A STUDY OF THE EPIDEMIC OF TYPHOID FEVER IN BELFAST, 1898.

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THE EPIDEMIC OF 1897-98.

The number of cases of typhoid fever in Belfast rose early in 1897 markedly above what has been regarded as the endemic average. This high rate continued until the autumn of 1898, when the outbreak became formidable, and in the end of August the Public Health Committee of the Corporation determined to have a bacteriological investigation carried out with the view of discovering the source of infection. The report was furnished to the Corporation a short time ago, and in the present paper we describe some of the observations of scientific interest which were made during the investigation.

THE WATER SUPPLY.

Various local circumstances indicated that the water supply could not be regarded as beyond suspicion. In examining the water, however, no typhoid bacilli were isolated, but a large number of varieties of the bacillus coli communis were found. The significance to be attached to the presence of this organism in drinking water is a matter which has never been definitely settled. It seemed to us that the natural way to attack the question in this case was to study the relation of these bacilli to those directly obtained from cases of typhoid fever in the epidemic. In carrying this out it became evident that it was necessary to investigate also the relation of these bacilli to the process of infection in typhoid fever.

RACES OF B. COLI.

Many of the varieties obtained from the water conformed to the ordinary intestinal type of *B. coli*, but from time to time races were isolated which, when tested with the serum of typhoid patients, showed by their reactions that they possessed a special relation to the typhoid disease. The presence of a serum reaction to various races of *B. coli* has an important bearing on the question of *B. coli* infection in typhoid fever, and we have confined our attention to the interpretation of observations on patients in regard to this subject.

In their morphology the races vary slightly among themselves. Differences exist as regards average length, the number and length of the flagella, rapidity of milk clotting, of indol production, and of the production of gas bubbles from sugars at room temperature. When compared with the classical type of the *B. coli*, they all conform in general to the accepted description of this bacillus. We have, however, compared them in some detail with a number of *B. coli* races which we isolated from the healthy human intestine, and find that these bacilli differ from many of the latter in that they all possess a high motility, in more rapid production of indol in peptone solution (Dunham), and of gas bubbles in gelatine shake cultures. Most of the varieties also possess more numerous and longer flagella than those commonly described in this bacillus. Gordon, however, considers this character in regard to flagella as not uncommon.¹

In the second place, the pathogenicity of several varieties was tested, but does not call for special remark. It was observed usually after they had been cultivated for some time. One bacillus (Coli H) was tested soon after its isolation from the water. A guinea-pig of 350 grams weight was inoculated subcutaneously with 1.5 c.c.m. of a twelve hours' broth culture of this bacillus. The animal died in eleven hours and a-half, and the bacillus was recovered in pure culture from its blood. Several rabbits were inoculated with small doses of three other varieties which had undergone repeated cultivation on artificial media. Local sores always formed, and some of the animals died. On the whole, we may say that these bacilli appeared to have a greater pathogenicity for small animals than is possessed by the varieties of *B. coli* commonly present in water.

THE SERUM REACTION.

The investigation, however, was concerned chiefly with the direct evidence of the connection of these bacilli with typhoid fever, which was obtained by observing the effect on them of the diluted serum of typhoid patients. We examined over 200 cases, and found that in a large proportion of them the serum possessed the power of clumping one or other of these bacilli. Before going into our observations in detail, we may shortly refer to the results of previous investigations on the subject.

SYMBIOSIS OF B. COLI AND B. TYPHOSUS.

A large amount of work has been done to prove that races of *B. coli* are modified by their occurrence along with the typhoid organism. The symbiosis apparently increases their pathogenic power. Pisenti and Bianchi-Mariotti have shown that the races of *B. coli* which are found in normal stools are less pathogenic than those which have been isolated from the faeces of a typhoid patient. The same feature is observed by them *in vitro*. If a culture of coli be planted in the gelatine in which a growth of typhoid has been, it increases markedly in its virulence.² This observation is confirmed by Sanarelli.³ His opinion is that when the typhoid process sets up, this bacillus acquires virulence, and takes part in the disease. The work of Sanarelli is essentially experimental, and will be more fully discussed later in the paper.

