REMARKS
ON
VACCINATION AGAINST TYPHOID FEVER.

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MR. HAFFKINE suggested rather more than twelve months ago to one of us that the method of vaccination which has proved so effectual in combating cholera epidemics in India might, *mutatis mutandis*, be applied also to the prophylaxis of typhoid fever. Since that time, this question has been constantly engaging our attention, and we have gradually elaborated the method of antityphoid vaccination, which is to be briefly described in this paper.

Our first vaccinations against typhoid were undertaken in the months of July and August of last year. These vaccinations were put on record by one of us in the *Lancet* on September 19th, 1896, in a paper which dealt primarily with the question of serous hæmorrhage. A reprint of this paper was sent among others to Professor Pfeiffer.

Nearly two months after the date of this paper Professor Pfeiffer[1] published, in conjunction with Dr. Kolle, a paper on Two Cases of Typhoid Vaccination. The method of inoculation which these authors have adopted, is exactly similar to the one that we had previously adopted. Like our own method, it was based upon the methods which have been so successfully employed by Mr. Haffkine in his anticholera inoculations.

After this historical discursus, we may without further prologue proceed to consider, first, the general principles upon which these typhoid vaccinations are based; secondly, the methods which are adopted in preparing the vaccines; thirdly, the dosage and the strength of the vaccines; fourthly, the clinical symptoms which supervene upon the inoculation of those vaccines; fifthly, the method of gauging the effect of these vaccinations; lastly, we shall consider certain questions with reference to the probable duration of the immunity and in connection with the application of these vaccines.

PRINCIPLES UPON WHICH THE PROPOSED METHOD OF TYPHOID VACCINATION IS BASED.

The object of all vaccination processes is, first, to achieve a degree of immunity which shall be equal or greater to that which accrues to a patient who undergoes and recovers from an actual attack of the disease; and, secondly, to achieve that immunity without any risk to life or health.

The first of these objects can, as far as is known, only be satisfactorily achieved by inoculating the patient with the micro-organisms (or the products of the micro-organisms) of the particular disease. The second object can be achieved in several ways. We may either, as in the Jennerian vaccination against small-pox, inoculate the patient with micro-organisms which have lost their virulence for man by being passed through a whole series of appropriately chosen animals. Or we may, as in the Pasteurian method of vaccinating against anthrax, employ in our inoculations artificially attenuated micro-organisms. Or, lastly, we may inoculate the patient with measured quantities of dead, but still poisonous, micro-organisms.[2]

It is this last method which we have adopted in the case of our typhoid vaccinations. The advantages which are associated with the use of such dead vaccines are, first, that there is absolutely no risk of producing actual typhoid fever by our inoculations; secondly, that the vaccines may be handled and distributed through the post without incurring any risk of disseminating the germs of the disease; thirdly, that dead vaccines are probably less subject to undergo alterations in their strength than living vaccines.

METHOD OF PREPARING THE ANTITYPHOID VACCINES.

These vaccines are made from agar cultures of typhoid bacilli which have been grown for twenty-four hours at blood heat. The cultures which are thus obtained are emulsified by the addition of measured quantities of sterile broth. The resulting emulsion is then drawn up into a series of sterile and duly calibrated glass pipettes. The capillary ends of these pipettes are then sealed up in the flame so as to form vaccine capsules. These capsules are then placed in a beaker of cold water, which is then brought to a temperature of 60° C., and is kept at that temperature for five minutes. The sterility of the vaccines is then controlled by allowing a drop of their contents to run out on to the surface of an agar tube, which is subsequently incubated. If, as in our experience always occurs, the contents of the vaccine capsules are now found to be absolutely sterile, the vaccine is ready for use.

In proceeding to the inoculation of these vaccines, the capsule is first thoroughly shaken so as to distribute the bacteria through the fluid. The contents are then drawn up aseptically into the syringe in the manner which was proposed by Mr. Haffkine, and which is described and illustrated in a paper which was written by one[3] of us in conjunction with Surgeon-Major D. Bruce. The vaccines are inoculated into the flank.

DOSAGE AND STRENGTH OF THE ANTITYPHOID VACCINES.

