Preliminary Note on the Use of Antityphoid Vaccine in the Treatment of Enteric Fever.

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With a Note by Lieutenant-Colonel W. B. Leishman, R.A.M.C.

At the International Congress of Hygiene and Demography, held in Berlin in September, 1907, a further communication on the treatment of enteric fever by means of an antityphoid serum was made by Professor A. Chantemesse (Paris). Lieutenant-Colonel W. B. Leishman, R.A.M.C., who was present at the Congress, published (Journal of the Royal Army Medical Corps, March, 1908), an account of Chantemesse's article, but it may, perhaps, be of benefit to recapitulate here some of the striking results obtained and the interesting statements made by Chantemesse for purposes of comparison with what follows hereafter.

In the first place, it is to be noted that Chantemesse treats his patients on the usual lines, with the one exception that he injects, subcutaneously, one, sometimes two, doses of his antityphoid serum. He does not use the cold bath treatment of Brand. His mortality figures are as follows: In the six years 1901-1907 there were 1,000 cases with 4.3 per cent. of deaths. Moreover, in those six years, among the cases treated by serum within the first seven days of the disease, there was no case of perforation and no death.

The figures of three other physicians using his serum are similar, and a comparison is also given between the mortality obtained by them prior to the use of the serum and that during its use, thus:

<table>
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<th>Prior to use of serum</th>
<th>While using serum</th>
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<td>I. 10 to 12 per cent.</td>
<td>3 per cent. (100 cases).</td>
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<td>II. 10 to 12</td>
<td>4 &quot; (200 &quot; ).</td>
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<td>III. 10 to 12</td>
<td>5.5 &quot; (90 &quot; ).</td>
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The mortality from the ordinary methods of treatment varies from 12½ per cent. to 20 per cent. By means of Brand's cold bath treatment mortality has been reduced in some cases to 7 per cent. The serum is prepared by the injection into horses, over a period of years, of the toxin obtained from the growth of virulent typhoid bacilli on a special medium. ¹

¹ For details on this and other points readers are referred to the original article, "Bericht über den XIV. Internationalen Kongress für Hygiene und Demographie," Berlin, September 28th, 1907, Band i., p. 195, or to Colonel Leishman's article, referred to above.
His practice is to inject a few drops of the serum under the skin of the arm as early as possible in the course of the disease. He rarely finds it necessary to give a second dose; when he does so he uses half the amount. He has come to the conclusion from experiments in animals, and from phagocytic estimations in patients, that the good results observed are due to a process of "opsonisation," to an increased phagocytic activity on the part of those cells of the body which are concerned in increasing the resisting power of the patient. Accepting this explanation, the idea occurred to Colonel Leishman that the injection of doses of the ordinary prophylactic antityphoid vaccine ought to produce a similarly increased phagocytic activity and a corresponding amelioration in the course of the disease. The outcome of this was that Quetta was chosen as a suitable place in which to try the effect of such injections. In all, thirty-six cases have received therapeutic injections of the vaccine during the past five months, the observed effects of which may now be detailed. In the first place, it may be noted that the cases treated were diagnosed bacteriologically, in the main by means of Conradi's blood-culture method; two or three by isolation of the organism from the faces. One exception to this will be noticed later.

The initial difficulty was the question of dosage. It was decided, in consultation with Colonel Leishman, to begin by giving that amount of vaccine which would contain, approximately, 100 million organisms. It was soon seen, however, that the effect of this amount on the course of the disease was in most cases slight or absent. Following the procedure of Chantemesse, second doses were given after an interval of nine or ten days in the earlier cases. Subsequently, the dosage was gradually increased and the intervals shortened, with the result that, in the later cases, good effects have been noted much more frequently.

