On the "sero-diagnosis" of typhoid fever / by A. Sheridan Delépine and E.J. Sidebotham.

Contributors

Delépine, Sheridan, 1855-1921.
Sidebotham, E. J.
University of Glasgow. Library

Publication/Creation

[London] : [Lancet Office], [1896]

Persistent URL

https://wellcomecollection.org/works/bvqd6nxn

Provider

University of Glasgow

License and attribution

This material has been provided by This material has been provided by The University of Glasgow Library. The original may be consulted at The University of Glasgow Library. where the originals may be consulted.
This work has been identified as being free of known restrictions under copyright law, including all related and neighbouring rights and is being made available under the Creative Commons, Public Domain Mark.

You can copy, modify, distribute and perform the work, even for commercial purposes, without asking permission.

wellcome collection

Wellcome Collection
183 Euston Road
London NW1 2BE UK
T +44 (0)20 7611 8722
E library@wellcomecollection.org
https://wellcomecollection.org

ON THE "SERO-DIAGNOSIS" OF TYPHOID FEVER.

BY

A. SHERIDAN DELÉPINE, M.B., C.M. EDIN.,

PROCTER PROFESSOR OF PATHOLOGY, OWENS COLLEGE, MANCHESTER;

AND

E. J. SIDEBOTHAM, M.B. CANTAB., M.R.C.S. ENG.,

HONORARY RESEARCH FELLOW IN PATHOLOGY, OWENS COLLEGE, MANCHESTER.

Reprinted from THE LANCET, December 5 and 12, 1896.

ON THE "SERO-DIAGNOSIS" OF TYPHOID FEVER.

By SHERIDAN DELÉPINE, M.B., C.M. Edin.,

PROCTER PROFESSOR OF PATHOLOGY AT OWENS COLLEGE, MANCHESTER.

Part I.

Widal's method for the rapid diagnosis of typhoid fever is beginning to be generally known. He has himself established his claims to the discovery of this new method of "sero-diagnosis," as he calls it, in an article published recently in The Lancet.[1] Previously to that communication the only complete account of this method which had appeared in English journals was the one published in the *Medical Chronicle* of October.[2] In this paper an attempt has been made at tracing the discovery up to its origin and to review the share which Charrin and Roger,[3] Metchnikoff,[4] Pfeiffer,[5] Bordet,[6] Max Gruber,[7] and Durham[8] have had in the study of those properties of the blood serum of immunised animals so happily utilised by Widal. It should also be mentioned that Dr. Wyatt Johnston of Montreal had already in the month of September last made arrangements for the

---

[1] Fernand Widal: On the Sero-Diagnosis of Typhoid Fever, The Lancet, Nov. 14th, 1896, p. 1371.

[2] Sheridan Delépine: "Sero-Diagnostic" of Typhoid Fever, Medical Chronicle, Oct., 1896, New Series, vol. vi., pp. 60 to 70.

[3] Charrin and Roger: Comptes Rendus et Mémoires de la Société de Biologie, Nov. 23rd, 1889, p. 667.

[4] E. Metchnikoff: Annales de l'Institut Pasteur, 1891, tome v., p. 473; 1894, tome viii., pp. 714–716; 1895, tome ix., p. 433, &c.

[5] R. Pfeiffer: Zeitschrift für Hygiene, 1894, Band xviii., p. 1; 1895, Band xix., p. 194, &c. Pfeiffer und Kolle: Zeitschrift für Hygiene, 1896, Band xxi., p. 203.

[6] J. Bordet: Annales de l'Institut Pasteur, 1895, tome ix., p. 462, and 1896, tome x., p. 191, &c.

[7] Max Gruber: Münchener Medicinische Wochenschrift, 1895, Band vi., p. 14. Wiener Klinische Wochenschrift, Feb., 1896.