The strength of a typhoid vaccine will obviously be determined (1) by the number of bacilli which it contains, (2) by the virulence of these bacilli. We have in all our later experiments employed a typhoid culture of such strength that one-fourth tube of a twenty-four hour culture constituted a lethal dose for a guinea-pig of 350 to 400 grammes when hypodermically inoculated. The quantities of this culture which we have employed for our antityphoid vaccinations have varied from one-twentieth to one-fourth of a tube. The latter quantity (that is, the quantity which, if injected alive, would have proved fatal to a 350-gramme guinea-pig) constitutes a somewhat severe dose for a man.

CLINICAL SYMPTOMS WHICH SUPERVENE UPON THE INOCULATION OF THE ANTITYPHOID VACCINES.

When the smaller doses (one-twentieth to one-sixth of a tube) are employed, the symptoms are comparatively slight. The local symptoms consist in a little local tenderness; the constitutional symptoms in a subjective feeling of chilliness, which comes on about two to three hours after the inoculation of the vaccine; further, in a very slight rise of temperature, and a little restlessness at night. The symptoms have quite passed off in twenty-four hours.

With larger doses, such, for instance, as were administered in Cases 4 to 14 inclusive (*vide* Table of Results given below) all the symptoms are more severe.

Local Symptoms.—About two or three hours after the injection a certain amount of local tenderness develops about the site of injection. This tenderness gradually increases in severity and extends upwards into the armpits and downwards into the groin. Corresponding with these subjective sensations a patch of congestion 2 to 3 inches in diameter develops round the site of the inoculation. Red lines of inflamed lymphatics can be distinctly traced, extending upwards into the armpits. The local tenderness is at its worst twelve hours after the injection. It is still very sensible twenty-four hours afterwards. It finally disappears about forty-eight hours after the injection,

Constitutional symptoms, consisting in some degree of faintness and collapse, begin to manifest themselves generally in two to three hours. In 4 out of 11 cases inoculated with these larger doses the faintness and nausea, resulting in one case in vomiting, were already well marked after three hours. In the other 7 cases these symptoms supervened somewhat later. Appetite was abolished. Only 3 out of the 11 cases were able to put in an appearance at dinner. A good deal of fever was developed in all cases, and sleep was a good deal disturbed. These constitutional symptoms had to a great extent passed away by the morning, and laboratory work went on without interruption. By the next day 8 out of these 11 patients reverted to their normal condition of health; 3 of the 11 looked somewhat shaken in health for some three weeks after.

It may be well to note that these symptoms, which are here described, are the symptoms which actually manifested themselves in patients each of whom had received doses of 45 to 60 grains of calcium chloride cryst. This calcium chloride was administered with a view to preventing such a

decrease[4] of blood coagulability and such a condition of œdema,[5] as supervened in the case of Case 1 (*vide* Table of Results given below), where the inoculation of one-twentieth of a tube of a weaker typhoid resulted in the production of an œdematous swelling, which extended from the site of inoculation as far forwards as the linea alba and as far downwards as the pubis.

EFFECT ON THE BLOOD OF ANTITYPHOID VACCINATION.

Owing, in the first instance, to the researches of Pfeiffer on immunity against cholera, and, in the second instance, to the subsequent researches of Gruber and Durham on the differential diagnosis of bacteria by means of the serum of immunised animals, we are now in possession of a method which enables us not only to detect the effect that a vaccination exerts on the blood of the patient, but also accurately to measure that effect. Professor Pfeiffer and Dr. Kolle have, like ourselves, gauged by this method the effect of their antityphoid vaccinations. In order to appreciate the exact nature of the test which has been put into our hands by the ingenuity of Durham and Gruber, and in order, further, to form an exact estimate of its value, we have briefly to consider the basis upon which the method of serum diagnosis depends. Put briefly, that basis is to be found in the fact that whenever the micro-organisms which are causally associated with a specific fever are brought in contact with the serum or plasma of an animal or a patient who is undergoing, or who has undergone, an attack of the specific fever in question, the following succession of phenomena manifests itself: (*a*) The bacteria become agglutinated together, (*b*) the bacteria lose their motility, (*c*) the clumps of agglutinated bacteria sink to the bottom, and the culture fluid, which was previously evenly turbid, becomes clarified; (*d*) the bacteria shrink up into the form of minute spherules, (*e*) lastly, the bacteria are definitely devitalised.