A few observations have been recorded indicating a close connection between the agglutination of the typhoid bacillus and races of *B. coli*. Courmont, at the time when the facts of agglutination were first studied, stated that the serum of typhoid patients clumped the *B. coli*.⁴ This result was controverted by Chantemesse and Achard. Bordet states that an "antityphoid" serum clumps *B. coli*.⁵ Gilbert and Fournier, on the other hand, investigated the agglutination of *B. coli* with typhoid serum with negative results.⁶ Durham, working with the serums of patients and of animals experimentally inoculated with typhoid, failed to find any effect on a number of cultures of *B. coli*.⁷ Christophers has shown that with certain races of *B. coli* a reaction may be observed in the normal human serum also. We found that we had to avoid coli races of this type.

The method of testing this reaction which we employed was to leave the diluted serum in contact with a young culture of the bacillus under observation in a moist chamber, and to examine the hanging drop microscopically after a suitable interval. After a considerable number of experiments we adopted a dilution of 1 in 100, and allowed a period of two hours for the action of the serum. A 1 per cent. dilution seems to us very suitable for examining a series of cases with various cultures, with a view to determining the nature and relation of the organisms which are supposed to have had an action on the serum. The serum is still concentrated enough to bring out a clear reaction in the majority of cases, and yet not so strong as to obscure the differences in reaction which the various races and species of bacilli manifest when acted on by a given sample of serum. The method was amply controlled by repeated observations on the same serum, and in no case was there a discrepancy which could be taken as casting doubt upon it.

GROUP OF BACILLI STUDIED.

The bacilli we observed were of the following groups: (1) Typhoid, 8 races; (2) *B. enteritidis* (Gaertner), 3 races; (3) *B. coli* communis from the water which clump with the serum of typhoid patients, 6 races; (4) *B. coli* communis from spleens of typhoid patients. Varieties were tested as they were isolated. Owing to the difficulty of obtaining *post-mortem* examinations, only five such spleens were examined for *B. coli*. In one we found several races of *B. coli* which clumped, and we selected for constant use that which gave the clearest reactions. In another we found a race of *B. coli*, which reacted in only a few cases. The races of *B. coli* in the others did not clump. (5) *B. coli* communis from the normal intestine. A large number of races were isolated and tested, several of them being used constantly as controls. No reactions were obtained.

We attempted as far as possible to make observations on cases from other centres also, and we have to express our indebtedness to Dr. Darling, of Lurgan, who provided us with

samples of blood from 30 cases in his practice. We have also to thank Dr. O'Sullivan, Trinity College, Dublin, for sending us samples of blood from cases which came under his notice. These cases we have studied separately, but from the examination of them we were unable to discover any differences in the nature of the infection in these three localities.

We also made control observations on the serum of normal individuals. These observations were done at a 5 per cent. dilution of the serum, and except in two cases no reaction greater than a slight indication of agglutination occurred with any of the bacilli. One of the two exceptional cases was a boy employed in the laboratory, whose only illness had been of one day's duration, and was due to indiscretion in diet. The other was an adult who has had no illness since infancy. These two cases support the contention of Durham that a dilution of 1 in 20 is fallacious in clinical diagnosis. Both gave a very clear reaction at this dilution, but only a trace at a dilution of 1 in 100. It is important to observe that the action of these two healthy sera on the group of *B. coli* we were investigating was as marked as on the typhoid and Gaertner groups.

RESULTS OF SERUM TESTS.

Putting together the cases from Belfast, Lurgan, and Dublin, the following table shows the percentage in which each bacillus gave the reactions which we considered standard, namely, the clumps large, and most of the bacilli clumped. The cases numbered 168. We have not included in this table a large number of cases which were examined by other methods. The bacilli are designated by initials and numbers. H.S., B.T.A., B.W., "Gaertner" and "Hatton," were races kindly sent by Dr. Durham.

