CONCERNING INOCULATION AGAINST PLAGUE AND PNEUMONIA AND THE EXPERIMENTAL STUDY OF CURATIVE METHODS.

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The present notes have been written in connection with official correspondence regarding the prophylactic inoculation against plague and the study of this and other health problems in India.

PART I.

On prophylactic Inoculation against Plague and Pneumonia.

The method of anti-plague inoculation was introduced in January, 1897; and in the year following its effects were subjected to an enquiry by a Government commission known as the Indian Plague Commission, 1898–99.

The report on that enquiry was published in 1900–01, and therein the Commission formulated views different from mine on a variety of subjects, some of considerable importance. Among the members employed on the enquiry were professors of Medical Colleges and civil officials serving in high posts with the Governments of India, Bombay and the Punjab, and their findings have been and are, very properly, viewed as a guide in matters affecting the plague inoculation. It is, therefore, essential that such of their pronouncements as were due to incomplete information available at the time or to misunderstanding should be rectified when the subjects become clear.

Two of the members of the Commission, Professor, now Sir Almroth E. Wright and Dr Armand Ruffer, had, sometime previously to their appointment on the enquiry, been initiated by me in the principles and

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methods of preventive inoculation against cholera[1]; and, at a subsequent date, in 1896, I had started one of these members, Prof. Wright, upon the work of preventive inoculation against typhoid fever[2]. It will appear from a statement by Sir A. E. Wright, quoted lower down, that it was largely his views—but, no doubt, also Dr Ruffer's—that guided the Plague Commission in their conclusions regarding certain aspects of anti-plague inoculation. Latterly, Sir A. E. Wright, together with Drs W. Parry Morgan, L. Colebrook and R. W. Dodgson, have been employed, for some two years, in investigating the pneumonia among the Rand Mine labourers in South Africa. The account of their findings throws light on certain subjects dealt with by the Plague Commission of 1898–99; and in view of the part which Sir A. E. Wright had taken in the framing of the Commission's conclusions, the result of the above authors' studies may be taken as supplementing the materials for a right understanding of the questions involved.

Accordingly, in the notes which follow, the points of divergence between the Commission of 1898–99 and myself which have come within the scope of the enquiry in South Africa have been gathered together and reviewed in consecutive order. Part of the matter concerns fundamental principles. I need hardly add that, in the years that have intervened, I continued to study carefully all the subjects on which the Commission of 1898–99 or any other experts had dissented from me; the present review is, however, limited to the items specified, on the grounds already explained.

The text of this note is divided into sections according to the several subjects dealt with; and each section is arranged, for facility of reference, under three heads, viz., as follows:

Sub-division *A* refers to the information and views placed by me before the Plague Commission of 1898–99 and reported in the

[1] *Vide* A. E. Wright and Surgeon-Captain D. Bruce, "On Haffkine's method of vaccination against Asiatic Cholera," *British Medical Journal*, 4th February, 1893, pp. 227–231; and W. M. Haffkine, "Injections against cholera," *The Lancet*, 11th February, 1893, pp. 316–318. The latter paper was read by Dr Ruffer at a meeting in the Conjoint Research Laboratories of the Royal Colleges of Physicians of London and Surgeons of England, where, in co-operation with him and with Prof. Sims Woodhead and Dr Cartwright Wood, I had demonstrated the principal experiments connected with the subject. The operations performed with Prof. Wright and his then assistant, Surgeon-Captain, now Surgeon-General Sir David Bruce and the Surgeons on probation at the Army Medical School in Netley were, however, of a more elaborate and detailed character, as may be seen from the first of the publications just mentioned.

[2] A. E. Wright and Surgeon-Major (now Colonel Sir David) Semple, "On vaccination against typhoid fever," *British Medical Journal*, 30th January, 1897, pp. 256–259.

"Minutes of Evidence," vols. I and III of their *Report* ("Indian Plague Commission, 1898–99." Government Publication, printed for Her Majesty's Stationery Office, Eyre and Spottiswoode, London, 1900);

Sub-division *B* contains the Commission's analysis and conclusion regarding the subject concerned, and is quoted from their *Report*, vol. v, issued in 1901; and

Sub-division *C* gives the results arrived at by Sir Almroth E. Wright and Drs Morgan, Colebrook and Dodgson, in the course of their present enquiry, as recorded in the "Report to the Witwatersrand Native Labour Association on the Results of an Inquiry into the Causation, Prophylaxis, and Treatment of the Pneumonia which affects the Native Labourers, and in particular the Tropical Native Labourers in the Rand Mines.—Observations on Prophylactic Inoculation against Pneumococcus Infections, and on the Results which have been achieved by it. By Sir Almroth E. Wright, M.D., F.R.S., in conjunction with W. Parry Morgan, M.B. Cantab., L. Colebrook, M.B. Lond., and R. W. Dodgson, M.D. Lond." *The Lancet*, 3rd and 10th January, 1914, pp. 1–10 and 87–95.

SECTION I.

The subject of this section has been touched upon in my "Epidemiological Notes," dated Calcutta, October, 1911, in which I had occasion to refer to inoculation against plague and remarked, with regard to the Indian Plague Commission of 1898–99, as follows: "A general source of error was created by their rejection of the thesis established by the work of anti-plague inoculation, viz. that *the treatment was effective in people who were already harbouring infection in their system*, and that it was thus possible to influence an outbreak of plague in a few hours."

The statements which I had made to the Commission regarding this thesis are contained in the following quotations.

A.

Passages in the evidence given to the Indian Plague Commission, on their 1st day's sitting, the 29th November, 1898, concerning the *effect of inoculation in the incubation stage of plague*. ("Indian Plague Commission, 1898–99. Minutes of Evidence," vol. I, pp. 5 and 6.)

(Section 34): "From the next morning (after the operations performed in the Byculla House of Correction, Bombay, where 154 prisoners

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out of a total of 337 had been inoculated) a difference appeared between the inoculated group and the non-inoculated."

(Section 35): "The difference in their relation to the disease appeared from the next morning."

"From the next morning after the inoculations there were altogether twelve cases of plague, of which six proved fatal, amongst the non-inoculated; and two cases, both of whom recovered, among the inoculated." (Section 36): "The prophylactic was powerless to repress the symptoms of plague already started, or which developed within a few hours after inoculation. (Section 37): (*The President.*)—In that quantity?—Yes, in the quantity used. This conclusion was drawn from the fact that the only prisoners who did not seem to have benefited by the inoculation were the one who had a bubo at the time he came to be inoculated and the two who developed undoubted symptoms of plague within a few hours after inoculation. (Section 38): (*Dr Ruffer.*) —How many hours after inoculation?—The inoculations were performed between four and six o'clock (in the afternoon) and the buboes appeared the same evening[1]." (Section 44): "I repeat that the second conclusion drawn from the Byculla observations was that the prophylactic was powerless to arrest symptoms already started or which developed a few hours after inoculation. (Section 45): (*The President.*)—I understand that you mean in that dose?—Yes, certainly. The next deduction was that not only did the prophylactic do no harm to persons already infected, but that there was the possibility of its influencing the disease in the incubation period, in an individual infected three or four days previously. This conclusion was based on the following consideration. The examination of the occurrences which took place subsequent to the time of inoculation shows that, day after day, with the exception of one day, the fourth after inoculation, cases of plague continued to occur among the non-inoculated group of prisoners. The incubation period of plague, according to the facts collected up to now, appears to be between two and ten days. A large proportion of the non-inoculated patients were, therefore, likely to have been infected already on the day when we dealt with the prisoners. Such being the state of

[1] *Vide* the Commission's Report, vol. v, p. 197, table summarising the events in the Byculla House of Correction. The dates corresponding to what is referred to in that table as "Mr Haffkine's figures" are, as explained by me in a letter to the Commission, those of the first appearance in the patients of morbid symptoms; the dates corresponding to what is mentioned as the "Official figures" are those on which the patients were ultimately transferred from the observation ward to the plague hospital, and were reported officially as plague occurrences in the jail.

affairs in the non-inoculated group, and seeing that the inoculated had been living under the same conditions and had had the same chances of infection as the non-inoculated, I had ground to infer that a similar group had been infected in the inoculated also at the time when they were inoculated. Under these conditions, the reduction of the number of cases and the suppression of deaths among them pointed to the possibility of inoculation influencing the disease in the incubation stage." (Section 47): "The time necessary for the plague prophylactic to produce a useful effect is shorter than in any preventive treatment known, this period being in the anti-cholera inoculation four days, in vaccination against small-pox seven days, in the inoculation against anthrax 12 days, in the inoculation against rabies 15 days, and in the present treatment apparently less than 24 hours. This conclusion was drawn from the fact that the beneficial difference between the inoculated and the non-inoculated appeared from the next morning after inoculation. The third question which was to be decided was answered in this manner: the question was how long would the operation take to produce the required immunity? and the answer was, it required between 12 and 24 hours."

(Section 48): "In sending these observations to the authorities I added the following remark: 'The above conclusions are temporary and refer only to the teaching of the particular outbreak in question. There remains fully the possibility of further experiments compelling us to modify these conclusions, though the expectation is justifiable that the general bearing of the results as above detailed will remain unshaken.' The conclusions in question have, indeed, remained unshaken. In all the subsequent observations, the facts, collected under the strictest possible conditions, such as imitated the conditions of laboratory experiment to an extent probably not equalled in any other set of investigations, confirmed the deductions drawn from that first experiment."