For the purposes of serum diagnosis, it is not essential that this whole train of phenomena should come under observation. It suffices if any one of this series of phenomena comes distinctly under observation, provided always that we keep in view the fact that the subject matter of our observations is no longer the actual bactericidal effect of the particular serum, but either its agglutinating, immobilising, sedimenting, or spherulating effect. Provided we keep this in view, we shall be well advised if we, for purposes of serum diagnosis, select as the subject matter of our observations that particular effect which is most easily accessible to observation. Now, as Gruber and Durham were the first to show, the effect which is most accessible to observation is the agglomeration and the sedimentation of the bacteria. This effect can readily be appreciated by the unaided vision, even when, in accordance with the method which has been suggested by one of us in a recent issue of this JOURNAL, minimal quantities of the serum and of the bacteria are mixed together in capillary "sero-sedimentation tubes."[6]

Having thus settled that the sedimentation of the bacteria is the phenomenon which will best serve as a criterion of the specific power of a serum, it will be obvious that we shall be able readily to determine in what measure the serum possesses this specific power if we make a series of successive dilutions of the serum, and determine how far the blood may be diluted without forfeiting its sedimenting powers.

The quantitative results which are obtained by this method of successive dilutions may be conveniently expressed in terms of "sedimentation units," or, if the term shall afterwards appear to be justified, in terms of "preventive units." We may, for instance, speak of a blood which manifests this power of sedimentation in tenfold dilution as a blood which contains one "sedimentation" or "preventive unit." Similarly we may speak of blood which exhibits this sedimenting power in a hundredfold dilution as blood which contains ten "sedimentation" or "preventive units."

TABULAR STATEMENT OF THE RESULTS OF OUR ANTITYPHOID INOCULATIONS.

With two exceptions all these vaccinations were performed upon Medical Officers of the Army or Indian Medical Services, or upon Surgeons on Probation who were preparing to enter those services. The blood which was required for testing the effect of the vaccination was obtained by pricking the finger. This blood was filled into capsules and allowed to clot. The serum was then drawn off, diluted, and mixed in a capillary sero-sedimentation tube with a small quantity of typhoid culture in the manner described by one of us in the JOURNAL *of January 16th.*

In the Table a voluminous sedimentation is denoted by the sign ×, *a slighter but still distinct characteristic sedimentation is denoted by the sign* *, *a negative result is denoted by the sign* o.