B. Typhi.

H.S.	Spleen 1.	Flh.	Mn.	B2.	D5.	B.T.A.	B.W.
24.8 %	26.4 %	30 %	37.5 %	36.6 %	39 %	50 %	52.4 %

B. Enteritidis.

Spleen 2.	Gaertner.	Hatton.
18.5 %	17.5 %	7.6 %

B. Coli Communis.

L.	H.	F.	No. 25.	C.P.	No. 7.	No. 6.
32.7 %	26.0 %	26.0 %	19.8 %	15.0 %	11.3 %	10.7 %

It will be observed that the highest percentage of reactions of any typhoid bacillus is only 52.4. The cases from which this table is compiled were all clinically diagnosed as cases of typhoid fever. A less marked agglutination than we adopted as our standard reaction is diagnostic of typhoid infection. Minor reactions were recorded, and have been analysed so far as they form control observations or contribute to the elucidation of the others.

If we sum up the results in a different way, we find that one or more of the typhoid races reacted to 73 per cent. of the cases, one or more of the Gaertner races to 25 per cent., and some of the races of *B. coli* to 50 per cent. There were very few cases where all the eight typhoid races gave a standard reaction, and in cases where the serum acted on races of *B. coli*, the degree of the reaction varied with the race, and there were always some which were unaffected. We have not been able to trace any particular association of reactions between the different races of *B. coli* which we investigated. There are, however, certain races amongst the seven which obtained the highest averages in the cases from each of the three centres we studied.

This table raises a number of questions, but the only one which we can discuss in this paper is whether we have to deal with a single or with a multiple infection.

In a given case it is common to find the reaction as follows :

FOURTH DAY OF DISEASE.

B. Typhi.

H.S.	Spleen 1.	Flh.	Mn.	B2.	D5.	B.T.A.	B.W.
×	—	×	×	×	✓	✓	×

B. Enteritidis.

Spleen 2.	Gaertner.	Hatton.
✓	✓	×

B. Coli Communis.

L.	H.	F.	No. 25.	C.P.	No. 7.	No. 6.
×	×	—	✓+	o	✓+	o

In these tables × means a standard reaction, ✓ a slight reaction, and / a mere trace. The symbols + and — further differentiate them.

Here we have a serum which is capable of agglutinating members of each of the three groups of bacilli. It is well known that the serum of an animal which has been infected with the typhoid bacillus exercises an agglutinating power, not only over the infecting bacillus but also over the allied species of *B. enteritidis*. This fact was first described by Grüber in relation to the Eberth and Gaertner bacilli. To this association in agglutination the name of "mutual reaction" has been given by Durham. Thomassen obtained the same results with these two groups of bacilli,⁸ and Gilbert and Fournier observed a similar relationship between *B. typhi* and *B. psittacosis*.⁹

While recognising that this mutual relationship exists, we must also note that a serum which clumps both species of bacilli yet clumps the infecting species when it has been so highly diluted that it has only a slight, if any, effect on the allied species. From this fact is derived the principle on which depends the method of studying the reaction of bacilli to a serum at increasing stages of dilution. We applied this method of dilution in the investigation of the reaction of the *B. coli*, and in a few cases the bacillus which reacted at the highest dilution was one of the *B. coli* group. The method is, however, clearly inapplicable if the possibility of a mixed infection be granted. We were led, therefore, to take up other lines of investigation regarding the question of infection.

Certain cases were examined in which, at a dilution of 1 per cent., a standard reaction was obtained only in the members of the *coli* group. The following is an example :

SIXTEENTH DAY OF DISEASE.