The particular thesis here affirmed was demonstrated with great precision in a certain experiment at Undhera, in the Baroda territory, concerning which the Commission reprinted a detailed report of mine to Government. In an address which I delivered at the Royal Society in London, on the 8th of June, 1899 (vide *Proceedings of the Royal Society*, vol. LXV), and which the Commission made use of in discussing my evidence, I described the result of the operations in the village in question as follows:

"Deaths from plague among the non-inoculated and the inoculated occurred after the following number of days had elapsed subsequent to the date of inoculation, viz.:

Among the non-inoculated:
after 3, 4, 5, 7, 8,—10, 11, 12, ——— 15, 16, 19, 20, 21, 24, 32 and 42 days;

and among the inoculated[1]:
after ——— 9, ——— 12 and 14 ——————————— days.

"There had elapsed, therefore, eight days, during which eleven deaths from plague had occurred among the uninoculated members of the families, before the first death took place in an inoculated case. The inoculation had again acted, so to say, immediately; or, as we have adopted to formulate the result, had acted within the time necessary for the subsidence of the general reactionary symptoms produced by the operation." The Plague Commission, on its part, summed up the position during the first week of the epidemic in question in the following terms: "In Undhera, though plague continued among the uninoculated at the rate of ten cases in the first week after inoculation, there were among the inoculated two persons at most who can be regarded as having contracted plague at the time of inoculation." (*Report of the Indian Plague Commission*, vol. v, 1901; p. 256, section 461.)

I further emphasized the thesis under consideration by separating (the Commission says, "excluding") the events which had occurred within the first 24 hours after the date of inoculation, from the events which had occurred subsequently. In this way, in recapitulating the facts of the Byculla Jail, I stated that there had occurred in the morning of the day of inoculation, in non-inoculated persons, six plague cases, and in the evening, in inoculated persons, three cases, viz. one in a man who had a bubo at the time of inoculation, and two cases in whom buboes developed a few hours afterwards. Separately from these nine cases I cited the events of the rest of the period of the outbreak.

B.

The following are *the Plague Commission's pronouncements with regard to the analysis of the Byculla Jail outbreak and the effect of inoculation in the incubation stage of plague* (vol. v, p. 197): "The second discrepancy relates to three patients who are excluded from consideration by Mr Haffkine in calculating his results on the ground that they had

[1] Half the members of each family had been inoculated.

already contracted[1] plague at the time when the inoculations were performed. If, however, cases are to be excluded for the reason that the full incubation period had not elapsed between the date of inoculation and the date of attack[2], we should, assuming that the incubation period may last as long as five days, omit not only the three prisoners omitted by Mr Haffkine, but also every one who was attacked up to the 4th February[3]. If this be done, and we think that it ought to be done, there would remain seven cases among the uninoculated, with two deaths, contrasted with one case, which recovered, among the inoculated. The comparison would thus be greatly in favour of the inoculated. The results, however, do not seem to justify the conclusion drawn from them by Mr Haffkine that protection is acquired within 24 hours of inoculation, for during the first five days after the inoculation there were five cases among the inoculated as compared with four among the prisoners who remained uninoculated," a statement which was arrived at by placing the cases under the dates of admission to the plague hospital, instead of under the dates of the first onset of the disease in them (*vide* footnote on p. 67 above).

Page 255, section 461: "We have now to consider the possibility that certain of the less favourable results shown in the tables which are now under discussion may be due to the assignment to the inoculated of attacks and deaths due to infection contracted shortly before or shortly after inoculation....The experiment in the Byculla Jail is of particular interest in this connexion. If we compare the number of attacks that occurred among the uninoculated and the number among the inoculated from the date of inoculation, we find that there was a percentage of 6·9 and 3·9 cases respectively, among these two classes, giving a ratio of 1·8 to 1. But if, allowing five days for the incubation period, we exclude all cases that might have been incubating plague at the time of inoculation, we arrive at the results which have been tabulated above, and which give a ratio of 6·6 to 1." (P. 256, sections 462 and 463): "In view of the short incubation period of plague, and in view of the fact that our experience in the case of other diseases, both in animals and men, indicates that protection is not at all rapidly established, it seems to us unlikely that the anti-plague inoculation can

[1] Should be "developed."

[2] For summing up my reason (as quoted above) the last words should have been: "*had* elapsed *prior* to the time of inoculation."

[3] In pursuance of the procedure adopted by me, only those who were attacked within 24 hours after the date of inoculation were to be "omitted." (See Section 47, quoted on p. 68.)

exert any favourable influence on persons who are already incubating plague. The matter, however, is one which can be definitely determined only by scrutinising the records of actual observation to ascertain how soon protection becomes established. We have, therefore, endeavoured to gather indications regarding this matter from the evidence laid before us.

"It would seem possible to test how soon protection is achieved by determining what percentage of the total attacks among the inoculated are attributable to each successive day or week after inoculation. We may consider first what details are necessary to apply this test. If we are dealing with a group of persons all inoculated on the same day, we should require to know the number of inoculated persons composing the group, the period for which they were kept under observation, and the number of cases that occurred among them in each day or week of the period of observation. It would, moreover, be necessary to know to what extent plague continued among the uninoculated during each day or week throughout the period of observation[1], in order to determine whether the inoculated in the concluding days or weeks of that period were or were not exposed to less infection than those in the earlier days or weeks. We could then calculate out the daily or weekly percentage of attacks, for the first day or week, on the original number of inoculates, and afterwards, on the number of those remaining over unattacked on each day or week. A comparison of the percentages which occurred later would give the required information as to the date on which protection was achieved. When the results of a series of inoculations done on successive days in one community are in question, the same particulars regarding each successive group of inoculates will be required. That is not the method that has been adopted in the preparation of the statistics placed before us. The method adopted has been to bring the period of observation for a number of successive groups of inoculates to a conclusion on one and the same day, to sort out the cases that have occurred before that day into groups according to the length of time after inoculation at which they occurred, and then to compare the numbers of attacks in different days or weeks with a view to drawing conclusions with regard to the protection achieved at varying periods after inoculation. This method[2] leads to erroneous results. How erroneous these results may be will

[1] The operations in the Byculla House of Correction and in Undhera were performed at one sitting. The particulars enumerated by the Commission formed part of the description of the experiments in question.

[2] Not employed by me in any of my studies.

be manifest when we consider what would be the effect of applying the method to an extreme case. In such an extreme case as that of a community composed of two groups of inoculates, inoculated on two days separated by a considerable interval of time, if the period of observation was brought to a close within, let us say, a week after the second series of inoculations, it is plain that the ratios which the percentage of attacks occurring in the first week after inoculation would bear to the percentage of attacks occurring in weeks remoter from the dates of inoculation would be vitiated by the fact that the figures for the first week would include the cases that occurred in both groups of inoculates, while the figures for the subsequent weeks would exclude the attacks that might have occurred among the second group of inoculates after the date on which the period of observation was brought to a close."

C.

The portion in *Prof. Wright and Drs Morgan, Colebrook and Dodgson's Report which bears on this subject* contains a table showing the results of inoculations with various doses of pneumonia bacilli. The table is as follows (*The Lancet*, January 10th, 1914, p. 91):

TABLE XVIII.

		Number of cases of Pneumonia which developed													
		First day		Second day		Third day		Fourth day		Fifth day		Sixth day		First six days	
	Number in group	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Group A (inoculated with 250 millions)	646	—	—	—	—	1	1	2	1	—	—	—	—	3	2
Control group	626	1	1	4	1	3	1	2	2	—	—	2	2	12	7
Group B (inoculated with 500 millions)	759	—	—	2	—	1	1	—	—	3	1	1	—	7	2
Control group	764	1	1	5	2	3	1	2	2	—	—	2	2	13	8
Group C (inoculated with 1,250 millions)	1,582	8	4	2	—	1	1	1	—	—	—	—	—	12	5
Control group	791	1	1	2	.2	—	—	—	—	—	—	1	—	4	3
Group D (inoculated with 500 millions glucose vaccine)	463	1	1	—	—	1	—	—	—	—	—	—	—	2	1
Control group	457	1	1	3	1	3	1	1	1	—	—	2	2	10	6
Group E (inoculated with 1,000 millions glucose vaccine)	650	—	—	1	—	2	—	2	—	—	—	1	—	6	—
Control group	595	1	1	4	2	3	1	1	1	—	—	2	2	11	7
Group E (inoculated with 2,500 millions glucose vaccine)	1,582	7	3	11	2	1	1	3	—	2	2	—	—	24	8
Control group	791	1	1	2	2	—	—	—	—	—	—	1	—	4	3

The authors make the following comments on this table:

"The facts which are set forth in the table are, as will be seen, very remarkable. Associating together the figures which apply to Groups A, B, D, and E, *i.e.* the groups which received doses up to 1,000 millions of pneumococci, we find that, in the first four days after inoculation, 2,500 inoculated had an incidence-rate of 0·52 per cent., and a death-rate in connexion with these cases of 0·16 per cent., while 750 controls had an incidence-rate of 1·4 per cent., and a death-rate in connexion with these cases of 0·84 per cent. In other words, the uninoculated had an incident-rate nearly three times, and a death-rate five times greater than the inoculated.

"*Again, associating together the figures which relate to Groups* C and F—groups which received doses of over 1,000 millions of pneumococci—we find that 3,200 inoculated had for the same period an incidence-rate of 1·1 per cent., and a death-rate in connexion with these of 0·32 per cent., while 800 controls had an incidence-rate of 0·4 per cent., and a death-rate also of 0·4 per cent.