No. of Case.	Initials.	Dates of Inoculation.	Whether Culture was Dead or Alive.	Quantity Inoculated.	Dates of Blood Examination.	Dilutions. 10 fold.	25-fold.	50-fold.	100-fold.	200-fold.
				Tube						
1	M. D.	July 31, 1896	Dead	$\frac{1}{20}$						
		Aug. 14, 1896	,,	$\frac{1}{10}$	Aug. 14, 1896	—	×	×	×	—
		Sept. 5, 1896	,,	$\frac{1}{4}$	Sept. 5, 1896	—	×	×	×	×
		Sept. 25, 1896	Alive	$\frac{1}{2}$	Sept. 25, 1896	—	×	×	×	*
2	J S.	Aug. 19, 1896	Dead	$\frac{1}{20}$						
3	R. W. S.	Nov. 6, 1896	,,	$\frac{1}{4}$	Nov. 9, 1896	×	×	o	o	o
		Nov. 16, 1896	,,	$\frac{1}{2}$						
4	A. E. W.	Nov. 19, 1896	,,	$\frac{1}{4}$	Nov. 18, 1896	?	—	o	o	o
					Nov. 20, 1896	×	×	*	*	—
					Nov. 21, 1896	×	—	*	*	o
					Nov. 22, 1896	×	×	*	?	o
					Nov. 23, 1896	×	×	*	?	—
	,,	Dec. 2, 1896	,,	$\frac{1}{4}$	Dec. 2, 1896	×	×	—	*	—
					Dec. 3, 1896	×	×	×	×	—
					Dec. 6, 1896	×	×	×	×	*
					Dec. 15, 1896	×	×	×	×	*
					Dec. 30, 1896	×	×	×	*	*
					Jan. 13, 1897	×	×	×	*	*
5	D. S.	Nov. 19, 1896	,,	$\frac{1}{4}$	Nov. 18, 1896	o	o	—	—	—
					Nov. 20, 1896	×	—	—	—	—
					Nov. 22, 1896	×	—	—	—	—
					Dec. 6, 1896	×	×	×	×	*
6	J. S.	Nov. 19, 1896	,,	$\frac{1}{4}$	Nov. 18, 1896	o	o	—	—	—
					Nov. 24, 1896	×	*	—	—	—
					Dec. 5, 1896	×	×	×	?	—
					Jan. 13, 1896	×	×	×	*	—
7	G. E. S.	Nov. 20, 1896	,,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	*	—	—	—	—
					Dec. 8, 1896	×	×	×	×	—
					Jan. 13, 1897	—	×	×	*	*
8	J. G. B.	Nov. 20, 1896	,,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	×	×	×	—	—
					Dec. 9, 1896	×	×	×	—	o
					Jan. 13, 1897	×	×	×	*	*
9	A. A. F. McA.	Nov. 20, 1896	,,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	*	o	o	—	—
					Dec. 9, 1896	×	×	×	*	o
					Jan. 13, 1897	—	×	×	*	o
10	R. B.	Nov. 20, 1896	,,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	*	—	—	—	—
					Dec. 5, 1896	×	*	*	—	—
					Jan. 13, 1897	×	×	*	*	*
11	F. J. G.	Nov. 20, 1896	,,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	*	*	o	—	—
					Dec. 5, 1896	×	×	×	×	?
					Jan. 13, 1897	—	×	×	*	*
12	W. E. H.	Nov. 20, 1896	,,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	*	?	?	o	—
					Dec. 9, 1896	×	×	×	×	*
					Jan. 13, 1897	×	×	×	×	*
13	R. H. P.	Nov. 20, 1896	,,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	×	*	o	—	—
					Dec. 9, 1896	×	*	o	o	—
					Dec. 12, 1896	×	*	o	o	—
	,,	Dec. 21, 1896	,,	$\frac{1}{4}$	Dec. 30, 1896	×	×	×	×	*
					Jan. 13, 1897	×	×	×	*	*
14	C. H. S. L.	Nov. 20, 1896	,	$\frac{1}{4}$	Nov. 19, 1896	o	—	—	—	—
					Nov. 24, 1896	×	*	?	—	—
					Dec. 9, 1896	×	×	×	—	—
					Jan. 13, 1897	—	×	*	*	*
15	W. H. K.	Nov. 28, 1896	,,	$\frac{1}{8}$	Nov. 19, 1896	?	o	—	—	—
					Dec. 9, 1896	×	×	*	*	—
					Jan. 5, 1897	×	×	*	o	o
					Jan. 13, 1897	×	×	×	*	*
16	C. A. L.	Nov. 28, 1896	,,	$\frac{1}{8}$	Nov. 19, 1896	o	—	—	—	—
					Dec. 9, 1896	×	×	*	o	o
	,,	Dec. 23, 1896	,,	$\frac{1}{8}$	Dec. 31, 1896	—	*	*	o	o
					Jan. 4, 1897	—	*	*	o	o
					Jan. 13, 1897	×	*	—	—	—
17	M. P. C.	Nov. 28, 1896	,,	$\frac{1}{16}$	Nov. 19, 1896	o	—	—	—	—
					Dec. 9, 1896	×	×	×	*	o
					Jan. 13, 1897	×	×	*	*	*
18	T. B. K.	Nov. 28, 1896	,,	$\frac{1}{16}$	Nov. 19, 1896	o	—	—	—	—
					Dec. 5, 1896	—	×	×	—	—
					Jan. 13, 1897	×	×	—	—	—

Discussion of the Results which are Exhibited in the Table above.—The results which have been incorporated in the table above show in the most evident manner that the blood of patients who have submitted themselves to an antityphoid inoculation

becomes in some measure poisonous to the typhoid bacillus. For we may obviously assume that a blood which immobilises and agglutinates the typhoid bacillus is in some measure poisonous to that bacillus.

So much being certain, the next question we have to consider is the question as to whether we may legitimately conclude that a person who possesses a sedimenting power—say of twenty units—is absolutely protected against typhoid by the poisonous properties which have been imparted to his blood. Experiment shows that this is not so.

We find that undiluted blood which contains 20 sedimentation units fails to kill typhoid bacilli, even when these bacilli are exposed to its influence for as long a period as forty-eight hours.[7] It will be obvious from this fact that we cannot rely upon the blood of a vaccinated person being sufficiently poisonous to kill off such typhoid bacilli as may chance to effect an entrance into his system.