B. Typhi.

H.S.	Spleen 1.	Mn.	B2.	B.T.A.	B.W.
o	/	/	/	✓	✓

B. Enteritidis.

Spleen 2.	Gaertner.	Hatton.
✓	✓+	o

B. Coli Communis.

L.	H.	No. 25.	C.P.	No. 7.	No. 6.
×	✓+	✓	×	✓	✓

The serum, unfortunately could not be obtained a second

time. The disease ran a typical course, resulting in death a fortnight after this examination was made. Had this serum been examined at a later date it would in all probability have given much clearer evidence of typhoid infection. In this case the reaction of the *B. coli* is clearly independent of that of the *B. typhi*.

There were also many cases in which the serum reacted to the typhoid and coli groups only. The large number of observations which have been made showing the absence of agglutination of the *B. coli* with typhoid serum clearly indicate that a mutual reaction does not exist, at least to the same extent as it has been shown to exist between the typhoid and Gaertner groups. When, therefore, we find that a given serum has an effect on the typhoid races, and also on the *B. coli*, but has no effect on the Gaertner varieties, it is more natural to regard the two reactions as independent of each other. We may refer to the following example:

SIXTH DAY OF DISEASE.

B. Typhi.

H.S.	Spleen 1.	Fh.	Mn.	B ₂ .	D ₅ .	B.T.A.
× +	×	×	×	×	× ×	× +

B. Enteritidis.

Spleen 2.	Gaertner.	Hatton.
°	°	°

B. Coli Communis.

L.	C.P.	No. 7.	No. 6.
×	×	°	°

There were, in the third place, many cases in which the reaction modified essentially as the case progressed. It has been recognised by several investigators that important information in regard to the reaction of the serum in a given case can be obtained by making successive observations during the course of the disease.¹⁰

A number of the cases when first examined gave a clear reaction to the *B. coli* group alone. We were fortunately able to obtain the serum a second time in several of these cases, and we usually found that at the later period it showed a distinct power of agglutinating the *B. typhi* also. The following instance is an example of this type of reaction:

TWELFTH AND FORTIETH DAYS OF DISEASE.

B. Typhi.

	H.S.	Spleen 1.	Mn.	B ₂ .	B.T.A.	B.W.
12th day	...	/	°	/	/	/
40th day	...	\	× -	\ -	×	\

B. Enteritidis.

	Spleen 2.	Gaertner.	Hatton.
12th day...	—	°	\
40th day...	\	\ -	\

B. Coli Communis.

	L.	H.	No. 25.	C.P.	No. 7.	No. 6.
12th day	...	×	—	×	\	×
40th day	...	×	\	×	\	×

In cases such as this it would be difficult to believe that the reactions from the first are due simply to the invasion of the typhoid bacillus. If so, it would mean that the bacilli infecting an organism may so act on it that the serum of its blood becomes possessed of the power of agglutinating bacilli of another species before it has any effect on bacilli of its own species. The more natural supposition is that the reaction of the *B. coli* in such cases is due to some process of infection for which it itself is responsible. We may therefore conclude on these grounds that the reaction of the *B. coli* indicates an independent infection by a member of this group.

COMPARATIVE STUDY OF THE GROUPS.

The problem which now awaits solution is the following: Since the serum of the patient gives indication of an independent infection, can we, by the aid of this reaction, proceed directly to the isolation or discrimination of the race or races of *B. coli* which are concerned in the infection?

To answer this question we must compare the three groups of bacilli whose reactions we have tabulated. Not only do the three groups differ from each other as groups, but within each group individual races of bacilli differ from one another both in their morphology and in their serum reactions. We need not discuss the slight morphological differences among the typhoid races. We may refer to a statement by Sanarelli on this subject.¹¹ The differences in the serum reactions are abundantly illustrated by all our cases. One race of typhoid bacilli may show a standard reaction in a given case while another is apparently unaffected. Amongst the *B. enteritidis* races morphological and physiological differences of a more pronounced kind are observed; while the *B. coli* group may be said to be specially characterised by the morphological differences which its members present.¹²

THE TYPHOID GROUP.