"Two important conclusions follow: the first is that pneumococcus inoculation undertaken with doses up to 1,000 millions had a marked effect in aborting pneumonia and in diminishing the case mortality. Or we may phrase it otherwise. Vaccine therapy as applied to the treatment of pneumonia is successful when doses of 250 to 1,000 millions are given in the incubation stage of the disease. The second conclusion is that inoculation undertaken with doses of over 1,000 millions of pneumococci may perhaps temporarily increase the incidence-rate of pneumonia.

"It is perhaps of interest to point out that these conclusions are essentially the same as those formulated in connexion with plague vaccine by Mr Haffkine, immediately after he had carried out his first mass-experiment in the Byculla Jail, Bombay, in 1898[1]. In that experiment, as in the mass-experiment we are here dealing with, a decisive difference in favour of the inoculated half of the population manifested itself already within 24 hours. And the view that Mr Haffkine maintained (in contravention to that held by one of us) that plague vaccine does not produce a negative phase, and that it has the power of aborting an incipient attack, was afterwards established by evidence accumulated by Miss Alice Corthorn, M.D., and Surgeon-General W. B. Bannermann, I.M.S. In connexion with this, all that requires to be said is that the generalisations in Section II of this

[1] **In January, 1897.**

Report—generalisations which have been reached only after years of further work—have made it intelligible that a negative phase should manifest itself with large doses of typhoid vaccine[1], a vaccine which is easily broken down in the normal organism, and again with all vaccines after the organism has, by foregoing immunising response, acquired bacterioclastic power, and that this phase should make default in the uninfected organism, and in the early stages of infection when vaccines, such as plague vaccine and pneumococcus vaccine[2], which are with difficulty broken down in the body, are inoculated."

Section II.

In the quotation given in the preceding section Prof. Wright and Drs Morgan, Colebrook and Dodgson suggest, for the first time, I believe, that by the term "*vaccine therapy*" should be designated that form of vaccine treatment the effects of which were described in my evidence to the Plague Commission of 1898–99, viz. *the treatment by vaccine of patients in the incubation stage of the disease.* The notes which follow refer to *the extension of that treatment to patients in whom infection has progressed beyond the incubation stage* and is manifested by morbid symptoms.

A and B.

On page 67 above are reproduced my statements to the Commission regarding the effect of inoculation when applied to a person

[1] *Vide supra* the statement as to the effect of large doses of pneumonia vaccine.—In carrying out the work of anti-typhoid inoculation, the operators introduced, amongst others, a certain formula for determining the volume of the dose, which the Plague Commission defined as "the quantity of broth culture which is lethal for 100 grammes of guinea-pig." (Vol. v of their Report, page 183, section 395.) My criticism of this procedure was made in a Report to Government, No. 1269 of 9th August 1900, "On the present condition of manufacture of the plague prophylactic in the Plague Research Laboratory," Government Central Press, Bombay, 1900; pages 14–17. It was seen shortly afterwards that the dose as above defined was apt to cause to the inoculated increased incidence of typhoid, or, in the terms of the statement quoted above, to produce "a negative phase." Subsequently, a special "Anti-Typhoid Committee," appointed at the War Office, and of which Sir Almroth E. Wright at first formed part, rectified the procedure as regarded the dose and some other particulars, and the inoculations, which had been suspended by the orders of the War Office, were resumed. (Cf. Sir W. B. Leishman, "Anti-Typhoid Inoculation," *Journ. of the Royal Inst. of Public Health*, July, August and September, 1910; and *Report of the Anti-Typhoid Committee*, 1912, His Majesty's Stationery Office, London.)

[2] Cf. the paragraph before the last and the second conclusion in the last.

very shortly before or very shortly after the appearance of plague symptoms, as compared with its effect when applied *prior* to the last stages of incubation; also the President, Sir T. Fraser's queries concerning the doses to which my statements referred, and my replies that they referred to doses effective when used prior to the final incubation stages.

The relative position of these two applications of "vaccine treatment" and my attitude on the question were indicated in a further query by the President and in my reply to it, which was as follows (vol. I of the Commission's *Report*, page 12, section 79): "(*The President.*)—Have you any definite reason to suppose that your substance is not purely therapeutic as well as preventive or prophylactic?—No, Sir. I have not subjected this question to any accurate examination; but the general impression which I have had up to now is that the inoculation is not likely to influence the course of the disease when symptoms have already started."

I described to the Commission what I considered an accurate examination of such a question (or, as I expressed myself on that occasion, what I thought to be "the only reliable method for finally testing a curative treatment"). I had subjected to such a test a serum prepared on the plan of Dr Yersin's curative serum for plague; and I stated concerning this as follows (vol. I, page 14, sections 140–141):

"We (my assistant and myself) visited the hospital daily, from the early morning, and took the name of every new patient admitted. With the exception of those who died within an hour or a few hours, that is before we could attend to them, we treated with plague-antitoxic serum every second patient admitted during the hours we were at the hospital, irrespective of the information as to the serious or promising condition of the patient, or the duration of the disease before admission. Without selecting patients according to our personal impressions or according to the statements supplied by the medical officer or by the patient or his relatives, we subjected to the treatment every second arrival. After about 200 patients had passed into the hospital, we compared the mortality statistics among the treated and among the non-treated. I expect it was an accident, but the mortality among the treated was higher than among the non-treated. The moment this became clear, we suspended further treatment....I consider this the only reliable method for finally testing a curative treatment. We suspended the treatment in Poona where we had injected considerable doses of the serum. Further attempts were made in Bombay with

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some homoeopathic doses,—injecting 1 to 5 c.c. of serum, or so.... We varied the treatment in many ways. For instance, a patient would receive only 1 c.c.; or he would receive that amount repeatedly, every five hours; or again he would receive a dose of 10 c.c. once in two days. The patients were always observed comparatively with others admitted at the same time. In no case did we find a noticeable advantage on the side of the patients treated."

As regarded the *prophylactic inoculation*, the beneficial effects obtained from it in the incubation stage, in the case of a disease of such rapid course as the plague, led me to admit the possibility of profitable results from it also in ailments actually developed, but having a long-standing, non-acute character, while some of my co-workers were induced to try the method even in the case of acute ailments. The queries of the President of the Plague Commission indicated that, on his part, he was inclined to believe in the possibility of good effects in the case of developed plague.

Soon after the Commission returned from India, and prior to the publication of their criticisms quoted on pages 69–72 above, viz. in October, 1900, Prof. Wright began to apply the principle therein under consideration, as a basis for therapeutic practice[1], and since then, under the name of "vaccine-therapy," the plan has been extensively used, in all infectious diseases.

C.

In their present enquiries on pneumonia, Prof. Wright and Drs Morgan, Colebrook and Dodgson have, for the first time since its introduction[2], submitted this form of vaccine treatment to the test described above in connexion with the studies of Yersin's serum. They state the results as follows (*The Lancet*, 10th January, 1914, page 87):

"It will be well to realise at the outset under what disabilities of ignorance we here pursued our work. The methods of blood examination which so often disappointed us when we were endeavouring to compare from day to day the opsonic power of the inoculated with that of the uninoculated natives, left us quite in the lurch when we set ourselves to make similar daily measurements in the case of our

[1] *The Lancet*, 10th January, 1914, p. 92, quoted on p. 78 *infra*, and A. E. Wright, "Notes on the treatment of Furunculosis, Sycosis and Acne," *The Lancet*, 29th March, 1902.

[2] *Vide* Part II of this memoir.

pneumonia patients. We were unable to trace upon 50 immunisation curves which we plotted out in connexion with this work the effect of the doses of vaccine which we administered.

"Accordingly, from first to last, we had to guide ourselves in our choice of doses and of the intervals between our doses only by *à priori* considerations, and by the uncertain and flickering light which is furnished by temperature charts and the clinical symptoms. Influenced by the anticipation that the infected natives would be much more sensitive to pneumococcus vaccine than the uninfected native, we employed only doses of $2\frac{1}{2}$ to 50 millions of pneumococci; and we conformed to the principle of giving in the less serious conditions larger, and in the more serious ones smaller, doses. In the ordinary case we repeated the dose at intervals of 24 to 48 hours.

"These experiments—they have only the value of properly controlled reconnoitring experiments—were carried out in the hospital of the Witwatersrand Native Labour Association on tropical native patients. Many of these were, when admitted to hospital, already in an advanced stage of pneumonia. We accepted for our experiments only those who presented quite typical physical signs, and these were taken for treatment by vaccine-therapy or for treatment by the expectant method, alternately, and strictly in the order in which they were admitted to hospital. We took for every uninoculated patient who was treated by vaccine-therapy an uninoculated control, and for every inoculated patient an inoculated control.

"As the net effect of our treatment, we obtained the results which are set out in the subjoined table:

"TABLE XI.

"*Showing the Case-Mortality of Pneumonia in Tropical Natives treated respectively by repeated Small Doses of Pneumococcus Vaccine and by Expectant Methods.*

Therapeutic method employed	Number of cases	Number of deaths
Vaccine-therapy	159	50
Expectant treatment	149	48

"We would in connexion with these results specially emphasise (1) that they apply only to tropical natives who, having a very low power of resistance, have contracted virulent infection; and (2) that they apply only to inoculations carried out on such natives with the doses specified above."

Page 92: "In connexion with the vaccine-therapy of pneumonia we have, on the one hand, the fact that inoculation in the form of small doses frequently repeated was absolutely ineffective (Table XI); and, on the other hand, the fact that inoculation in the form of a single large dose, administered in the incubation period, often arrested the disease and averted death (Table XVIII[1]).