This matter having become clear, we may next proceed to consider whether we have any warranty for inferring that the vaccinated patient's blood will, short of killing the bacilli of typhoid fever, yet exert such a deleterious influence on them as will result in the effectual protection of the patient against typhoid.

Everything that we know seems to show that this inference is perfectly warranted. We know, for instance, that guinea-pigs, upon whom this sedimenting power had been conferred by vaccination processes, are extremely resistant to infection by the specific micro-organisms with respect to which they possess this sedimenting power. Again, experiments which are in progress in this laboratory have already shown that monkeys who have been vaccinated against Malta fever, and who have acquired a sedimentation power with reference to the micro-organisms of that disease, have acquired also a power of at least inhibiting the growth of the micro-organisms of that disease in their system. Again, in our first case of typhoid vaccination (*vide* Table of Results) we had proof of the association of this sedimenting power with a condition of "bacteria-proofness." For our patient, who, on September 25th, 1896, possessed a sedimentation power of 20 units, suffered no ill effects from an inoculation of one-sixth tube of living virulent typhoid bacilli, which was made upon him on that day.

Finally, we have the fact that, so far as we know, every convalescent from typhoid or Malta fever (and we may legitimately assume that such convalescents are, at any rate for a time, immune against reinfection with these specific fevers) shows a notable[8] sedimentation reaction. It appears to us that the only conclusion that can be reasonably deduced from this series of facts is the conclusion that the sedimenting power of the blood is a trustworthy criterion of the immunity of the patient who furnishes it.

This conclusion cannot, however, be regarded as absolutely assured until we are in a position satisfactorily to account for the fact that the typhoid fever patients and Malta fever monkeys who succumb to these diseases show the specific sedimentation reaction in exactly the same way as the typhoid fever patients and Malta fever monkeys who recover from these diseases.

The complete explanation of this fact is still to seek. It would, however, appear that every animal must be assumed to be working its way up to the acquirement of immunity from the very moment of infection to the time at which its struggle with the disease finally ceases. The sedimenting power of a patient, who afterwards succumbs to the disease, would thus appear to indicate only the degree of immunity which has been acquired at the particular moment at which blood was drawn off. And our experience of infective disease in general tells us that a degree of immunity which would, if already attained on the first day of the disease, amply suffice to ward off a fatal issue, will be of no avail if it is acquired later on in the course of the attack. We have an example of this in the case of the guinea-pig, who, before he finally succumbs to an injection of diphtheritic poison, not infrequently elaborates in his system considerably more antitoxin than would, if given in time, have sufficed to immunise him against a much larger dose of toxin than that which is accomplishing his death. Now it may well be that, just in the same way as the antitoxin is produced in the guinea-pig too late to save the animal's life, so likewise, in the case of the typhoid or Malta fever patient, the sedimenting power of the blood may be acquired too late in the attack to save the patient's life.

Having discerned that this may be the explanation of the paradoxical fact of the development of the sedimentation power in the blood of the patient who afterwards succumbs to the disease, we need no longer hesitate to accept, at least as a working hypothesis, the conclusion that the possession of a sedimenting power connotes also the possession of a certain measure of "bacteria proofness" against the bacteria in question.

We may reasonably surmise that this condition of bacteria proofness, inasmuch as it does not depend upon the presence of any absolutely bactericidal power in the blood, depends in large measure at least upon the fact that the typhoid bacilli which have been exposed to the poisonous influence of the blood fluids[9] are likely to fall an easy prey to the phagocytes.

We have next to turn to the consideration of a certain number of practical questions in connection with the application of these typhoid vaccinations.

Question of Risk associated with the Antityphoid Vaccinations.

When we appreciate that the bacteria which are employed in these vaccinations are dead bacteria, and that they are incapable of generating new poison in the system, it will be obvious that the injection of small and measured quantities of these dead bacterial cultivations involves no more risk to life or health than the injection of a medicinal dose of morphine. That there is no unknown factor of risk in the case of the injection of bacterial toxines will be evident when we consider that Mr. Haffkine has performed nearly 100,000 anticholera inoculations without a death, and, as far as we can learn, without the supervention of a single serious symptom.

Outlook with Respect to the Duration of the Immunity.