[8] Gruber and Durham: Münchener Medicinische Wochenschrift, March, 1896. Durham: Royal Society, Jan. 3rd, 1896. Journal of Pathology and Bacteriology, July, 1896, vol. iv., p. 13.

diagnosis of typhoid fever by this method. I think, however, that it might have been better for him to do what we have done in Manchester before using the method for public health work. Immediately after reading Dr. Widal's communication to the Paris Société Médicale des Hôpitaux [9] I spoke of it to Dr. Niven. I was, however, anxious not to use the method before I had had a sufficient personal experience of it, based on the examination of typical cases of typhoid fever and other fevers. Dr. Niven offered at once to give me all the help he could by obtaining blood and secretions from cases received at the Monsall Fever Hospital. Dr. Marsden, the resident medical officer at the hospital, showed himself very willing to give us all the assistance possible. Before the end of July we had already obtained results which could leave no doubt as to the value of the method. The number of cases recorded in France by Widal, Widal and Sicard, Achard, Courmont, and others had already at that time reached a sufficient size to inspire confidence.

Some simple experiments which I made at the beginning of this inquiry convinced me of the very close relations existing between the phenomena which have been described successively by Charrin, Roger, Metchnikoff, Bordet, Gruber and Durham, and others. As these may help the readers who have not paid special attention to this branch of bacteriology I will describe some of them briefly.

1. To 5 cubic centimetres of neutral peptone bouillon, 0·5, 1 or 2 cubic centimetres of the serum of an animal immunised against typhoid fever are added, then the tube is inoculated with typhoid bacilli, and incubated at a temperature of 37° C. A control tube of bouillon without serum is inoculated at the same time with the same quantity of typhoid bacilli and incubated in the same way. At the end of ten hours the bouillon containing no serum will be evenly turbid from the growth of the bacillus. At the end of the same time the bouillon to which serum has been added will be clear or nearly clear, and the bacilli will be found to have formed a precipitate at the bottom of the tube, where they form a number of small clumps.

2. The same experiment is repeated, with this difference, that the blood of a patient suffering from typhoid fever at the end of the third week of the disease is added to the bouillon of one tube instead of the serum of an immunised animal. The results are the same, though in some cases the reaction is not quite so clear.

3. To ten, twenty, or fifty drops of a twenty-four hours old culture of typhoid bacillus in neutral bouillon (or to a similar quantity of an emulsion of the bacillus grown on

---

[9] June 26th, 1896.

gelatin) one drop of immunised serum is added, the bacilli become almost instantaneously motionless, or nearly so, and then become massed together in clumps of various sizes. If to similar quantities of the same cultures similar quantities of normal human serum be added the bacilli will continue to move about freely and will not form clumps.

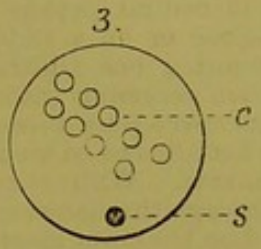
4. The same experiment as No. 3 repeated with the blood or blood serum of a patient affected with typhoid fever will give the same reaction In the first few days of this illness the reaction may not be observed, but as the disease advances the reaction becomes exceedingly clear. If one watches a preparation in which normal human blood has been added in any proportion to the bacilli these are seen to move actively about and do so with such power that the blood corpuscles move to and fro and are in a state of agitation. This might well be described as "a dance of the corpuscles." The bacilli, even though they may still be animated with some movement, after they have come in contact with the blood of a patient suffering from typhoid fever never produce this "dance" to any marked extent. If drops on which these phenomena have been observed are kept in a moist chamber for hours and days the reaction or absence of reaction remains quite evident. In some cases, not of typhoid fever, an imperfect clumping is sometimes observed after 24 hours. The blood plasma of normal individuals may also give this appearance. This cannot be easily mistaken for the typhoid reaction. I have seen the clumping still distinct at the end of 144 hours. When they have not formed good clumps and have not been completely immobilised from the first, the bacilli for a time become more and more immobilised and form more and more distinct clumps. After a while, however, the process is often reversed and a few are seen to regain their motility. It seems also that the number of bacilli increases. Some of those forming the clumps seem to get longer and to multiply. The bacilli are not killed, they rather seem to be paralysed, and on watching the formation of clumps under the microscope it has seemed to me that the stoppage of the motion of the flagella has something to do with the formation of clumps. The bacilli in a clump are at first kept at a distance from each other, probably by the cilia, and then, for some reason which is not evident, they get more closely packed together. They, however, never look as if they were glued together by some agglutinating substance. In some cases they become very granular, but in others their appearance does not alter much. For these reasons I think the phenomenon should be described by terms indicating simply that the bacilli form clumps; such terms as "glabrification" or "agglutination" should be avoided. The share taken by various observers in the discovery of the phenomenon makes it also invidious to associate