"That the difference of dose determined the difference of event, is to us as good as certain. Let us—recalling to mind the general propositions formulated in Section II—here take note of the fact that the doses which we found inoperative were doses from which there could, at best, have been expected that they should elicit a local immunising response. Further, let us note that the evocation of such response would be dependent upon a sufficiency of antigen passing into solution in the lymph at the seat of inoculation.

"Lastly, let us note that it is quite likely that microbes which are ingested by phagocytes may, from the point of view of the immunising reaction, be left quite out of regard. In connexion with this it is almost superfluous to point out that when comparatively small numbers of microbes are inoculated, and when they come into contact with a lymph which possesses opsonic power, but only inappreciable bacterioclastic power, they will almost certainly sooner or later be ingested by phagocytes.

"In general contrast with all this would be what would happen when a large dose of vaccine is inoculated. In this case the microbes would be carried on into the main lymphatic current or blood-stream, with the result that inevitably some would escape phagocytosis, and inevitably some of these would, even if the blood had but very little bacterioclastic power, be broken down. And there would supervene upon the convection of the antigen to the tissues through the blood a systemic immunising response.

"As we see no reason to suppose that the conditions appreciably alter, and as we know that the bacterioclastic power of the blood does not sensibly increase when pneumonia developes, we think it reasonable to expect that the favourable results which were obtained by the inoculation of doses of 250 to 1,000 millions of pneumococci would repeat themselves if this treatment were applied in the early stages of pneumonia."

[1] Reproduced on p. 72; *vide* also p. 75.

SECTION III.

A and B.

The present section concerns a subject which, though not clear to me at the time, I was obliged to refer to in a certain report to Government dealing with *the inoculations in the Khoja Community of Bombay*. The Indian Plague Commission, in discussing the report in question, constructed from a portion of its data a table of which it says (vol. v, pp. 209 and 210): "This table shows that among the inoculated deaths from plague were 12½ times less numerous, and deaths from general causes were 19 times less numerous, than among the uninoculated[1]. *Primâ facie*, therefore, it would appear that Mr Haffkine's anti-plague inoculation protects against plague, but that it protects more against ordinary diseases. This result is so striking and so difficult to accept that we first addressed ourselves to the task of enquiring whether the inoculated were a picked body, and whether the uninoculated contained a large proportion of the sick and feeble, and of the very young and very old. Surgeon-General Harvey, I.M.S., who made a special personal enquiry into the results of the inoculations performed in the Khoja Community, was of opinion that, in the main, the explanation of the disproportion between the deaths from general causes among inoculated and uninoculated Khojas must be sought in the assumption that in many families the sick, the weak, the elderly people, and the children, did not present themselves for inoculation, and that only the strong and healthy undergo the operation. In view of this opinion[2], we have tested the proportion in which the different age groups were represented among the inoculated and the uninoculated Khojas respectively.... These percentages indicate that, in point of age at least, the two communities were not sensibly incomparable. In view of these percentages the next point to determine was whether the excessive mortality from general causes assigned to the uninoculated was really due to excessive deaths in any particular class of the uninoculated community.... From this table it will be apparent that excessive

[1] My own analysis pointed approximately to a proportion of 9·6 and 3·8, as against the Commission's 12½ and 19. Subsequent consideration has shown me that the figure relating to general causes (3·8) required to be further reduced, and that relating to plague (9·6), correspondingly increased.

[2] *Vide* foot-note (2) on p. 80.

mortality from general causes occurred in all three classes of the uninoculated community (*i.e.* in children under seven, persons of intermediate age, and old people of 61 and over)....In view of the facts that are thus summarised here, Mr Haffkine sums up the case of the Khojas in his Report as follows: 'After making all allowances for inaccurate classification of deaths in the uninoculated group, with which the inoculated is being compared, and admitting that a part of the excess of deaths in the uninoculated may be due to a certain number of sickly people having abstained from inoculation, the result still contains an indication that, besides the protection against plague, this inoculation influences also favourably the resistance to certain other diseases than plague.' We find ourselves in agreement with Mr Haffkine in holding that the difference in mortality among the inoculated and uninoculated cannot be fully accounted for, either by the excess mortality of the uninoculated children and old people, or by the incorrect assignment of plague deaths among the uninoculated to general causes....Therefore, there remains to be considered, of the explanations offered by Mr Haffkine, only the suggestion that his anti-plague inoculation exercises a protective influence against diseases other than plague. This question is discussed elsewhere in the Report[1]. We cannot, however, accept Mr Haffkine's view that the low mortality among the inoculated can be accounted for on this hypothesis. It seems to us very probable, on consideration of all the circumstances, that the figures of mortality which have been given above must be accounted for by assuming that deaths which occurred amongst the inoculated were wrongly assigned to the uninoculated[2]."

[1] *Vide* next quotation.

[2] This view, and not the one quoted on p. 79, had originally been held by Surgeon-General Harvey, I.M.S. On 7th August, 1898, after first perusing my Khoja Inoculation Report, he wrote to me from Simla, in conjunction with the late Lieutenant-Colonel J. T. W. Leslie, I.M.S. (subsequently Sanitary Commissioner with the Government of India), as follows: "There must be a fallacy somewhere unless you have unconsciously hit upon the *Elixir vitae*. It seems to me that your figures make the uninoculated accountable not only for their own proper deaths, but for those among the difference between the total ultimately inoculated and the mean daily average of such." In the March following, upon my suggestion, he came to Bombay, made a detailed enquiry, which lasted several days, in the Khoja quarters of the town and ascertained that the view in question was not tenable. His statement to the Commission after this investigation was as follows ("Minutes of Evidence," vol. III, p. 347, section 26, 435): "I think that the records of the community are kept in a much more full and proper way than those of any average people. Several points have come out in addition to the fact that the records are correct. ...We know, I should think, with practical accuracy from the Jamaat books those who

The Commission's ultimate statement on the subject was as follows (vol. v, p. 261, section 469): "Only one question now remains to be dealt with in connexion with the influence on the organism exerted by Mr Haffkine's anti-plague prophylactic fluid. This question relates to the suggestion, to which we have already referred, that anti-plague inoculation protects not only against plague but also against other diseases. This suggestion emanated from Mr Haffkine. It appears that in the course of his inoculation work a certain number of cases were brought to Mr Haffkine's notice in which fevers of an undetermined nature were favourably influenced by the injection of his vaccine. An idea that anti-plague inoculation might possibly protect against other diseases having thus suggested itself to him, Mr Haffkine proceeded to seek in this idea an explanation for the extraordinary absence of mortality from general causes which was noted in the case of the Khojas inoculated in Bombay. We have, however, pointed out that the exceptionally light mortality recorded for the inoculated Khojas is capable of being explained in quite a different way. What we have just said applies not only to the case of the Bombay Khojas, but also to the case of the inoculated Karachi Khojas, among whom there was a similar extraordinary absence of deaths from general causes, which was similarly attributed to the effects of inoculation. The instances which have just been referred to constitute the only statistical evidence which has been brought forward in support of Mr Haffkine's claim that his vaccine favourably influences diseases other than plague. As this statistical evidence is untrustworthy, we have to fall back on *à priori* considerations, the two isolated instances which Mr Haffkine has adduced of cases of fever favourably influenced by inoculation, and a few other isolated instances adduced by other witnesses. According to the more or less indefinite statements of the two or three witnesses who are in question, the plague prophylactic is capable of favourably modifying every possible class of disease, from ringworm to leprosy. It is obvious that statements of this kind are not deserving of serious attention. That vaccination against one disease may influence the

have been inoculated and those who have not, so that we can get a very fair index as to the mortality among the two classes." "I find that the original investigation of Prof. Haffkine was one which involved an enormous amount of energy and thought. Although it is a very short report (see App. No. IV in vol. I of these Proceedings), the amount of work involved in it was enormous."—Surgeon-General Harvey's statement concerning the Jamaat records referred, as he mentioned, to the assignment of deaths among the inoculated and the non-inoculated, and not to the diagnosis of the causes of deaths.

course of another is, however, *à priori* quite credible, inasmuch as it is known that one disease may influence the course of another. But since no trustworthy evidence has been adduced before us to show that this obtains in the case of anti-plague inoculation, the suggestion, though one that might be kept in view by future observers, need here no longer engage our attention."

C.

The Report under consideration, by Sir Almroth E. Wright and Drs Morgan, Colebrook and Dodgson, does not refer to the Khoja investigations, but contains the following statements:

The Lancet, January 10, 1914, p. 91: "In concluding this account of the results obtained in mass-experiment No. 5 we may profitably advert to one more general consideration. It is, as will presently be brought out more fully in Section V, reasonable to expect that an effective inoculation will give an additional bonus in the form of a diminution in the morbidity which comes upon the record under the heading of 'Other Diseases.' In point of fact, the records which relate to the particular mass-experiment we are here discussing show such a reduction. We have our bonus in the form of a 15 per cent. reduction in the 'other diseases' of the inoculated, the figures being: *inoculated*, 6,224; *uninoculated*, 1,545. Cases of sickness other than pneumonia: in *inoculated*, 2,154; in *uninoculated*, 620.

"We now pass to our 6th and last mass-experiment."