We may, therefore, raise the question in the first instance in regard to the typhoid group, since the various members of it resemble each other so closely. Can we, by means of the serum reactions, identify the race which produced an infection?

Early in our study of the Belfast epidemic we isolated from the spleen of a patient the race we have called in our table Spleen 1. This bacillus, it should be noted, gave a reaction in 26 per cent. of the cases, while B.T.A. and B.W. reacted in 52 per cent. and 50 per cent. of the cases respectively. Similarly the bacillus D₅, isolated from a spleen sent to us by Dr. Darling, reacted only in 45 per cent. of Dr. Darling's cases, while B.W. reacted in 60 per cent. of them.

We put the question finally to the test of experiment. A rabbit was inoculated with repeated doses of the bacillus Spleen 1 until its blood gave a strong reaction. It was then found that with the serum at a dilution of 1 in 1,000, Spleen 1 gave merely a trace of reaction, while B.T.A., B.W., and B.T.H. showed a standard reaction.

These observations, which confirm those of Widal and Sicard,¹³ prove that within the typhoid group it is impossible from the serum reactions to detect the infecting race of typhoid bacilli. Since each race of *B. typhi* possesses a certain facility in clumping, it is only when the infecting bacillus is at the same time the bacillus least resistant to agglutination that it gives the best reaction to the serum of the infected animal. The bacilli which in the table of reactions obtain the highest average did not give the most pronounced reactions in every case. Unusual reactions are difficult to explain, but may be supposed to depend upon some individual peculiarity of the patients. In making our control observations we noticed that the serum of normal individuals frequently possessed a slight power of clumping a particular race of typhoid bacilli, while other races were unaffected. The extent of the action on a given race of bacilli of the serum of a particular case depends probably on three factors: (1) The species of the bacillus, (2) its facility in clumping, and (3) the individuality of the serum. The reaction should therefore be regarded as that of a group of bacilli rather than that of a particular member of the group.

THE *B. COLI* GROUP.

When we pass to the study of the *B. coli* reactions, it is uncertain how far we can apply the principles which obtain

in the interpretation of the reactions of the typhoid group. Compared with the *B. typhi* group, the *B. coli communis* group is more variable, not only morphologically, but also in regard to its serum reactions. We may exemplify both these points by the varieties which we can discover in the same typhoid spleen. In that, for example, from which *Coli 7* was isolated, there were other races, among which some were morphologically identical with it, while others differed. Many of these did not react in cases where *Coli 7* reacted, and some never reacted at all. Another point in which the group showed a general similarity to the typhoid group was the fact that the same members of it obtained the highest averages of reactions in each of the three series of typhoid cases we examined. We have not in our possession as yet sufficient observations on the subject; but the conclusion suggested by the experiments already carried out is that the principles regulating the occurrence of reactions in the typhoid group are also applicable to the *B. coli* group.

Sanarelli has suggested autointoxication as a process which takes place in typhoid fever. The data we have at present are insufficient to lead to a conclusion on this; but, in considering the races of *B. coli* which react, we wish to emphasise the fact that they do not separate themselves into a morphological group distinguishable from the other members of the species. The bacillus *L.*, which reacted most frequently, has in its cultural features very pronounced *coli* characters, and the six races we have selected differ only slightly from the traditional *B. coli communis*.

We may, speaking generally, compare the *B. coli* group with many other bacteria which possess pathogenic power. The pneumococcus found in inflamed lungs is only pathologically distinguished from the innocent diplococcus of the healthy mouth. A similar remark applies to the streptococcus of erysipelas. The vibrios are a notorious example of a group of microbes which are differentiated chiefly by their pathogenic characters. Should similar results be arrived at in relation to the *B. coli*, it would only be placed on the same footing as other bacteria if we selected from it a subgroup differentiated solely by their possession of pathogenic properties.

SUMMARY.

