus having the composition A, B, C, D, E, and an agglutinine having a composition a, b, c, d, e. Again, the affinity between a bacillus whose composition is represented by A_{10}, B_{10}, C_{10}, D_{10}, E_{10}, and an agglutinine represented by a_{10}, b_{10}, c_{10}, d_{10}, e_{10}, *i.e.* with a corresponding composition, will be greater than between a bacillus represented by A, B_{10}, C_5, D_{10}, E, and an agglutinine represented by a_{10}, b_2, c, d_5, e_5. Again, a much greater affinity will exist between a bacillus A, B, C, D, E, and an agglutinine a, b, c, d, e, than between those represented A, B, C, D, E, and d, e, f, g, h, respectively, though some affinity would still exist between these two latter owing to the presence in each of the corresponding components D, E and d, e. Examples such as these might be multiplied, but in short, when any component part of a bacillus corresponds to a component part of an agglutinine an affinity exists between them; and the greater the number of corresponding component parts, and the closer these parts approximate quantitively to one another the greater is the affinity between the bacillus and the agglutinine and the more marked will be the reaction. If one considers the question in the light of Ehrlich's side chain theory the explanation really corresponds, but the conception of the phenomenon is then represented diagrammatically, instead of arithmetically. This explanation of the reaction given by Durham may at present then be taken as a working theory.

What then is the practical value of immune sera? Apart from the interest they possess in view of their bearing on the subject of immunity in general, to put the matter briefly, these sera are of value to the bacteriologist in two ways :—

(1) As a means of identifying bacilli quickly.

(2) As a means of showing the more exact relationship of bacilli to other members of a family or group.

Suppose from the stools of a patient suffering from an indefinite acute febrile illness, in whom at an early stage the serum reactions are negative, a bacillus is isolated which, as far as can be seen without going through the various cultural methods, belongs to the coli typhoid group. If the sera of animals immune to certain organisms are brought into contact with the bacillus, and if a well-marked positive reaction is given with the serum of an animal immunised by, *e.g.* the bacillus paratyphoid "B," but with none of the other members of the coli typhoid group, then the bacillus will be proved to belong to the paratyphoid "B" class and the patient to be suffering from paratyphoid

fever. Or again, suppose that culturally the bacillus belongs to the group of "Gärtner and its allies," but that the serum reactions are negative. If an animal is immunised by the suspected bacillus and its serum is found to give a positive reaction with bacillus paratyphoid "B" but not with the bacillus of Gärtner, it proves that again the bacillus is a paratyphoid "B" bacillus, and that the patient is suffering from paratyphoid fever.

As an instance of the second point, it has been shown that the bacillus paratyphoid "B" is more nearly related to the bacillus typhosus than is the bacillus paratyphoid "A." For example, Korte (10) showed that the sera of rabbits immunised by his bacillus, which was of the "B" type, and giving with that bacillus and other bacilli of the type "B" a positive reaction of 1 : 10,000, gave with bacillus typhosus a positive reaction of 1 : 320, while on bacilli of the "A" type they were not potent to any appreciable extent. Further, he showed that the sera of rabbits immunised by Kurth's bacillus, which was also of the "B" type, and giving with Kurth's bacillus and other bacilli of the "B" type a positive reaction in dilutions of 1 : 5000, gave with the bacillus typhosus a reaction of 1 : 640, while with paratyphoid "A" bacilli the reaction was not produced at any dilution. Hewlett (20), on the other hand, found that the serum of a guinea-pig immunised by his bacillus, which was an "A" paratyphoid bacillus, gave with two other "A" paratyphoids a positive reaction of 1 : 5000, but that on "B" paratyphoid organisms as well as on the bacillus typhosus it had no action. Brion and Kayser (6) found a similar result. From these and other results it is evident that the bacilli of the type "B" have a closer relationship to the bacillus typhosus than have those of the "A" type.

It has further been shown by means of immune sera that varieties exist among the bacilli forming the coli family.