Page 92: "In connexion with the mass-experiment here in question (the 6th and last mass-experiment) we may give the figures for the corresponding period relating to the incidence and death-rate of 'other diseases' in the inoculated and uninoculated sections of the population. These figures are as follows: *Inoculated*, average daily strength, 9,909; incidence-rate, 47·2 per cent.; death-rate, 0·93 per cent. *Uninoculated*, average daily strength, 4,520; incidence-rate, 106·6 per cent.; death-rate, 1·90 per cent."

In connexion with the same "mass-experiment No. 6" the authors give on p. 94 the following table:

"TABLE XXI.

"*Showing for the Whole Native Population of the Premier Mine the Incidence and Death-Rate for Pneumonia; the Incidence and Death-Rate for 'Other Diseases'; and also the Number of working Days Lost through Illness; for the Months February to May*, in* 1911, 1912, *and* 1913 *respectively.*

	1911	1912	1913
Population (daily average strength)	10,426	12,549	15,284
Proportion of the population inoculated	0	About 50 per cent.	About 92 per cent.
Incidence-rate of pneumonia	4 per cent.	1·28 per cent.†	0·74 per cent.†
Death-rate from pneumonia	0·97 per cent.	0·31 per cent.	0·14 per cent.
Incidence-rate of other diseases	31 per cent.	20·7 per cent.	14·4 per cent.
Death-rate from other diseases	0·51 per cent.	0·38 per cent.	0·34 per cent.
Number of working days lost per hundred native labourers	275	177	131

* "We have been furnished with data for this comparison only up to May, 1913."

† "In 1912 the incidence-rate was 0·86 per cent. for the inoculated and 1·7 per cent. for the uninoculated. In 1913 it was 0·6 per cent. for the inoculated and 3 per cent. for the controls."

SECTION IV.

The subject referred to in the present section and in the one which follows concerns *the procedure for estimating numerically the effects of inoculation.*

A and B.

In making out the *plague ratios for the inoculated and the non-inoculated* in certain epidemics, viz. in Lanauli and Kirkee, where the inoculations had been carried out, early in the outbreak, during a succession of days, I referred the incidence of the disease to the mean daily strength of the population. The Commission stated regarding this procedure that "very considerable complications are introduced when the incidence of plague has to be calculated on the average instead of upon the absolute strengths" (vol. v, p. 203); "the comparison which Mr Haffkine has made is unduly to the disadvantage of inoculation" (p. 205); "his calculation gives a slightly lower value for inoculation than that obtained by the calculation on absolute strengths. The result is as close an approximation as can be expected in applying the complicated method of calculating on averages to figures of an individual epidemic which are to a large extent the result of undetermined

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causes'' (p. 207). In drawing up a "Synoptical Table'' of the results observed in various epidemics, the Commission, therefore, definitely put aside my figures based on average strengths, and recalculated the results upon ratios based on absolute strengths of population (vol. v, p. 251).

C.

In their present publication, Prof. Wright and Drs Morgan, Colebrook and Dodgson give an analysis of "a detailed synopsis of results'' obtained in a part of their operations in South Africa, and base all calculations from that synopsis on the "*Daily average Strength of the Group*," the "*Daily average population*," the "*average daily strength*'' (Table XIX and text, p. 92 of *The Lancet*, January 10, 1914), or the "*Population* (*daily average strength*)'' (Table XXI on p. 94).

Section V.

A.

Apart from the matter of ratios, the Commission differed from me as regarded the process which I had introduced for *calculating the protection obtainable from inoculation*. In studying epidemics from this point of view, I defined the question for enquiry thus: What percentage of plague cases and deaths had been averted by inoculation? The answer is supplied by the following formula, viz.:

$$100\left(1 - \frac{P_n \cdot C_i}{P_i \cdot C_n}\right),$$

where P_n and P_i represent the non-inoculated and inoculated portions of the same population, and C_n and C_i, the casualties observed in them.

B.

The Commission expressed the view (vol. v, p. 252, section 454) that the above mode of enquiry was "likely to give rise to misunderstanding, especially when it is made, as it has been by Mr Haffkine, the basis for such a general statement as the following: 'One can say in a general manner that the reduction in mortality, produced by inoculation, is between 80 and 90 per cent.' Such a statement, taken apart from the actual figures, might be taken to imply either that inoculation had averted death from 80 to 90 persons (*a*) in every 100 of the total population, or (*b*) in every 100 of the inoculated population, or (*c*) in every 100 inoculated persons attacked, whereas the statement really means that death was averted from 80 to 90 in every 100 of those who, without inoculation, would, judging by the mortality among the uninoculated, have died of plague." "With a view to avoiding such fallacies we have expressed our results in a form that is not open to these objections. In column 10 of our table we have set forth the ratio in which the deaths among the uninoculated stand to the deaths which actually occurred among equal numbers of the inoculated."

C.

In the publication under review the authors have, throughout their analyses, resorted to the calculation and used the verbal expressions objected to by the Plague Commission, and have on no occasion stated the results in the form substituted by the Commission for mine. Thus on p. 91 of *The Lancet*, January 10, 1914, they refer, as already quoted, to "a 15 per cent. reduction in the 'other diseases' of the inoculated, the figures being: *inoculated*, 6,224; *uninoculated*, 1,545; cases of sickness other than pneumonia: in *inoculated*, 2,154; in *uninoculated*, 620."

The "15 per cent. reduction" here mentioned, or, more precisely, 13·76 per cent., is the result of calculation summed up in the above quoted formula, 1·16 being the figure which would have resulted from the procedure proposed by the Plague Commission.

On p. 93 of *The Lancet* the authors give the results of "mass-experiments" Nos. 1, 3, 4, 5 (E), and 6, as "a reduction of 37·5 per cent. in the death-rate of the inoculated"; "a reduction of 31 per cent. in the death-rate of the inoculated"; "a reduction of only 10 per cent. in the incidence-rate and of 34 per cent. in the death-rate"; "a reduction of 35 per cent. in the incidence and 55 per cent. in the deaths" (the latter figure being referred to shortly before as "a maximum reduction of 50 per cent. in the death-rate of the inoculated"); and "a reduction in the incidence-rate of 50 per cent., or 58 per cent., and a reduction in the death-rate of 52 per cent., or 61 per cent." (the latter figure being referred to previously as "a reduction of 60 per cent. in the death-rate for the inoculated").

These results have been calculated by the authors in the manner summed up in the formula quoted on the preceding page, the precise figures being respectively: 39·38; 28·09; 12·43; 34·32; 35·28; 54·23; 50·38; 58·03; 51·55 and 61·16 per cent. According to the procedure substituted for mine by the Plague Commission the results would have been stated in figures of 1·65; 1·39; 1·14; 1·52; 1·54; 2·18; 2·01; 2·38; 2·06 and 2·57 respectively.

Section VI.

The foregoing notes refer to subjects on which the Indian Plague Commission of 1898–99 dissented from me, and concerning which Sir A. E. Wright and his co-workers, Drs Morgan, Colebrook and Dodgson, have now arrived at results coinciding with mine.

The Report under examination contains no findings of an opposite bearing; that is, among the matters that came within the authors' purview there were no subjects regarding which it appeared that the conclusions advanced by me required to be modified.

I propose, therefore, to complete this review by mentioning the same authors' finding on one further matter, which did not come under the consideration of the Indian Plague Commission of 1898–99, but on which other experts, called upon to advise on the plague, differed from me.

The matter concerns, indirectly, an opinion which I expressed in Poona, in January, 1898, to the effect that, independently from their mode of life, *certain human races*, like Europeans, Egyptians, Somalis, Kaffirs, perhaps also Arabs and the Felaheen, *appeared less receptive of plague than others*, the Chinese or Indians, for example; while in some respects, *e.g.* in regard to typhoid fever or the effects of the sun, the mutual position of Europeans and Indians appeared the reverse of the above. In an address delivered by me, in December, 1907, before the Royal Society of Medicine, in London, and entitled "On the present methods of combating the bubonic plague[1]," the subject of racial differences in regard to plague was referred to in five of the six following propositions mentioned by me on that occasion, viz.:

"(1) That in a native of that country (India), who is more susceptible to the disease than Africans, Europeans and some other races, the inoculation now in force in India reduces the liability to attack to less than one-third of what it is in a non-inoculated Indian.

"(2) That in the one-third of cases which still occur, the recovery rate is at least double that in the non-inoculated attacked, the ultimate result being a reduction of the plague mortality by some 85 per cent. of what it is in non-inoculated Indians.

"(3) That in an inoculated European an attack of plague, if it subsequently occurs, has so far always ended in recovery.

[1] *Proceedings of the Royal Soc. of Med.*, January, 1908.

"(4) That the inoculation is applicable to persons already infected and incubating the plague, and prevents the appearance of symptoms, or else mitigates the attack, a fact which disclosed a basis for bacterio-therapeutic treatment of diseases.

"(5) That in natives of India the degree of immunity conferred by this inoculation, though gradually vanishing, seems to last during several outbreaks of plague; and that

"(6) In Europeans the effect has not yet been seen to disappear in the space of time, since 1897, that this inoculation has been under study."

The publication by Sir A. E. Wright and Drs Morgan, Colebrook and Dodgson contains, on p. 10 of *The Lancet*, January 3, 1914, statements as to differences observed in Europeans and Africans in regard to the effect of germs on their respective bloods, the authors' conclusion being that the Africans have an advantage over Europeans as regards natural resistance to microbes of abscesses and suppuration, while Europeans have an advantage over the Africans as regards similar resistance to pneumonia. On p. 95 of *The Lancet*, January 10, 1914, the authors sum up their finding as to the germ of the latter disease by saying that "the blood of the African native is, so far as relates to its power of phagocytosing and killing the pneumococcus, very inferior to that of the European, and that the capacity for immunising response is also much less in the African than in the European."