We may therefore sum up the observations on the serum of patients in regard to infection as yielding the following results: (1) The occurrence of the reaction of *B. coli*, though subordinate to that of *B. typhi*, is yet independent. (2) The serum reaction is in itself probably insufficient for the discrimination of the races of *B. coli communis* which possess the power of invasion in typhoid fever.

Other methods of solving this question clinically and experimentally suggest themselves, and we have in progress experiments on the subject. The study, for example, of the races of *coli* which occur in the urine in a certain proportion of typhoid cases promises to yield important results.

EXPERIMENTS ON ANIMALS.

We have carried out a certain amount of experimental work for the purpose of controlling the observations upon patients. It was necessary to ascertain whether or not the serum of an animal inoculated with the typhoid bacillus acquired the power of agglutinating the *B. coli* races in question. Durham has confirmed his negative clinical observations by similar results obtained with experimental sera. On the other hand, the investigations already referred to on the mutual reaction of *B. typhi* and *B. enteritidis* suggest a similar relationship between *B. typhi* and the *B. coli* under discussion. The research of Demel and Orlandi, confirmed by Sanarelli, showing that immunisation against either *B. typhi* or *B. coli* confers immunity against the other supports the same hypothesis.¹⁴ Our observations would also point in this direction.

In examining at intervals the serum of a rabbit which was inoculated with repeated small doses of *B. typhi* (Spleen 1), we found that it acquired the property of agglutinating first the *B. typhi*, at a later stage the *B. enteritidis*, and still later the *B. coli* with which we are concerned. We concluded therefore that the typhoid bacillus has a mutual reaction, well marked with certain varieties of *B. enteritidis*, less distinct with other varieties, and still less with the races of *B. coli*. Recently Gordon, working in Klein's laboratory, has

isolated a variety of *B. coli* which probably belongs to the group under consideration, for it was slowly clumped by the serum of a horse experimentally inoculated with the typhoid bacillus.

Rabbits were inoculated with three varieties of *B. coli* also—namely, *L.*, No. 6, and No. 7. These three bacilli were found to have a moderate degree of mutual reaction with the other four races of *B. coli*, and somewhat less with the *enteritidis* and *typhi* races.

The observations we have just described are sufficient for testing the conclusions reached by the study of the agglutinating reactions of typhoid serum in this epidemic. The serum of the rabbit contrasts with that of the patient. The latter frequently clumps at an early stage the *B. coli* alone, and at a subsequent period the *B. typhi* also. The rabbit serum, on the other hand, at first clumps the *B. typhi* alone, and later the *B. coli* also—that is, when the agglutinating power is increased. This confirms our conclusion that in the patient's serum the *B. coli* reaction in many cases depends on something else than a pure typhoid infection. Those cases in which the serum shows a marked reaction to both *B. typhi* and *B. coli* and little or no reaction to *B. enteritidis* also differ essentially from the typhoid-infected rabbit, whose serum, when potent enough to clump the *B. coli*, had a still more pronounced effect on *B. enteritidis*.

Experimental evidence to further prove the double infection is not required in the cases where the reaction to *B. coli* was at first the only one, and was later accompanied by a reaction to *B. typhi* also.

THE *B. COLI* IN TYPHOID FEVER.

The question of what part in the process of typhoid fever the *coli* infection plays must for the present be left untouched. The solution requires more elaborate clinical and experimental investigation than we have yet been able to carry out.

As regards the time relations of the infection, we have been unable from our analysis of the cases to decide at what particular period, if any, in the history of the case the *coli* invasion commonly occurs. Other methods of research must, however, be applied to carry the investigation of this further.

It is unnecessary here to refer to recent researches on the pathology of typhoid fever farther than to point out that the problem raised in this investigation is one of the main problems in recent experimental work.