the name of the reaction with the name of any one observer. It would be advantageous to use a name which would be clear to workers of various nationalities, and for that reason I think the term "agglomeration" is preferable to the shorter and otherwise more convenient word "clumping" Though I would prefer not to see the name of any writer attached to the reaction itself, I think it is well to recognise (1) that the method of diagnosis of a micro-organism by the changes occurring in the peritoneal cavity of an animal immunised against that microbe must be associated with the name of R. Pfeiffer; (2) that the discovery of the clumping phenomenon outside the body in the serum of immunised animals must be associated with the names of Charrin and Roger, Metchnikoff and Bordet; (3) that the utilisation of this method for the diagnosis of microbes must be associated with the names of Gruber and Durham, who have worked out the method with more care than previous observers; and (4) that the discovery of the method by means of which a case of typhoid fever can be diagnosed (before immunity has been established) by means of the reaction which the serum of such a patient will produce when brought in contact with a pure culture of typhoid bacilli must be associated with the name of Widal. The discovery of Widal consists in that, starting from a typical bacillus as a known quantity, he determined the nature of a doubtful case by the action which the serum of that case will have on the bacillus. All the previous observers used the serum of an immunised animal as their known quantity and considered that a high degree of immunity was an important element of diagnosis. It is true that the reaction was also proposed to test the potency of sera, but this was not proposed for the purpose of diagnosis of cases of typhoid fever.

There were many points which it seemed to me desirable to settle before using Widal's method on a large scale. Soon after the beginning of this investigation I was fortunate enough to obtain the friendly coöperation of Dr. E. J. Sidebotham, with whom I continued to make the observations to be recorded in my next communication. It will be unnecessary to describe here the plan of the investigation since the results obtained will sufficiently indicate what was aimed at. I may say, however, that after trying various methods I came early to the conclusion that to obtain comparative results it was advantageous to proceed as follows. The finger of the patient is thoroughly cleaned and, if time permits, the skin carefully disinfected. A prick is made in the usual way with a sharp lancet-shaped needle so as to obtain two or three large drops of blood The patients show no objection whatever to this procedure. This blood is at once aspirated in a modified Pasteur's pipette the point of which has been kept sealed till then and is broken and sterilised just

before use.[10] The point of the pipette is then sealed again. The constricted portion is drawn out in a flame and sealed. This small sealed tube is taken to the laboratory. The point

Fig. 1. A, Point through which the fluid is aspirated. B, Constriction sealed after collection of blood. C, Mouthpiece. D, Space generally occupied by the blood after collection when A and B are sealed.



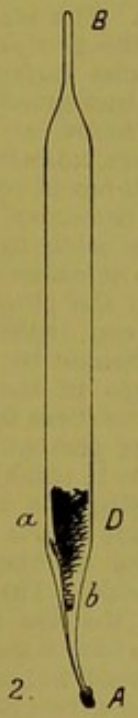


Fig. 2. Small tube sent to the laboratory. D, *a*, clot. *b*, serum sometimes quite clear. B, Part to be heated after A has been opened.