The modifications in the course and terminations of the disease which have been observed up to the present are:—

(1) Temperature.—The first case which showed what, in the light of after experience, seems to be a typical good effect is that of No. 1. The dose being given in the forenoon, in the evening a rise of a degree or two is seen (stage of reaction). The following morning there is the usual fall, but this is found to become progressive for about three days; then the temperature begins to rise again in a fashion which recalls the usual method of onset of the disease. At the end of three days, if the good effect has been produced, comes what we now think to be the appropriate time.
for the second dose. These effects will be specially well seen in the charts numbered 2, 3, 4, 5, and 6.

(2) Appearance of the Patients.—As insisted on by Chantemesse, they have an "unexpectedly good appearance," and it was no

uncommon thing to go into the ward when full and find nearly every patient quietly and comfortably sleeping. The "typhoid facies" was in most cases conspicuous by its absence.

(3) Increased Amount of Urine.—This, also pointed out by
Chantemesse, is apparently comparable to that usually occurring with the beginning of convalescence. It will be seen that, on the day after injection of the vaccine, the amount of urine was frequently doubled.

Chart 3.

(4) General Effects.—There has been an unusual absence of prolonged cases, of complications, of sequelæ and of relapses.

(5) Low Mortality.—Out of the thirty-six cases treated there
were three deaths, giving a percentage of 8.3. Of the three deaths, two were fulminating cases who died about a week after admission and who had received only one dose of vaccine. These will be referred to again later. In connection with low mortality the effect of prophylactic dosage with vaccine is to be remembered, it being now a well-established fact that an inoculated man usually has a very mild attack of the disease, should he become
infected. Four only of the cases in this series were inoculated men, one of whom perhaps may be left out as he apparently suffered from a paratyphoid infection and was not treated with vaccine.

(6) Effect of Local Injection of Vaccine into Local Infections.—In two instances there has been, during convalescence, a commencing periostitis of the tibia. Both were treated, following Chantemesse, by the injection of 1 minim of the vaccine deeply, i.e., to the bone, into the middle of the lesion. In the first case, situated in the upper third of the tibia, the effect was almost startling. The injection was given at mid-day. At 6 p.m. the pain suddenly disappeared and did not return. The redness and swelling were seen next morning to be increased, due, of course, to local reaction, but they both began to subside from that time, and in three days from the time of injection no trace of the lesion was left. The second case was not quite so striking, yet here again the pain suddenly diminished after about the same interval, but there was a (?) reactionary rise of temperature and the redness and swelling took about four days to disappear.

Everyone who has been concerned in the care of these patients has been quite convinced that the injection of vaccine does produce an undoubted good effect. Moreover, no bad results have so far been noted. The question of dosage, however, still remains. Undoubtedly, the scientific method of arriving at this, in any particular case, is by the frequent estimation of that antitropic substance which can be shown to be the best index as to the resisting power of the patient. Whether this will prove to be due to a bactericidal substance or to an increased phagocytic activity remains for further investigation. On the other hand, it may prove to be an increased activity in the fixed cells of the patient whereby they acquire a greater power of destruction of the infecting bacilli. There are at least two considerations which point in this direction, viz.: (1) the modern view that typhoid bacilli may live and multiply in an individual without his having enteric fever, and that he only has enteric fever when the bacilli overflow from the internal organs, the local manufactory, into the blood-stream; and (2) the fact that a local infection can be dissipated by the local injection of the vaccine.