Bruns and Kayser (29) have found from experiments with paratyphoid and other organisms that in the case of immune sera the microscopic is ten times more sensitive than the macroscopic method. They are of the opinion that for speedy diagnosis by the help of rabbits' sera, it is of advantage to use sera which have only a medium agglutinative power. A quickly positive result in a dilution of 1 : 100 is in their opinion sufficient to identify the organism when the immune serum gives with its homologous organism the following reactions:—

In the case of bacillus typhosus, 1 : 1000—1 : 5000.
With bacillus paratyphoid "A," 1 : 1000—1 : 2500.
With bacillus paratyphoid "B," 1 : 1000.
The lower dilutions are in their opinion to be preferred.

As has already been mentioned it is possible to protect small animals against lethal doses of bacteria by immune sera. Korte (10), for example, in the case of mice, injected two animals of a similar weight with equal lethal quantities of a paratyphoid bacillus. Along with the bacillus he injected in the first animal .01 c.c. of homologous immune serum. The animal was not affected. Along with the bacillus in the second case he injected normal serum. The animal died after twelve hours. This was done on several occasions with the same result. A protective power was thus shown to exist in the immune serum against the bacillus injected. He found, moreover, that .5 c.c. of the same immune serum did not protect against a single lethal dose of the bacillus typhosus.

Conradi, Drigalski and Jürgens (8) found that one loop of the Saarbrück bacillus was sufficient to kill guinea-pigs of 160-200 grammes weight, and that while .1 c.c. of a normal serum was powerless to save animals of a corresponding weight from death when injected along with one loop of the Saarbrück bacillus, .01 c.c. of the serum of one of the patients of the epidemic was sufficient to protect the animal. Such an amount of serum had no effect in preventing death when a corresponding dose of the bacillus typhosus was injected. They also showed that of the serum of a rabbit immunised by the Saarbrück bacillus, .008 c.c. protected guinea-pigs against one loop of the bacillus typhosus, but that .006 c.c. protected animals of the same weight against the same quantity of the Saarbrück organism ; and they further demonstrated the fact that using the serum of a goat immunised by the typhoid bacillus, it required .01 c.c. of this immune typhoid serum to protect guinea-pigs of 160-200 grammes against one loop of the Saarbrück bacillus, while .00005 c.c. protected animals of the same weight against equal doses of the typhoid bacillus. These experiments tend to show that immune sera can be produced which have a protective power against lethal doses, not only of homologous organisms but also of organisms which are related ; but that the protection against the latter is much less than against the former. This subject, however, is one which requires further elucidation before any large definite statements can be made regarding it.

Resumé.

What inferences, then, may one draw from the results of this enquiry? In particular we may conclude :—

(1) That there exists a disease which simulates the disease

known as typhoid fever so closely that they can only be distinguished by bacteriological means.

(2) That the disease is caused by an organism which exists in two varieties and which may be regarded as bacteriologically intermediate between the bacillus typhosus and the bacillus coli communis.

(3) That this disease is on the whole mild and that the prognosis is good.

(4) That the treatment of the disease is similar to that of typhoid fever.

(5) That the disease spreads in the same manner as typhoid fever and that the same hygienic and general measures should be taken in cases of this disease as are adopted in typhoid fever.

(6) That in suspected typhoid-like cases a bacteriological examination is of the greatest importance both for diagnosis and prognosis and should be made wherever it is possible.

(7) That up to the present the disease must be regarded as acute general infection in which no definite local lesion has been shown to exist.

One may also draw some general conclusions from the facts collected in this paper. The various investigators have shown by their results the necessity for bacteriologists and clinicians going hand in hand, and the benefits which result from such a combination, and also that some indications have been obtained of the possibility of a new line of treatment in cases of infectious diseases, more especially in view of the protective power shown to exist in the sera of animals immunised to certain organisms.

Already there is a great trend in the medical world towards such a line of treatment. In addition to the antitoxin treatment of diphtheria which has now become universal, it is considered by many that such diseases as typhoid fever can be warded off completely in some cases and in others made less severe by injections of dead cultures, and especially is Wright of this opinion. It may be that the indications given by the results of the experiments on animals with protective sera in the case of the bacillus typhosus and allied organisms is but the initial stage of the beginning of a new curative method of treatment. One can only hope that such facts give but an indication of the approaching dawn of a new era in the world of therapeutic medicine.