Fig. 3. Appearance of a cover-glass on which the drops have been deposited before mixture—*c*, culture; *s*, serum.

through which the blood has been aspirated is sterilised, broken, and a little of the fluid blown out by heating slowly

[10] It is important to allow the pipette to cool before the blood is drawn into it. It is also important in sealing the pipette not to heat the blood. This can be easily avoided.

the other sealed end of the tube; the small drop of fluid is received on a sterilised slide. The tube is sealed again for further observation if necessary. Some drops of a twenty-four or at most forty-eight hours old culture of typhoid bacillus in neutral peptone bouillon are then poured into a watch-glass or on a slide (sterilised). With a platinum loop measuring one millimetre in diameter nine drops of the bouillon swarming with bacilli are taken and deposited on a clean cover-glass three-quarters of an inch in diameter; they are not allowed to touch each other (to ensure accurate measurement). With the same loop, after it has been passed through the flame, a drop of the serum is taken and deposited on the cover-glass. When the serum is very active it may be desirable to dilute it previously with a definite proportion of neutral bouillon. This may be done with the platinum loop. The ten drops are then thoroughly mixed together with the platinum loop, the cover-glass placed on a clean slide (moist surface downwards), and the appearance of the preparation examined one, two or three minutes, five minutes, two hours, and for special puposes twenty-four, forty-eight hours, &c., afterwards. After the first few minutes the preparation has of course to be kept in a moist chamber, but it is not necessary to place the moist chamber in an incubator. By using this mode of procedure it is easy to study the rate at which clumps are formed and the changes which occur in the preparations from day to day. As the blood has been collected aseptically the observations are not complicated by the growth of extraneous microbes. The blood kept in the sealed pipettes can be examined day after day, as there is no loss of material. Drying of the blood does not prevent the reaction, but it diminishes its intensity, and I think the little advantage that can be gained by drying the blood for the purpose of sending it from the bedside to the laboratory is dearly bought at the expense of the doubts which it gives rise to when the reaction is feeble. The use of the pipette is very nearly as convenient as the use of a slip of sterilised paper, and it is quite easy to have a good supply of, or to manufacture, such pipettes. I need not say that it is easy to estimate the potency of the serum of patients suffering from typhoid fever by varying the proportions between the serum and the culture. The proportion $\frac{1 \text{ serum}}{10 \text{ culture}}$ indicated by Widal I have found to be extremely convenient. Some serums, however, react in much smaller quantities; in one case it was found that $\frac{1 \text{ serum}}{150 \text{ culture}}$ still gave the reaction clearly. Except in very doubtful cases it is unnecessary to increase the proportion of serum; but after drying it may be necessary to increase the proportion to $\frac{1 \text{ serum.}}{1 \text{ culture.}}$ I have so far preferred recent cultures in neutral bouillon to emulsions of the bacillus grown on agar or on gelatin. The bouillon