Meanwhile it may be of use, to others who wish to use the vaccine therapeutically, to indicate the amounts which would appear from the experience of this series of cases to be safe and useful. The initial dose latterly used is 300 to 350 millions of
organisms, and as this sometimes produces a reactionary rise of temperature to 105° F., it would seem that perhaps this is a safe limit. It may be that Chantemesse's dictum, "the more ill the patient, the less ought to be the dose," would apply here. My experience up to the present is insufficient to enable me to say, though it may be noted that four or five fulminating cases, amongst whom the three deaths occurred, did not react to the vaccine in the typical way, although the dose varied in them from 100 to 356 millions. The natural assumption is, I think, that not enough vaccine was given, or that a second dose should have been given after a short interval. One should, perhaps, be guided mainly by the temperature chart; if no effect is produced in three days, another dose may be given. But the amount of variation, as regards dosage, seems to be as great as that in every other aspect of this variable disease. Thus in one case (chart 1) the effect was produced by an initial dose of 142 millions, followed in a few days by half that amount; whereas in another case the total amount given was over 1,800 millions, spread over seven doses; from which it would appear that the chief indication for dosage is to continue until the good effect is produced. It would also seem that Chantemesse's contention that, by giving a second dose after a short interval (or one large dose), one adds to the danger of the patient by setting free in his blood toxins in addition to those already circulating in it, does not hold good here, at all events, to the same extent. In this case, an amount was given in excess of that contained in the ordinary two prophylactic doses combined. It would also seem that here we have some corroboration of the statement made in the Aldershot work that no evidence of a "negative phase" was found. If one can give, during the course of the disease, without apparent bad effect, an amount larger than that of the ordinary prophylactic doses, it would appear that one can with safety inoculate in the presence of an epidemic, the chief argument against which was, that harm might be done by the production of a negative phase in an already infected individual.

Perhaps the best result in the series was that of an officer of the Royal Engineers (chart 6). He received the first dose of vaccine on the eighth day; the reactionary rise of temperature was to 105° F. After this a slight fall occurred and the temperature then continued at a slightly lower level for four days, when another dose was given; this produced a marked fall for four days to 99° F., after which it began to rise again; another injection, however, cut it short. The amounts given at each dose are shown on
the chart. This patient, when convalescent, volunteered the interesting statement that five or six hours after the first injection, although he felt cold and shivering (the time of the reactionary rise), he felt also a marked change in himself for the better. He did not have the same experience after the other two injections. This is corroborated to some extent by other patients asking to have the vaccine injected.

The constancy of this fall of temperature after injection of the vaccine is such that in one case it was useful as a means of confirming the clinical diagnosis. In this case one failed to isolate the organism from the blood or faces. Clinically, the only indication was the high temperature, combined with a slow pulse. He was dosed on the twentieth day, the effect of which was to alter the character of the temperature for two days, after which the fall began, lasting for the usual three days or so. A second injection on the twenty-seventh day produced, again after a little delay, a fall to normal in three days. A relapse took place, and a third injection on the thirty-eighth day produced a fall to normal in five days. If other experience shows that the fall of temperature following an injection of the vaccine is fairly constant in typhoid fever and absent in fevers due to other causes, it may be that we have in the vaccine a diagnostic agent of no little value, comparable to the tuberculin reaction. Chantemesse has already shown that an ophthalmo-reaction is obtainable in enteric fever. Whether it may also prove to be of value in distinguishing between a typhoid and a paratyphoid infection remains to be seen. Unfortunately enough, in the only two doubtful cases of paratyphoid fever which have occurred here during this "enteric season," the vaccine was not used.

Another probable advantage accruing from the use of the vaccine is that, by continuing the injections into the period of convalescence, the number of relapses may be reduced.

The charts of the thirty-six cases show that there is little evidence, so far, of appreciable shortening of the disease below the classical twenty-one days. On the other hand, the number of prolonged cases is small. It is hoped that, by further experience and improved dosage, the duration of the disease will appreciably be shortened.

The vaccine used in these cases belonged to the batches numbered 48, 49, 51 and 53, and was used at no greater age than three months after manufacture, with the one exception, probably
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unimportant, that for three days on one occasion, vaccine No. 49 was used when it was three months and thirteen days old.

The site of injection chosen was the one I am in the habit of using for prophylactic injections, viz., the extensor surface of the forearm.

The local effects produced by an injection are similar to, but slighter than, those caused by the usual prophylactic injections, and, as a rule, trouble the patients but little.