In connexion with the above remarks, I would mention that, soon after the present epidemic had spread over the plains of India, and shortly before the Commission of 1898–99 began their work, viz. in June, 1898, I endeavoured to obtain a modification of the general measures devised against the plague, in favour of persons who had undergone preventive inoculation.

The modification in question was indicated by the analysis of the main features of the outbreak, which showed that, for vast masses of the population exposed to the disease, *personal immunisation was the only accessible means of protection.*

I recognised at the time that the policy advocated would be unavoidably retarded by the existing divergence of views, and would be adopted only after a prolonged expenditure of effort in many other directions.

These conclusions regarding the measures for protecting the population in the plague epidemic areas are now shared, I believe, by many authorities; and the publication with which the present Note is concerned is some sign that unanimity is attainable also on questions regarding the nature of the prophylactic inoculation. Further progress is, however, required in many directions.

PART II.

On experimental Study of curative Methods.

I.

The description quoted on p. 75 *supra* of *the mode of testing the Yersin plague serum* in the Poona Hospital was given by me to the Indian Plague Commission on the 30th November, 1898, and was preceded by the statement which is reproduced below (*vide* "Indian Plague Commission, 1898–99. Minutes of Evidence," vol. I, p. 14, section 140):

"At first, while I had only a small quantity of serum at my disposal, I attempted to see its curative effect in the following way. I visited the Arthur Road Hospital, which had the largest number of plague patients in Bombay, and requested the Medical Officer in charge to point out to me those cases which he considered *hopeless*; that is, cases which, he thought, could not recover without the assistance of some new, additional treatment. He told me that he had a patient who had had, on the day before, a temperature of 107°, and that up to that time not one patient had passed through the hospital who had recovered after having had that temperature. In the same manner he pointed out to me a certain number of other patients who, in his opinion, had no chance of recovery. I reasoned that, if a proportion of such patients recovered under the specific serum treatment, we would have an indication that the treatment under enquiry produced a greater effect than the ordinary treatment adopted in the hospital. Very soon I had to abandon that plan, as no such indication was obtained. A curative treatment which has not the power of helping in critical cases may, however, still be useful. When the hospital authority sees before him, say, a hundred patients, there are, of course, amongst them three categories: one which will for certain recover, another which will for certain succumb, and a third category in whose case the balance, by a useful treatment, may be turned towards recovery. The serum, even when powerless with regard to the second category, would prove valuable if it were to assist with regard to the third group of patients. I suspended temporarily further attempts until I had accumulated a sufficiently large amount of serum; and then went to Poona where the plague epidemic was on the increase, and the number of patients admitted to the General Plague Hospital was between 20 and 30 per day."

II.

At the time of giving the above explanations to the Commission I dealt with the recovery rate, which, in an acute disease like the plague, clearly dominates all other questions. Subsequently, I applied the same plan of study to all *clinical features of that disease*, or, more precisely, to all those features which were reliably observed and recorded. This included symptoms and particulars which were common to all categories of plague patients, as well as those which were observed only in the distinctive types of the disease. In this manner the effect of the treatment was investigated in relation to the age, sex, nationality and caste of the patients; their condition as to previous inoculation; the duration of illness prior to admission to hospital and prior to the application of the specific treatment; the state of consciousness or coma on admission; the type of the illness, viz. the presence or absence of outward lesions (buboes); the number and mode of distribution of these, if present; the condition as to pneumonic symptoms; the detection or otherwise of germs in the circulation at stated periods of the disease; the temperature, pulse and respiration at the time of arrival at hospital and of commencement of treatment; the variation of these particulars after the first administration of serum and throughout the time of observation; the duration of febrile symptoms in recovery cases; the recurrences, if any, of high temperature and high rates of pulse and breathing subsequent to the first restoration of normal conditions; the recovery rate corresponding to variations of treatment; and the prolongation, if any, of life in fatal cases. The relative gravity of each of the above symptoms was at the same time minutely investigated. Of the observations which, at that period, were taken and recorded with regard to plague patients, I omitted, for the time being, to take account only of those which conveyed general opinions of the observers, or were based on mental records, that is, those in the estimation of which personal inclination and idiosyncrasies, not admitting of control and verification, played an important part. In no case, however, were general impressions of this nature required for forming definite conclusions.

The studies here referred to were made with the serum of Prof. Lustig of Florence, which was used in Bombay in 1899–1900; with Drs Terni and Bandi's serum, from Messina, used in 1903 and 1904; and with Dr Vital Brazil's serum, from San Paolo, Brazil, and Drs Roux and Yersin's serum, from the Pasteur Institute in Paris, which were tried in 1904. Detailed reports, in each case, were submitted to Government, and a budget of these was subsequently edited and published, during my absence from India, in the *Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India*, No. 20, under the title of "Serum-Therapy of Plague in India, reports by W. M. Haffkine and Officers of the Plague Research Laboratory, Bombay." (Office of the Superintendent of Government Printing, India, Calcutta, 1905.) Subsequently, I made analogous experiments with the sera prepared by Dr Macfadyen and Prof. R. T. Hewlett for the treatment of plague and of cholera. A few of the facts established in these investigations will be briefly recalled here with the object of indicating the nature of the information thus obtained. The result showed that the injections tended to mitigate the symptoms of the disease, to an extent which was carefully determined with regard to each symptom. At the same time the fact first communicated to the Plague Commission was observed again, viz. that the remedy had no appreciable effect on the mortality from plague.

In the case of *Dr Lustig's serum*, the patients, 484 in number, presented the most marked difference in the rate of mortality as compared with the 484 patients not treated with serum. The proportion was 68·18 per cent. of deaths amongst the serum patients, and 79·55 per cent. amongst the others. Examination showed, however, that the patients who had received serum included a clearly defined preponderance of cases which had, from the first, comparatively benign symptoms, whilst those left without serum had a preponderance of grave cases. The average survival in hospital of the patients treated with serum, but who ultimately succumbed, was 3·89 days, while that of the non-serum patients was 2·76 days. Among the patients admitted with fever and given at once a serum injection, the proportion of those in whom the temperature fell within 24 hours and did not again rise to the level of the admission temperature, was 27·95 per cent. Among the patients admitted in a similar condition and not treated with serum, the proportion was 23·83 per cent. The fever, however, did not disappear in the serum treated patients sooner than in the non-serum patients. Indeed, the number of cases in whom the maximum temperature was over within the first 24 hours of admission formed 68·14 per cent. of non-serum patients and 64·20 per cent. of serum patients. In the most serious of the non-serum cases, who recovered, the temperature became permanently normal in an average of 19·95 days; in the corresponding serum cases, in an average of 21·05 days.

Among the patients treated with *Terni and Bandi's serum* the mortality was, in one hospital, 89 deaths in 110 cases, or 80·90 per cent., while among the non-serum cases, admitted to the same hospital at the same time and alternately with the above, it was 90 deaths in 110 cases, or 81·81 per cent. In another hospital, the figures were 12 deaths in 16 serum cases, or 75 per cent., and 11 deaths in 16 alternate non-serum cases, or 68·75 per cent. When the two hospitals are considered together, the mortality is 80·16 per cent. in either category of patients. Taking the case of the hospital with the larger number of patients, the serum treated patients, who ultimately succumbed, lived, on the average, eight hours longer, after admission to hospital, than the others; the figures being 3·27 days and 2·93 days respectively. Advantage from an early administration of serum was not consistently observed; nor did cases in less susceptible ages, or with a less dangerous manifestation of buboes, or with a lower admission temperature, benefit by injection more than severer cases. On the other hand, patients admitted with a less dangerous condition of the circulation or breathing appeared to be so benefited. The proportion of patients who were treated with serum, and who, within 24 hours, showed improvement of condition, was, with regard to temperature, 58·22 per cent.; with regard to circulation, 46·42 per cent.; and with regard to breathing, 36·47 per cent. Among the non-serum cases the corresponding figures were 45·78 per cent., 32·55 per cent. and 34·88 per cent. Similarly, the proportion of cases in whom the gravest condition of temperature, circulation and breathing was passed in less than 24 hours after admission, was, for the serum cases, 38·09 per cent., 20·31 per cent., and 17·46 per cent., and for the non-serum cases, 26·31 per cent., 13·55 per cent. and 10·00 per cent. respectively. Yet, ultimately, the mortality in all these groups of cases was higher in the serum patients than in the others. In the patients treated with serum, who ultimately recovered, the highest temperature and rate of pulse and respiration showed an average of 102·6°, 127 and 37 respectively; in the corresponding non-serum patients the figures were 102·8°, 138 and 41. Among the serum treated cases there were also fewer relapses of high temperature than among the non-serum cases. The recovery rate was not improved by increasing the initial dose or the total amount of serum.

In the case of *Dr Brazil's serum*, the mortality was, in one hospital, deaths in 20 serum cases (85 per cent.), against 15 deaths in 20 non-serum cases (75 per cent.); and in another, 41 deaths in 50 serum cases (82 per cent.), against 45 deaths in 50 non-serum cases (90 per cent.). When the two hospitals are considered together, the rates are 82·86 per cent. for the serum patients against 85·71 per cent. for the others. The difference in the two hospitals was again traceable to the inclusion of a few more serious cases in one of the two groups of patients. In both hospitals the injections tended to reduce the temperature and pulse rate within the first few hours of admission, the degree of that tendency being manifested in figures analogous to those mentioned above for the other sera. In both hospitals the serum patients who ultimately succumbed lived longer than the non-serum cases, the average advantage being, in one hospital, 7½ hours, and in the other, 2·55 days. The hospital which showed a longer survival of the serum cases had also a further advantage over the other in that the recovering patients, in the serum group, reached normal temperature, pulse and respiration sooner than the non-serum recovering patients; yet the ultimate mortality of the serum cases in this hospital was higher than in the other hospital, and higher than among its own non-serum cases, thus showing again the absence of a parallel between the improvement of symptoms and of the ultimate result.