19 same as 32	93	About 5th	1	Fluid	1-10	5 m.	—	—	—	—
	94	,,	2	,,	,,	24 h.	—	—	—	—
32 same as 19	95	About 24th	3	Fluid	1—10	5 m.	Normal	—	—	—
42	96	18th	1	Fluid	1—10	5 m.	Delirious	None	None so far	
	97	—	,,	,,	,,	3 h.	—	—	—	—
	98	—	,,	,,	,,	24 h.	—	—	—	—
	99	—	2	Dry	,,	10 m.	—	—	—	—
							Co			
13	—	8th	1	Fluid	1—10	5 m.	—	—	—	—
38 same as 13	100	37th	1	Fluid	1—10	5 m.	—	—	—	Sub-cutaneous abscesses
	101	,,	,,	,,	,,	h.	—	—	—	—
	102	,,	,,	,,	,,	48 h.	—	—	—	—
	103	,,	6	Dry	,,	5 m.	—	—	—	—
	104	,,	,,	,,	1—5	5 m.	—	—	—	—
	105	,,	,,	,,	,,	10 m.	—	—	—	—
16	106	11th	1	Fluid	1—10	5 m.	Delirious	—	Double otitis, &c.	
17	107	18th	1	Fluid	1—10	5 m.	Delirious	—	Double otitis, &c.	
31	108	Weeks	1	Fluid	1—10	5 m.	—	—	—	
37	109	7th	1	Fluid	1—10	5 m.	Drowsy	—	Bronchitis	
41	110	5th	1	Fluid	1—10	5 m.	—	—	—	
	111	,,	,,	,,	,,	3 h.	—	—	—	
	112	,,	,,	,,	,,	24 h.	—	—	—	
45	113	37th	1	Fluid	1—10	5 m.	—	—	Hæmaturia on 7th day	
	114	—	,,	,,	,,	24 h.	—	—	—	
46	115	23rd	1	Fluid	1—10	5 m.	—	—	Hæmaturia 19th day	
25	116	49th	1	Fluid	1—10	5 m.	Very neurotic	—	—	
5	Many	—	5 min	Fluid	1—10	2 m.	—	Typhoid fever 26 years ago	—	
	—	—	—	—	1—5	4 h.				
	—	—	—	—	1—1	24 h.				
						144 h.				
29	—	—	5 min	—	1—10	5 m.	—	No previous typhoid	—	
	—	—	—	—	—	4 h.	—	—	—	

* In Specimens 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 23, 24 and 22 the patient was under the care of Dr. Dreschfeld; in Specimens 39 and 40 the patient was under the care of Dr. Davies; in Specimen 3 under the care of Dr. Hamilton Fellland.

† By minimum temperature is meant the lowest temperature recorded. Bronchitis is mentioned only when it constituted a very marked symptom.

§ This

JULY 13TH AND NOV. 17TH, 1896—(*continued*).

Time of or after the Examination of the Blood for the Reaction—(continued).

Character of temperature curve.	Maximum temperature.	Minimum temperature.†	Diarrhœa.	Size of spleen.	Rose spots.	Mental condition.	Previous attack of typhoid fever.	Complications and sequelæ.†
Two abnormal sudden rises during fever with scarlatinal-looking rashes.	?	?	Yes	Enlarged	Several	—	None	Occurrence of two scarlatinal eruptions with sudden rise of temperature
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
Normal	102·6°	100·4°	None	Apparently enlarged	Numerous	Clear	None	None
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
Normal	103°	100°	None	A little enlarged	A few	Clear	None	None
—	—	—	—	—	—	—	—	—
Great fall from 12th to 17th day and again on 25th day	105·4°	96·4°	Yes	Enlarged	Fairly typical	Delirious and very restless during pyrexia	None	Slight bronchitis, vomiting, double otitis
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
Normal	104·6°	97·2°	None except on 15th day; pea-soup for 4 days. Blood on 28th day	Not enlarged	No rose spots	Slight delirium with headache and deafness	?	?

Blood and in which no further Evidence of Typhoid Fever was obtained Clinically.

—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—

cultures are remarkably uniform. The bacilli are extremely motile and are evenly distributed through the fluid.

The simplicity of the method may induce clinicians to use it at the bedside. I doubt whether this would be a wise application. The whole method depends for its success on the purity of the cultures, on their being in an active state of growth, on their being free from clumps, and on the observations being made by men to whom bacteriological observations are so familiar as to prevent those many slight sources of inaccuracy which attend experiments made by those who are not in constant training. The very simplicity of the method is for these reasons a source of danger, and I would not be surprised if the generalisation of the method were attended by disbelief in its value if it is to be used indiscriminately by anybody who happens to possess a tube labeled "typhoid bacillus" and a platinum loop.

ON THE "SERO-DIAGNOSIS" OF TYPHOID FEVER.