It may be contended that the evidence adduced in this short note as to the therapeutic value of the vaccine is inconclusive, and the experience too short to justify one in drawing any definite conclusions. But I think it will be agreed, at the least, that if by the injection of the vaccine in a small dose one can produce, with safety and with little discomfort, a fall of temperature for about three days, and that the process can be repeated several times, one is saving the tissues of that patient a considerable amount of wear and tear, and the conservation thus obtained may be vitally helpful to him in the later stages of the disease. If, moreover, one can cut short, in three or four days, a case of beginning periostitis, or other local infection, which might otherwise end in suppuration lasting for weeks or months, one is effecting something.

I greatly regret that time did not allow of my making phagocytic or other estimations of the blood of these cases treated by vaccine.

Some other points of interest which emerged in this series of cases, though not bearing on the subject of this note, may be quoted here. Of the four cases which had been previously inoculated against the disease, one nearly became an ambulatory case. Blood-culture on the fourth day after admission was negative, and the temperature fell to normal on the sixth day, but the organism was recovered from the faeces on the twenty-first day. In another, blood-culture was negative in the original attack, but positive during the relapse. In the third, the organism was recovered from the blood-stream. In the fourth, blood-culture was negative, and the temperature fell to normal ten days after admission, while from the faeces a paratyphoid organism (?) was obtained. The mildness of the disease in an inoculated man is now a well-established fact, and upon it depends the greater difficulty (here experienced) of obtaining the causal bacillus from the blood. One should therefore be on one's guard in such a case, to the extent of removing a larger quantity of blood, and of using more plates of the culture medium.

Referring now to blood-culture as a means of diagnosis of the
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disease. The total number done in the period of five months was seventy-one, of which forty-two were positive. Taking the cases actually in the hospital which were eventually diagnosed as enteric fever, their total was forty-four, of whom thirty-nine were positive, a percentage of 88.6. This figure compares well with that obtained by Coleman and Buxton,¹ viz., 89 per cent. The cases in this series correspond pretty well with their group "first week."

Again, in thirty-two of the cases where I was able to make the blood-culture within a few days of admission, the average interval between the day of admission and the day the diagnosis was complete worked out at 3.3 days. The advantages of the method, both from the point of view of treatment and of prophylaxis, are evidently great.

The method used was that of Conradi, viz., the withdrawal, by means of a syringe, of 5 cc. of blood from a vein at the bend of the elbow, and its introduction into 10 cc. of the bile glycerine peptone mixture. After incubation about 1 cc. was spread on three plates, consisting of McConkey's neutral red bile salt lactose agar, and incubated. The first plate is always very thickly covered with growth, the second often contains individual colonies, while the third always does when a positive result is obtained. The diagnosis is considered complete if the colonies have the typical dewdrop appearance. They are then "fished" and examined at leisure.

NOTE BY LIEUTENANT-COLONEL W. B. LEISHMAN.

This communication from Captain Smallman was accompanied by temperature charts of the whole of the thirty-six cases treated by antityphoid vaccine, but it was, naturally, impossible to reproduce them all in the pages of the Journal. Those which have been published were selected as being the ones to which most detailed reference was made in the text, and as serving to show the typical effects of the treatment upon the temperature curve, the output of urine, &c. They are neither the best nor the worst witnesses as to the beneficial effects of the vaccine.

It will, I think, be obvious from the report that this system of treatment shows considerable promise for good, and it is greatly to be hoped that it may be given a more extended trial. The virulence of epidemics of enteric being notoriously variable in

¹ American Journal of the Medical Sciences, June, 1907.
different localities and at different times, it is most desirable that the treatment should be tested in other stations and by other hands.

The ordinary prophylactic vaccine may be used, provided its age does not exceed three months, and the dosage may readily be estimated by remembering that each first dose of prophylactic contains 500 million bacteria, and each second dose 1,000 million.

Major Horrocks has suggested that it would be advisable to treat every alternate case with the vaccine, so as to furnish the necessary control to the results, and this would certainly add to the value of any future reports upon the method. I need hardly add that we must await the results of estimations of the protective substances in those treated before being in a position to judge as to whether the theoretical basis of the method is well founded.