It is obvious that a vaccination process has little chance of being widely adopted unless immunity of a more or less durable character can be conferred. A person who submits himself to a vaccination process will always desire to have some guarantee that he will not require to be constantly re-inoculated. Up to the present it has not been possible in any degree to forecast the duration of the immunity which is conferred by a particular vaccination. In the case, for instance, of small-pox, it has always been, and still is, impossible to tell whether a particular patient has lost his immunity and requires to be revaccinated. In such a case we depend entirely upon statistics of the incidence of disease. When Mr. Haffkine commenced his anticholera vaccinations three years ago he also was face to face with this difficulty. Now, however, that we are in possession of the method of serum diagnosis, it will probably be possible to ascertain the duration of an immunity by a series of successive blood examinations. As yet we have no facts to base definite conclusions upon.[10] In the meantime, if it is legitimate to judge from the extremely slow disappearance of the perfectly[11] comparable sedimentation power, which is acquired by undergoing an attack of typhoid, we see every reason to hope that the immunity which is conferred by these vaccinations may persist for a considerable number of years. If it does so it will obviously suffice to carry a young adult over the period of his extreme susceptibility.

Suggestions as to the Sphere of Application of the Proposed Antityphoid Vaccinations.

Since these vaccinations are unattended by risk, and since the general symptoms which supervene upon moderate doses of typhoid vaccines are comparatively slight, and since the local swelling at the site of the inoculation can easily be held in check by the administration of calcium chloride, and since further it will always be possible to control[12] the adequacy of the vaccination by a blood examination, we venture to suggest that it would be expedient for every one who is likely to be frequently exposed to the risk of typhoid infection to undergo the vaccination. In particular this would appear to be expedient in the case of young soldiers going abroad to typhoid infected districts, to nurses who are in attendance upon typhoid patients, and,

lastly, to persons who are living in any district which is being visited by an epidemic of typhoid.

In conclusion, we desire to state that we have a certain amount of typhoid vaccines which we shall be glad to place at the disposal of any practitioner who may desire to undertake these vaccinations.

REFERENCES.

[1] *Deut. med. Wochschft.*, November 12th, 1896. [2] Comparative experiments on monkeys inoculated with dead and living cultures of Malta fever have led us to believe that dead cultures in suitable doses give quite as effectual an immunity as living cultures. [3] BRITISH MEDICAL JOURNAL, February 4th, 1893. [4] This decrease of blood coagulability appears to be one of the most common effects of the introduction of a bacterial poison into the system. It becomes especially notable whenever there is already a natural defect of blood coagulability, especially if in such cases no provision has been made for forestalling this blood change. Instances in point are Cases 1 and 2 (*vide* Table of Results) where there was a natural defect of blood coagulability, and where calcium chloride was not administered along with the inoculation. Further, Cases 4 and 11, in which, although there was no natural defect of blood coagulability, the administration of calcium chloride was deferred till after an interval of 3 to 5 hours. In the last three cases blood coagulability decreased respectively from 7 minutes to 9 minutes, from 3¾ minutes to 5½ minutes, and from 4 minutes to 11 minutes under the influence of a typhoid vaccination. Under the influence of calcium chloride blood coagulability was in these cases brought up in a very few hours from 9 minutes to 5½ minutes, from 5½ minutes to 3 minutes, and from 11 minutes to 5 minutes respectively. [5] That local œdema is often dependent upon a defect of blood coagulability, and that it can be corrected by the administration of calcium chloride is a proposition which has been established by one of us in a series of papers dealing with serous hæmorrhage in general, and with urticaria and chilblains in particular. These papers were published in the *Lancet* of January 18th, 1896; September 19th, 1896; and January 23rd, 1897; and in the *Journal of Dermatology*, February, 1896. [6] BRITISH MEDICAL JOURNAL, January 16th, 1897, p. 139. [7] This, it may be noted, is in harmony with the fact that Pfeiffer has succeeded in cultivating cholera vibrios upon a goat's serum which exerted a sedimenting influence in much more than a 200-fold dilution. [8] It may be noted in passing that, so far as our observations go—and here, again, they are in harmony with those of Pfeiffer—the sedimentation power which is acquired by undergoing an attack of actual typhoid is not greater than that which is acquired by an inoculation of dead typhoid bacilli. [9] We have verified that there is no appreciable difference with respect to sedimentation power between the plasma and serum of a man who has received an inoculation of dead typhoid bacilli. [10] We have, however, arranged to be supplied from time to time with samples of blood from each of our vaccination patients, in order to investigate the question. [11] *Vide* Note 8. [12] The advantage of such a control will be obvious if we consider that Cases 13, after first vaccination, and 16, after second vaccination (*vide* table of vaccination cases) proved on examination to have acquired only a very small amount of sedimentation power. This fact could not have been suspected in Case 13, for this patient showed a very marked clinical reaction.