By A. SHERIDAN DELÉPINE, M.B., C.M. Edin.,

PROCTER PROFESSOR OF PATHOLOGY, OWENS COLLEGE, MANCHESTER

AND

E. J. SIDEBOTHAM, M.B. Cantab, M.R.C.S. Eng.,

HONORARY RESEARCH FELLOW IN PATHOLOGY, OWENS COLLEGE, MANCHESTER.

Part II.

Examination of Cases.

In Part I. of this paper the nature of the reaction on which is based the serum diagnosis of typhoid fever has been briefly given. The method adopted has also been explained.

During the last four months we have, with the assistance of several of our colleagues, examined the blood of patients affected with what was clinically typical typhoid fever in various stages. We have also investigated in the same way a smaller number of cases of some other kinds of febrile diseases. Somewhat against our will we have also been obliged in a certain number of instances to examine the blood of cases of a doubtful nature. We have to thank Dr. Niven, Dr. Leech, Dr. Ashby, Dr. Dreschfeld. Dr. Reynolds, Dr. R. W. Marsden, Dr Davies Dr. Melland, and others for the cases of which they have given us the opportunity to examine the blood or secretions. It is, however, to Dr. R. W. Marsden, the resident medical officer at the Monsall Fever Hospital, that we are most indebted for the supply of specimens answering exactly our requirements, and for giving us later the clinical data which we thought would throw light on the subject. Our examinations, with very few exceptions, have been carried out jointly, and the results observed by both of us. These we have recorded in the accompanying table under various

headings, which will be easily understood by reading the previous paper.

Our results confirm entirely those announced by Widal four months ago. We may safely make the following statements :—

1. Out of twenty-five cases of undoubted typhoid fever which were examined there was not one in which the blood did not give rise to agglomeration of the bacilli sooner or later.

In one case (Nos. 21, 22, and 34) a specimen taken on the seventh or eighth day of the illness (No. 21) gave a feeble reaction ; another specimen (No. 22) received by us the next day gave no reaction. In this case the quantity of blood sent for examination was very small and the blood was very near the sealed end of the tube, so that there was a possibility of the fluid having been over-heated. The same possibility had to be kept in mind in No. 20 ; in this case no reaction was obtained with the blood on the twelfth day, whilst it was distinct on the twenty-fifth day (No 30) of the illness. These discrepancies may not be due to error of manipulation, but there was good reason to believe that they were. They are the only two exceptions in a series of twenty-eight specimens In one case the error was corrected by the examination of another specimen collected nearly at the same time, so that the aberrant results amount to 1 in 27—i e., 3·7 per cent.—if we base our estimate on the number of specimens examined ; or 1 in 25—i e., 4 per cent.—if we refer more specially to cases.[1]

2. Out of ten cases which were certainly not cases of typhoid fever not one was found to give the reaction. Among these cases were some of scarlet fever, erysipelas, mumps, puerperal fever, tuberculosis, some of which were complicated with suppuration, angina, otitis, bronchitis, nephritis, diarrhœa, delirium, &c. (complications also present in cases of typhoid fever). This, when associated with results obtained by various other observers, shows that, in a case of fever, if a few days after the onset the blood gives a negative reaction when tested by Widal's method the case is not one of typhoid fever.

3. The blood of normal individuals does not give any reaction.[2]

4. Regarding the period of the fever during which the reaction was manifest we have observed only one case

---

[1] It must be remembered, however, that this source of error was temporary, for on further examination a positive reaction was obtained.