In the case of the *Roux-Yersin serum*, the mortality was 45 deaths in 68 cases, or 66·17 per cent., among the serum treated cases, and 41 deaths in 68 cases, or 60·29 per cent., among the others, the difference being referable in this case also to the condition of the respective patients at the time of admission. Notwithstanding the unfavourable termination of the disease, the serum cases, who ultimately succumbed, lived, in this as in all the other instances, longer, after the date of admission to hospital, than the non-serum fatal cases, viz. 7·57 days as compared with 4·19. The proportion of cases whose highest temperature and pulse-rate became lower within the first few hours of arrival in hospital, was 42·64 per cent. and 42·64 per cent. respectively in the serum group, and 39·85 per cent. and 32·35 per cent. in the other; yet the mortality, in each of these categories of serum cases, was higher than in the corresponding categories of non-serum cases. As regarded respiration, the figures were in a reversed order, viz. 38·23 per cent. for the serum cases and 41·17 per cent. for the others; and the mortality was in favour of the serum patients. In the case of this serum, as in the case of that made by Lustig, the maximum temperature and rate of pulsation and breathing were passed in the serum cases later than in the others; but, ultimately, the serum cases, which recovered, reached the normal, in respect of all these particulars, sooner than the others, the average delay being, for the serum cases, 6·24, 8·40 and 7·04 days, and for the others, 8·42, 9·20 and 9·02 days respectively.

III.

Sir Almroth E. Wright and Drs Morgan, Colebrook and Dodgson published their Report referred to in the preceding pages in two instalments. The results of the application of "vaccine-therapy" to pneumonic patients (*vide* pp. 77–78 *supra*) were given in the second instalment, which was issued in January, 1914. In December, 1912, the authors published the first part of their Report, and therein they stated their views on *the method of investigation* by which those results had been established. The method was that dealt with in the foregoing Section, and which, as stated above, had been applied by me, in 1898, to the examination of the Yersin treatment for plague, and in 1899 to 1904, to a study of Lustig's, Terni and Bandi's, Brazil's and Roux and Yersin's sera. Prof. Wright and his collaborators refer to that method under the name of "the statistical method," adverting by this to the fact that experimental study proceeds throughout, and of necessity, by careful measurement and calculation[1]. They contrast this method with "*the experiential method*," by which name they designate the process of taking into account the complex of impressions which have been left on the minds of practising medical men in the course of their experiences.

The authors say (*The Lancet*, December 14th, 1912, p. 1636):

"If we employ the *experiential method*—*i.e.* if we take into account the whole complex of impressions which have been left upon the mind

[1] *Vide*, however, on p. 98 *infra* the authors' reference to the "popular verdict on statistics."

by experience, we arrive at a *generalisation* (which is the general law or general evaluation of the class). This will express the result which we have witnessed in the majority of our cases; and it will, if our experience has been a typical one, hold good of a majority of every other series of such cases. If, on the contrary, we proceed by the *statistical method—i.e.* if we tabulate and count up our results—we arrive at a *statistical evaluation*. This will set forth the percentage of cases in which a particular result was achieved; and it will, if our experience is a typical one, give the correct odds in favour of that result reproducing itself in the case to which we are giving our attention.

"An objection will already have suggested itself: 'Is it,' it will be asked, 'beyond question that what is here called the "experiential method" is properly distinguishable from the statistical method? And does not the distinction between the methods consist only in this, that when we bring into application the so-called "experiential method" we are relying upon a badly kept and blurred mental record of the facts which warrants at best an evaluation in general terms, while we have in connexion with the statistical method an accurately kept written record which warrants an evaluation in precise figures?' The question may be answered by analysing somewhat more minutely first the statistical and then the experiential method.

"The statistical method of evaluation involves three separate operations: (1) a critical study of the raw material of experience with a view to selecting a suitable criterion upon which to build up our statistics; (2) the sifting of that raw material by aid of the criterion we have chosen[1]; and (3) the evaluation of the results which the sifting has yielded." (P. 1637): "The experiential is a much less sophisticated and a much less arbitrary method of evaluation. When we employ it we let the two separate streams of experience which correspond to the twin series of substantive and control experiments filter through our minds, and then compare the impressions which have been imprinted. While no complete account can be given of the psychological processes by which this comparison is carried out, the two following points may be noted. When we bring into application

[1] As may be seen from the brief summaries given on pp. 88–93, the plan of study described here as "the statistical method" embraces the *whole* of the "raw material of experience," the selection of one feature as a criterion, to the exclusion of others, not being necessary. In acute diseases, however, often one particular "feature," such as the recovery rate, may, indeed, be taken as an essential criterion of success. As already stated, I limited my enquiries to such a criterion in the first days of the plague epidemic in Bombay.

the experiential method we take into consideration every feature of each case and not, as in the case of the statistical method, only one selected feature[1]—in other words, the *experiential* is a method of *unrestricted*, the *statistical* a method of *restricted outlook*. And the mental record upon which we proceed need not be inaccurately kept or blurred. When, for instance, we obtain in a succession of consecutive cases one and the same result, each succeeding case will render more distinct the impression made by the preceding case; and when a case which is at variance with a series of previous cases turns up, it will by contrast stand out very clearly in our consciousness."

Having defined the two methods, the authors state, regarding *the application of the "experiential method"*: "The capacities of the human intellect are unequal to the task of carrying in mind and weighing one against the other a long procession of substantive and a long procession of control cases. There attaches to the use of the experiential method also another important limitation. It is impracticable, in the case where the evaluation of different observers diverge, to bring these together into a single judgment. For there is no method for finding the resultant of a number of non-numerical evaluations." Against this they point out, as *the disadvantages of the "statistical method,"* "that it is the exception to find in connexion with clinical material either a really critical feature by reference to which the cases can be sorted out into successes and failures, or a significant feature which is universally present and which lends itself to arithmetical evaluation[2]." "As a certain counter-weight against the disadvantages we have been considering is to be reckoned the fact that, once a satisfactory basis for statistics has been found, we can obtain in the form of a single expression the resultant of the evaluations of any number of independent observers." (*The Lancet*, December 21st, 1912, p. 1701): "Where such a criterion is not available, and where the personal judgment of the observer is called into requisition, it is very difficult, for him, in going through a long series of cases, to maintain exactly the same standard of value. The observer's estimate of what amounts to an "attack" or a "relapse" or a "cure" will, for instance, vary; and it will be impossible in the case of different observers to obtain conformity to a uniform standard[3]."

[1] *Vide* preceding foot-note.

[2] *Vide* foot-note (1) on p. 93 and remarks on pp. 88 and 90 concerning symptoms and particulars not universally present.

[3] *Vide* remarks on p. 90 on the idiosyncrasies of observers and on the question of recurrences of morbid symptoms.

Lastly, a comparison of the methods is made in the following respect (p. 1637): "When we evaluate by a method of restricted outlook, which takes into account only a single feature in each case (and we have seen that the statistical is such a method[1]), we must, before a trustworthy conclusion can be arrived at, pass in review a very large number of cases. When we evaluate by a method of unrestricted outlook (such as the experiential method) in which every feature in each case is taken into account, a much smaller number of cases will suffice. When there is a shorter and a longer way it will be well not to chose, *on principle*, the longer."

In the passages which now follow the authors refer to the value of the "statistical method," or "numerical evaluations," in medical research. They state (p. 1701):

"The suggestion which is here put forward is not that all numerical evaluations should disappear from medical literature. We shall have conceded to them their proper relative rank in science when we have put them upon a level with evaluations expressed in round numbers, and with approximate evaluations such as are obtained by the experiential method. They must, however, from the standpoint of ethics, rank below these. For, while approximative experiential evaluations are neither more nor less than what they purport to be, a precise numerical evaluation is a concession to that human weakness which insists that it must always be allowed to achieve, even at some sacrifice of truth, an absolutely definite mental image." "If we desire to learn in connexion with each individual only whether he remains well; or falls seriously ill, and whether he dies of his illness, or survives, the required statistics can quite well be compiled by perfectly unskilled labour. And it is by such agency that statistics are commonly compiled. But if we desire to learn what is the number of men who really fall ill of pneumonia, and the number who really die from it, the clinical skill that will have to be requisitioned will not be less than for an experiential evaluation." (P. 1702): "It has, in the course of the preceding analysis of the experiential and the statistical methods, been elicited that the statistical method employs, for purposes of numerical notation, a quite arbitrary scale of values; that it is, in contrast to the experiential method, a method of restricted outlook; that there are a very large number of cases to which the method cannot be applied; that it is not capable of bringing to light finer differences[2]; and that it demands,

[1] *Vide* foot-note (1) on p. 93.

[2] *Vide*, with reference to the four points mentioned, Section II, pp. 88–93 *supra*.

if the results are not to be of inferior value to those of the experiential method, the application of exactly the same measure of clinical skill."