The typhoid bacillus differs in the degree of its pathogenicity from the microbes of many infective diseases. When inoculated directly from the human spleen into guinea-pigs, the least resistant of small mammals, it possesses little or no virulence, an enormous dose being necessary to kill the animal. This is still more true when it has been cultivated. The large amount of work that has been recorded with regard to inoculation of animals with this bacillus is summed up in the researches of Sanarelli.¹⁵ Sanarelli notes the absence of pathogenicity in the bacillus as it is isolated from the spleen; but he finds that it acquires a high degree of virulence if it be passed through a series of animals, each inoculated from the abundant peritoneal exudate of its predecessor. In the earlier inoculations it is necessary to reinforce the bacillus, or to diminish the resistance of the animal, in order to enable the bacillus to diffuse itself. Sanarelli used for this purpose large intraperitoneal injections of the products of metabolism of other bacteria. He found the products of the *B. coli* most suitable, although he thinks the products of other bacteria may be equally effective. His practice was to inoculate the first of his series of guinea-pigs with 0.5 c.cm. of a broth culture of *B. typhi* subcutaneously, and at the same time to inject 10 c.cm. of sterilised culture of *B. coli* into the peritoneal cavity. The animal died usually within twenty-four hours. A culture from its peritoneum was injected into a second animal in the same way. It was found possible to diminish the dose both of bacilli and of *coli* products, and ultimately the bacilli became virulent enough to produce the effect without the assistance of the *coli* intoxication. Even at this stage the virulence is much inferior to that of many organisms, such as the pneumococcus, swine plague bacillus, etc., and the bacillus readily relapses to its original innocuous condition.

Sanarelli, in a similar series of experiments, observed the

effect upon the *B. coli* in the intestine of injections of the toxins of *B. typhi*. When the toxins were administered in repeated small doses in such a manner as to produce immunity, he found the contents of the small intestine to be sterile, the *B. coli* normally present there having disappeared. When an overdose of typhoid products was administered in the course of such an immunisation experiment, there occurred a coli invasion, which resulted in localised abscesses from which the bacilli could be isolated. The two results of Sanarelli's work which have a direct bearing on our observations in the recent epidemic are (1) the effect of *B. coli* products in increasing the virulence of this typhoid bacillus, and (2) the effect of the injection of typhoid toxins in bringing about an invasion of *B. coli*. Sanarelli himself thinks it probable that autointoxication with products of intestinal fermentation is a factor in the causation of typhoid fever, and this suggestion brings the theory of the disease into line with his experimental results.

Chantemesse and Vidal carried out simultaneously a research on the same subject. They consider the typhoid bacillus isolated from the spleen as having slightly more virulence than was ascribed to it by Sanarelli. But they also had recourse to adjuvants to procure a really virulent bacillus. They used, among others, the products of the *B. coli*. The conclusion, they state without reservation, is that some factor besides the typhoid bacillus is concerned in the production of typhoid fever.¹⁵

CONCLUSION.

The observations on the epidemic which we have recorded in this paper afford further grounds for the application of the results of recent experimental work to the interpretation of the disease in the human subject. The attempts to reproduce in animals typhoid fever as a disease have been, on the whole, unsatisfactory, and, as we have seen, the difficulty is not a simple one. The first stage of the process must consist in obtaining bacilli of such virulence that they can invade the tissues of animals, and this difficulty has been overcome by the use of adjuvants. The further stages in the process of reproducing the disease are still unknown.

The object before us in this investigation has been to show that in patients there can be obtained from the serum indications of coli invasion during the process of typhoid fever. In other words, there is a large body of evidence to prove that Sanarelli's experimental results are directly applicable to typhoid disease in the human subject.

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ON THE VALUE OF THE TREATMENT OF DIPHTHERIA BY ANTITOXIN.

Being an Introduction to a Discussion held at the Hunterian Society.

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THE INTRODUCTION OF ANTITOXIN.