FOUR CASES OF ENTERIC FEVER TREATED WITH ANTITOXIC SERUM.

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As few instances of the treatment of typhoid fever by antitoxic serum have as yet been published, the following details of four cases treated in the Leicester Infirmary may be valuable. The only selection that was made as to the cases in which the serum was used was that it was thought inadvisable to administer it to cases in a later stage than the end of the second week, as otherwise natural defervescence and that due to the remedy might have been confused.

The serum used was that prepared by Mr. T. J. Bokenham, and was obtained from Messrs. Burroughs and Wellcome. The injections were mostly made in the loins, and antisepsis was carefully observed. For the thorough manner in which this was done, for care in the treatment generally, and for the preparation of these notes, I am much indebted to Mr. C. H. Fagge, the House-Physician to the infirmary.

CASE I.—F. C., female, aged 18, admitted March 17th, 1896. Had been ailing 14 days. She had had diarrhœa and vomiting, and a good deal of bronchitis. There were three spots on the abdomen. She was restless and excitable, and took nourishment badly.

On March 18th she seemed worse; pulse 120. The abdomen was soft. The temperature was reduced by the cold pack, but rose again rapidly. The urine gave Ehrlich's colour reaction. She had 5 c.cm. of antityphoid serum at 4 P.M.

On March 19th there was not much change. The temperature was higher than the previous morning. The tongue was dry. The evening temperature was high, and she was very delirious. No injection was given. The pulse was 144 at night.

On March 20th she was very restless. There were traces of old hæmorrhage in the stools. There was much rhonchus and sibilus in the chest. She had 5 c.cm. serum. The pulse was 124 in the evening.

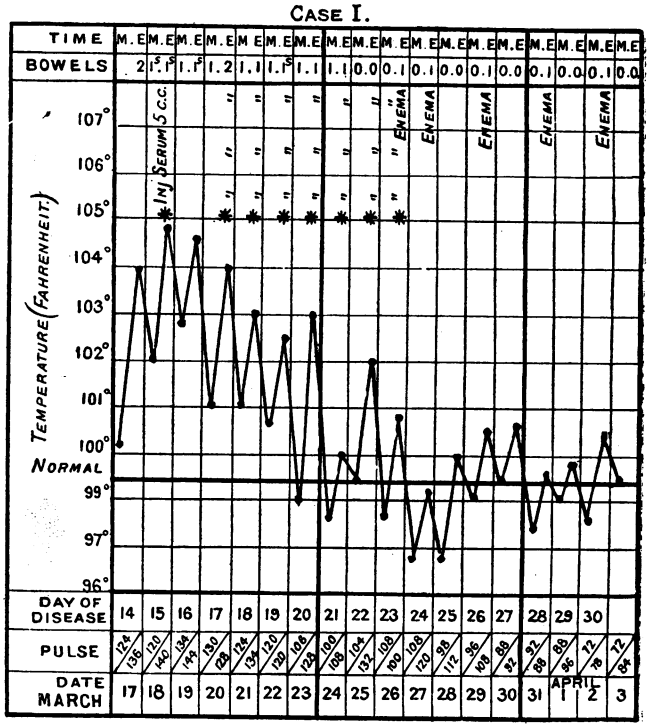
On March 21st she slept more. The motions were partly formed. The pulse was 134 in the evening, and she looked better; 5 c.cm. serum were injected. The evening temperature was lower.

On March 22nd the pulse was 120. She slept more, and had less delirium: 5 c.cm. serum were injected.

On March 23rd she was much quieter, and had a better night.

On March 24th she looked better; the tongue was cleaner. Ehrlich's reaction was not given by the urine. After this recovery was uninterrupted. Only 5 c.cm. were given as first injection in this case. The dose was probably too small. I also think that probably an unnecessary number of injections were given.

CASE I.



CASE II.—M. L., female, aged 25, was admitted on November 24th, 1896. She had been ill about fourteen days. The tongue was very furred. She was deaf, heavy, and stupid. There were several spots on the abdomen. The spleen was enlarged, and there was some general bronchitis. Ehrlich's reaction was present. Pulse 120, feeble.

CASE II.