"*Do considerations of intellectual morality prescribe that the statistical method should everywhere be brought into application?*" "The statistical method is believed to provide effective safeguards against moral shortcomings on the part of the observer and evaluator." "The observer who is blinded by intellectual, personal, or financial bias, but is constitutionally honest—and this is the type of observer against whom we have to be upon our guard—need only employ the statistical method to find himself estopped from overrating the cases which bear out his theories; and from underrating or putting out of sight cases which have turned out inconveniently for those theories. The experiential method gives opportunities for such departures from morality." "But there is something more to be taken into consideration. (*a*) It is important in connexion with the question of the warping of the observer's judgment by bias to realise that this cannot really count as a very formidable obstacle to scientific advance." "Bias, begotten as it is of self-interest, will affect only the verdicts of the original observer and of those who have definitely taken sides for or against him, and the rest of the world will be unprejudiced." "Whenever the statistician has free choice in the matter of the criterion which is to govern his classification—and he very often has such free choice—he can turn this choice to advantage in the interest of the particular cause which he happens to have at heart[1]." (*b*) "When we come seriously to make enquiry whether in the case of statistics the cards are really on the table, the answer must inevitably come that the mere setting down of the serial numbers, or, as the case may be, of the names of the patients, is not a fulfilment of the ideal of setting forth the data in such a manner as to make it possible for the reader to control the judgments of the observer." (*c*) "While it may be permissible to rank all men as equally competent observers with respect to things that admit of being measured by carpenter's rules, or of being weighed upon grocer's balances; and to rank as the most authoritative on these matters, the man who reports the largest number of observations; this doctrine cannot find application in medicine; for here in many cases truth can be arrived at only by exceptional skill and a very delicate calculation of probabilities." (P. 1703): "Looking back now over what has preceded, it will be borne in upon the reader, on the one hand, that medical statistics are nothing more than the data of imperfect clinical methods set out in

[1] *Vide* foot-note (1) on p. 94.

unwarrantably precise figures; and, on the other hand, that we have in connexion with the statistical method, just as with the experiential method, to reckon with opportunities for the intrusion of bias; with a defective realisation of the ideal of a complete disclosure of the data; and with the assumption of unwarranted authority on the part of the evaluator. The reader will probably have arrived at the conclusion that there is in all these respects little or nothing to choose between the two methods of evaluation[1]."

In the concluding passages, after criticising Prof. Karl Pearson's views on the value of expert opinion, when not supported by accurate data, the authors refer to the following "objection in the minds of the unthoughtful." They state (p. 1704): "The train of reasoning which commends itself to these runs somewhat as follows: 'Unanimity of expert opinion does not furnish any real guarantee of truth. If it did, the medical profession would not, time and again, have accepted unanimously—as it did for instance in connexion with blood-letting—experiential conclusions which the progress of knowledge has compelled it to abandon. And now just let me ask,' concludes our objector, 'is it conceivable that the medical profession would not have been saved from such gross errors if it had brought into application the statistical method?'" Concerning this the authors state that "it was not the bringing into application of the statistical method, but the undertaking of control experiments—that is to say, the treatment of patients without bleeding, and the comparison of these by the experiential method with the previous cases treated by bleeding—which led to the general abandonment of blood-letting[2]"; and that if a method of evaluation was to be discredited by the fact that an erroneous conclusion has been arrived at by its means, "both the experiential and the statistical methods of evaluation, but *in primis* the latter—upon which the popular verdict is that 'statistics will prove anything'—would be irretrievably discredited." "The doctrine of the probative value of a consensus of expert opinion is in no way invalidated by such a train of reasoning as that which we have been reviewing. In reality we are all of us recording machines—recording machines of the most diverse patterns—and when each several machine registers one and the same impression the correctness of such record is established beyond doubt. The

[1] *Vide* Section IV, p. 99.

[2] *Vide* the view quoted on p. 100 concerning the capacities of the human intellect for carrying in mind and weighing one against the other processions of substantive and control cases.

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general sense of mankind proclaims this in the dictum: *Securus judicat orbis terrarum.* It does so again in the formula: *Quod semper; quod ubique; quod ab omnibus.* And if it stands fast that what is given in the experience of all is true, how shall this not hold also—also with the proviso that untreated as well as treated cases are included in every experience—in our difficult and distracted science of medicine?"

IV.

In the interval between 1900, when Sir Almroth E. Wright first began to use "vaccine therapy" for purposes of professional practice, and the date of the South African experiment, he and his co-workers at St Mary's Hospital were, on one occasion, prevailed upon to try and ascertain the efficacy of that procedure in the way which had been commended by me, for such purposes, to the Plague Commission of 1898-99 (pp. 74 and 76 *supra*), and in which I had been testing curative treatments in India. The experiment on that occasion was not completed by them, and although the preliminary information which they published was favourable to the therapy, they did not persevere with the study, and the further use of the "statistical" or, as it was termed, "*quasi*-statistical," method was discouraged by them[1]. In the Hospital of the Witwatersrand Native Labour Association, in South Africa, the experimental testing of "vaccine therapy," by that method, was, therefore, carried to a conclusion for the first time since the therapy had been used in practice. The disease—pneumonia—on which the trial was made, was that in which, of all the graver infections, "vaccine therapy" promised to be the most successful[2]. The details of the actual experiment tabulated herein on p. 77 *supra* show that, of a total of 159 patients who were treated with "vaccine," 109, or 68·55 per cent., recovered; 149 others, admitted to the Hospital during the same time and alternately with the above patients, were, in accordance with the Poona procedure, treated by the current expectant method, and of these patients 101, or 67·78 per cent., recovered. The experiment having thus shown that the application of "vaccine therapy" made little difference, Prof. Wright and the other workers at the Hospital recorded

[1] *Vide* J. Freeman, M.D., Assistant in the Department of Therapeutic Inoculation at St Mary's Hospital, in the *Proceedings of the Royal Society of Medicine*, 1910, vol. III; or in J. Nachbar's "Vaccine therapy: its Administration, Value and Limitations," 1910 (Longmans, Green and Co.), pp. 99 and 100.

[2] *Vide* Sir A. E. Wright's address in the *Proceedings of the Royal Society of Medicine*, 1910, or in Nachbar's work just quoted, pp. 13 and 32.

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that the treatment "was absolutely ineffective," and they recognised that the verdict, in respect of the treatment tried, was final.

On the subject as to whether information of that definite character was obtainable by the "*experiential method*" the following statements by the authors, partly quoted already, contain, no doubt, the reply (*The Lancet*, Dec. 14, 1912, p. 1637): "The experiential method will be inapplicable in the case where the substantive and control cases are distinguished by only a very small average difference." "The capacities of the human intellect are unequal to the task of carrying in mind and weighing one against the other a long procession of substantive and a long procession of control cases." (*The Lancet*, Dec. 21, 1912, p. 1701): "We have already seen that our inability to carry in mind and evaluate such long sequences of cases as are, in the case here in question, indispensable, makes it futile to employ the experiential method for the detection of fine differences," that is, as in the above instance of pneumonia, for the detection of ineffective lines of treatment. It is also the case that the "experiential method" allows of the complementary misapprehension, that is, of the results of treatments, in reality ineffective, being believed for a long time to be indications of success.

These facts notwithstanding, the application of the other mode of study. "the statistical method," by which the Witwatersrand information was successfully obtained, is not countenanced by the authors under review, as has been observed already; and the grounds leading to their opinion, as well as the purport of the general analysis of methods, by which the publication of the Witwatersrand result has been prefaced by them, are stated as follows (p. 1701): "These general considerations have prepared the way for bringing forward the suggestion that the ideal of minutely accurate quantitative statement which is always floating before the vision of the statistician should in the field of clinical medicine be frankly abandoned. This would mean recognising that it is, in medicine, impossible by the method of cumulative experiments either (*a*) to detect minute differences, or (*b*) to arrive in any case at any accurate quantitative conclusions[1]. The frank recognition of this would, in point of fact, leave the practice of medicine practically unaffected. For, both in the case where the question arises whether we are, or are not, to apply a method of treatment which is doubtfully effective, and in the case where we have to elect between two alternative lines of treatment which are almost equally effective, it will not seriously matter what choice we make."

[1] Cf. Section II, pp. 88–93 *supra* and the results of the Witwatersrand evaluation.

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The latter conclusion will probably meet with some dissentient opinion, as the choice is apt to matter from the patient's and also from the physician's points of view. In the "vaccine therapy" treatment with which the authors were concerned in the Report referred to, the plans devised notoriously involve complicated procedures for the operators with a correspondingly great amount of bodily pain and trouble, and material sacrifices for the patient. There is sample-taking and microscopic and other scrutiny of the patient's lesions and blood; "autogenous vaccine," simple or "polyvalent," is manufactured in a laboratory for the individual use of the patient under treatment, if circumstances permit, and repeated appointments are required for injections of that "vaccine" and for one or several successive sample-takings of blood after each injection; technical work is again gone through in a laboratory, subsequent to each sample-taking, for the determination of the "opsonic index" and the plotting out of an "immunisation curve," and for the selection of the time and dose for the next injection, and so on. The knowledge that a complex plan of treatment like the one outlined, or a treatment on similar lines, does not exceed in efficacy an "expectant method," and is, in fact, "absolutely ineffective," as in the particular instance on pp. 77–78, must necessarily be considered essential; and even were a treatment devised for application by practising physicians in all respects simple, it must still be thought desirable to know, from the scientific and practical standpoints, whether its curative effects are real.

Bengal United Service Club, Calcutta,
February, 1915.