It is now upwards of four years since Roux at the Eighth International Congress of Hygiene at Buda-Pesth read his classic paper on the treatment of diphtheria by antitoxic serum. Before that occasion there had been furnished by certain German clinical observers no mean evidence that the treatment was of value, but it was Roux's paper that suddenly and prominently brought the method before the notice not only of the profession, but also of the public throughout the world, and for most countries the introduction of the antitoxic treatment dates from the latter part of 1894.

At first, even after the publication of Roux's paper, the new

remedy was looked on with much suspicion. So many specifics had from time to time been vaunted against the ravages of diphtheria, and though I will not go so far as to say that none of them were of service, yet certain it is that they never fulfilled a tithe of the promises made on their behalf; moreover, the tuberculin fiasco of 1890 was still fresh in the memory. But the previous terrible fatality of the disease, the stability of the experimental evidence upon which the new treatment was based, the openness with which the preparation of the serum was made known, and the weight attaching to the observations of one so eminent in science as Roux, compelled those who were concerned in the care of large numbers of diphtheria cases to give the method a thorough and unbiassed trial. Now, at the end of these four years, I think I can safely assert, without fear of contradiction, that all those who have employed the treatment in a sufficient number of cases have made up their minds regarding its value one way or the other, and that a large majority of these are agreed that all that was claimed for it has been fulfilled. There are a few who, even after more than a casual trial, are of the opposite way of thinking. Besides these two classes, there is another consisting of those who are, so to speak, of no way of thinking at all; they have either had few or no cases to treat, or they have not been able to procure the remedy, or they have not really troubled themselves about the question, but have preferred to go on with methods of treatment ancient but inefficient. The latter group, I fear, contains no small number of practitioners, judging by the evidence I daily encounter in the many children I see admitted to hospital in a hopeless condition who have not been afforded, while still there was time, the relief that antitoxin brings. I believe, moreover, that a study of such statistical facts as are available shows that the treatment has not been used to any marked extent outside hospitals.

EFFECT ON MORTALITY IN LONDON.

During the past three years there has been a lowering of the case mortality of diphtheria in London. The following table (Table I) shows to what extent this has occurred:

TABLE I.—Case Mortality of Diphtheria in London.

	1892.	1893.	1894.	1895.	1896.	1897.
Mortality per cent. of all notified cases	23.8	24.5	24.7	21.2	19.9	17.4
Mortality per cent. of notified cases admitted to Asylums Board hospitals	24.8	27.1	25.0	18.3	17.7	14.9
Mortality per cent. of notified cases not admitted	21.5	23.7	24.5	23.3	21.3	20.1
Percentage of notified cases admitted to hospitals	30.1	24.5	38.8	41.5	39.9	51.4

[The figures from which this table has been compiled are given in the annual reports of the Statistical Committee of the Metropolitan Asylums Board. They consist of the annual number of notifications, the annual number of registered deaths inside and outside the Board's hospitals, and the annual percentage of notified cases admitted to the hospitals. The actual number of notified cases admitted is not given except for the year 1897; but the number can be calculated pretty closely from the percentage. It must be understood that the table deals with cases admitted to hospitals as they are notified, and not as corrected for errors of diagnosis.]

The fatality (at its maximum 24.7 in 1894) fell to 17.4 in 1897; but it will be observed that this progressive diminution has been during the same time more marked among cases admitted to hospital than amongst those remaining outside, namely, from 25.0 to 14.9 in the one instance, and from 24.5 to 20.1 in the other. Usually the fatality of hospital-treated cases is higher than that of those not admitted to hospital. It was so for the years 1892, 1893, and 1894; in the latter year the difference was slight. But since 1894 this has not been the case. I think, therefore, it can be fairly claimed without laying undue stress upon the figures given in Table I, that some special factor has been at work to cause such marked changes, and knowing what I do of the value of the serum treatment, evidence of which I shall bring forward later, I am prepared to find this factor in antitoxin. It is impossible to say how many of the notified cases admitted to hospital have been treated with antitoxin; for the annual