[2] That is within the first four hours ; after twenty-four hours an imperfect clumping is sometimes observed.

at the end of the first week; in that case, which was mild and not typical, a very imperfect reaction was obtained at first (No. 21), but as the disease advanced the reaction became more marked (No. 34). We had a case on the ninth day which gave a good, though incomplete, reaction with the ordinary proportion of serum.[3] On the tenth day the reaction was rapid and good, but incomplete in the three cases we observed. On the twelfth day we had two cases, one of which (No. 20), already alluded to, failed to give the reaction; the other gave a rapid though incomplete one. On the thirteenth day one case reacted clearly but slowly and incompletely. On the fourteenth day the only case we observed gave a rapid and complete reaction—i.e., the bacilli were rendered almost instantaneously motionless and formed clumps very rapidly. From the fourteenth day to the end of the third week ten cases came under our notice; in all these cases but three the reaction was complete, and in all but two it was rapid, and sometimes remarkably rapid. In every one of them the reaction was exceedingly clear. We had five cases during the fourth week; three gave a rapid complete reaction and two a slow and incomplete reaction. Two cases on the thirty-seventh day of the illness gave different results, one a rapid complete reaction and the other a slow and very incomplete reaction It would seem from these results that the reaction was obtained easily from the end of the first week to the end of the fifth week at least, but that it is most uniformly perfect during the third week. (From the cases published by Widal and others we now know that the reaction can already be obtained on the fourth day and is also observable long after the fifth week, but we had no case after that date)

5. As to the rapidity with which the reaction appears we can say that with the proportion of serum which we generally used the reaction is almost always instantaneous after the ninth day. In one case it was, however, necessary to wait twenty minutes, and in another three hours, before a clear clumping could be made out In all other cases it was well marked within from two to five minutes.

6. Doubtful cases have on the whole yielded very satisfactory results. Several of those which reacted at a time when the clinical diagnosis was uncertain have proved to be cases which clinically were certainly typhoid fever or were more closely allied to typhoid fever than to any other fevers. One case (42), which has remained doubtful clinically, has

---

[3] By incomplete reaction we mean one in which the clumping is quite clear, but the bacilli are not rendered completely motionless by the proportion $\frac{1 \text{ serum}}{10 \text{ culture}}$; we say it is very incomplete when the motion is very marked.

remained doubtful from our point of view. *This is the only case where the reaction has seemed to us ambiguous*[4]; this was possibly due to the fact that we had not enough material to try various dilutions. In three other cases (Nos 3 and 4 and Nos. 19 and 32) we obtained a negative reaction; in two of these the clinical diagnosis confirmed our results later. In one case we were unable to obtain complete clinical data, but from what we were able to gather it is probable that the case was not one of typhoid fever. So that, with one exception, we can say that even in the four cases in which the clinical evidence was not clear the serum diagnosis gave results which seemed reliable. If one studied carefully the whole series of cases it will be evident that there is not one symptom or group of symptoms usually considered typical of typhoid fever, which has been as constant as the serum reaction.

7. The state of the blood or serum is of some importance. The reaction can be obtained both with dry and with fluid serum, but the dry serum loses its immobilising and also its agglomerating properties sooner than the fluid serum. We found in a few cases that fluid serum was still very active at the end of twenty-four days. Dry serum had in some cases lost much of its activity by the end of the sixth day. We have not, however, very accurate data on this point, for, owing to the small quantity of material we had at our disposal, it was difficult to make series of strictly comparable observations. Dry serum seems also less suitable for accurate work than the fluid blood or blood serum, because it is more difficult to measure accurately the quantities of serum and of culture used when the serum is dry than when it is fluid (These two objections seem to us to militate against the use of dry blood serum instead of fluid serum kept in a sealed pipette. Sealed pipettes are very convenient if a proper form is used and if care be taken to prevent the flame used in sealing the tube from coming too near the blood)

This paper with the table occupies so much space that we must leave a number of points for discussion on some future occasion. This we do all the more readily that in the present stage of this investigation a simple statement of facts will probably prove more useful than a full discussion based on incomplete data.

Manchester.

---

[4] This indicates possible error in one case out of forty—i.e., 2½ per cent.

PRINTED AT
THE LANCET OFFICE,
423, STRAND, W.C.