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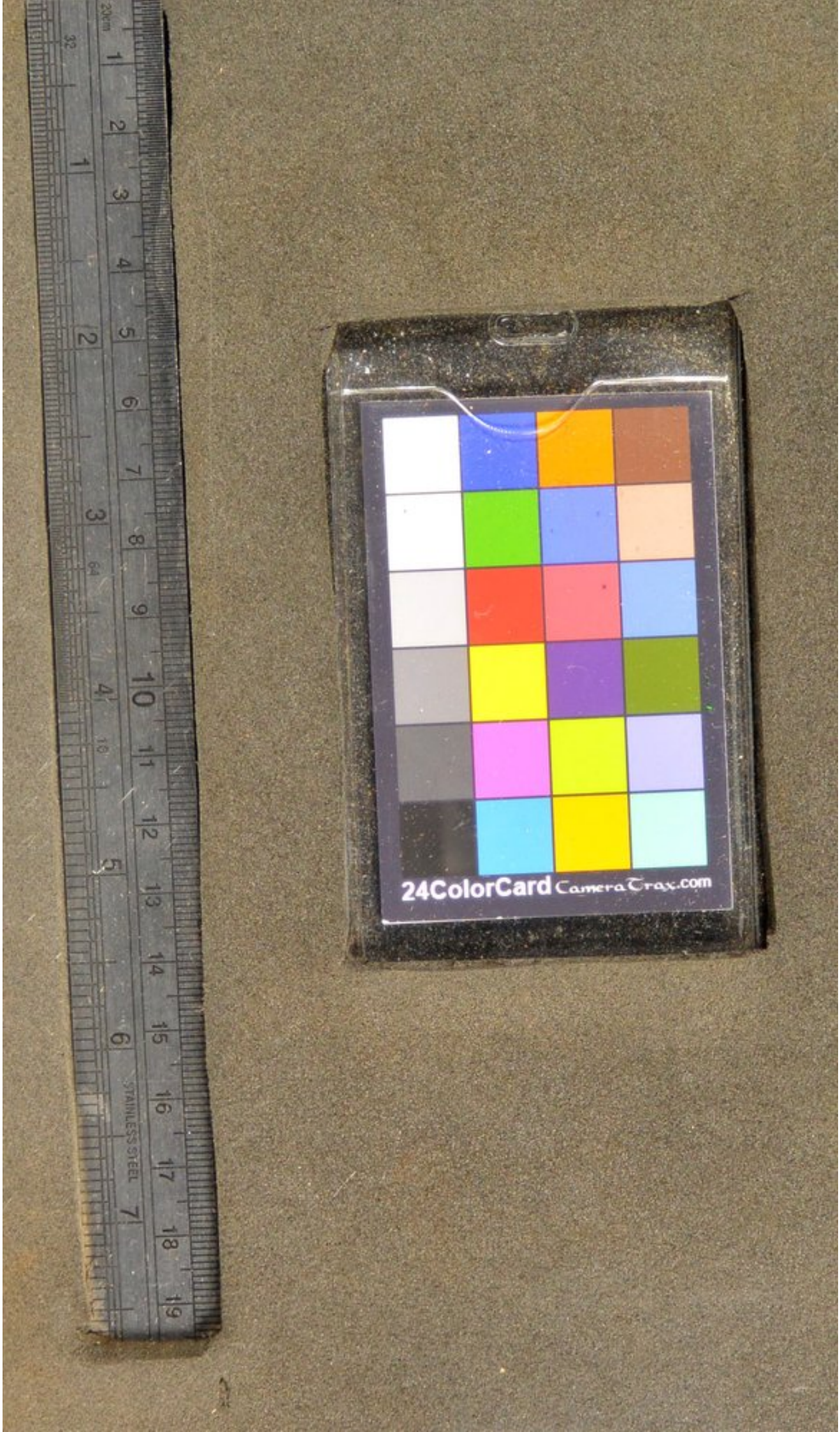
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