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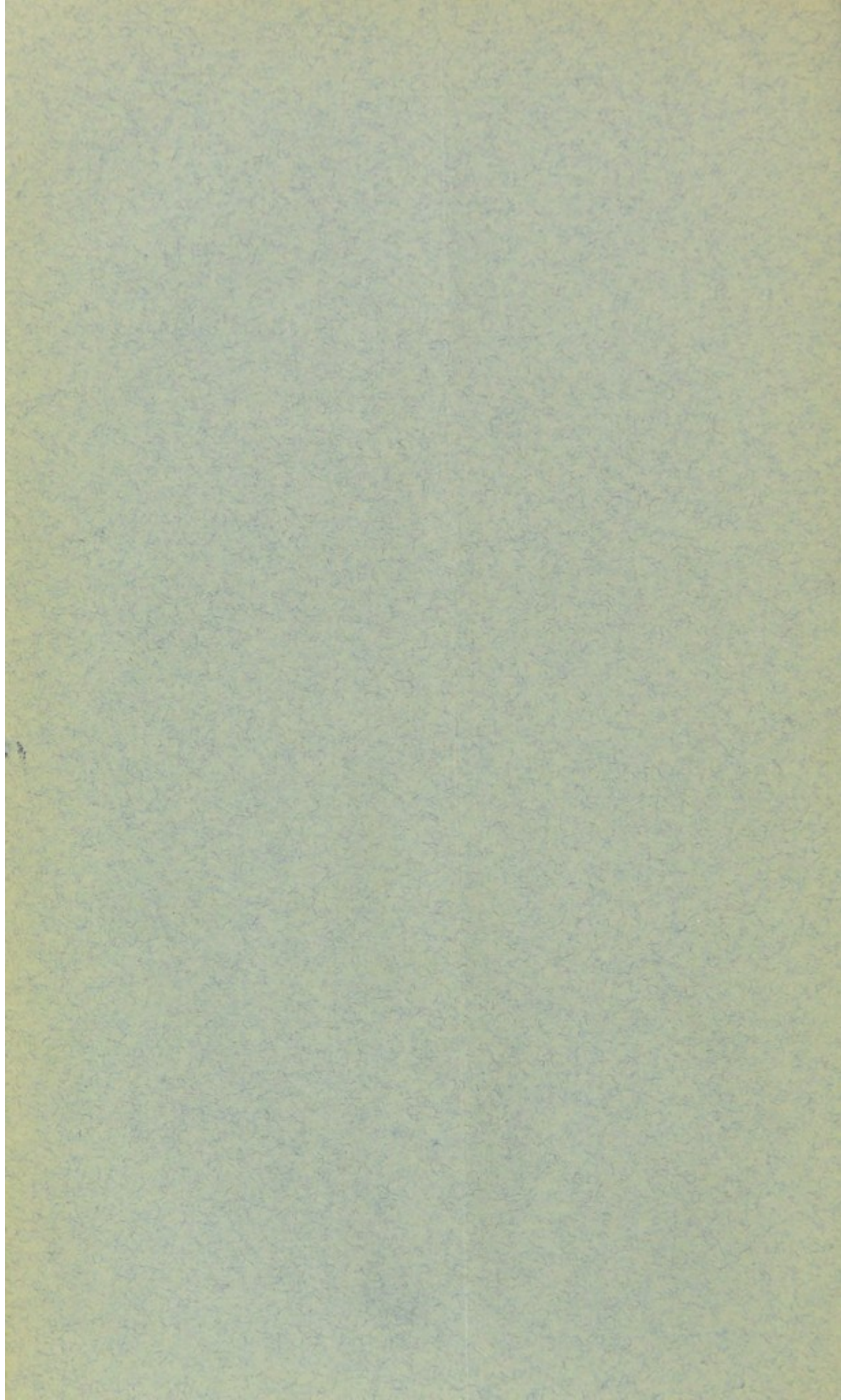
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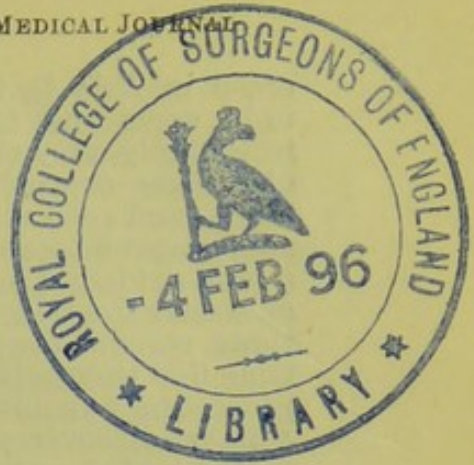
BY
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BY W. M. HAFFKINE, Sc.D.

THE PRINCIPLES OF PREVENTIVE INOCULATION.

BEFORE dealing with my work in India allow me to recapitulate here the chief circumstances connected with the problem of preventive inoculation. After experimental medicine had been inaugurated the efforts of bacteriologists remained for a long time concentrated on that classical form of infectious disease, splenic fever, in connection with which the fundamental laws of the new science have been elucidated. It was reserved to Dr. Koch to discover in the formation of spores the means by which the microbe of this disease, when outside the animal body, protected itself against the external world. Shortly after this it has been found that the spores not only preserved the life, but also all specific properties of the microbe, and that it is owing to this circumstance that the bacillus of anthrax is one of the most constant species of schizomycetes known. On the other hand, a great mutability of properties has been discovered in all microbial virus not possessing spores, or in which sporification is arrested for a certain period. On the bacillus of chicken cholera Pasteur observed for the first time the loss of virulence in a microbe of a high infectious power. Since then it has been found that the virus of every disease, although it remains constant in the nature of the affection it produces, varies without limit in virulence; that in one and the same specimen this property can be diminished or strengthened by special proceedings, and that in this we have the greatest part of the explanation of the variability of disease in individuals and communities.

This variation in virulence was familiar to all observers, and from time immemorial has been turned to advantage by the peoples of the East. It is known that the practice of inoculation against small-pox was originated from the observation that there are mild and severe epidemics of the disease, and that people affected in mild years remained immune in severe years. At the appearance of a non-fatal epidemic every one wished to get through the disease, and not only did not avoid infected people, but sought their presence and a close contact with them. A practice thus

arose in Asia to take artificially the infectious stuff from mild cases and to communicate it to healthy people. Unfortunately, very often in a resistant patient a mild semblance of disease conceals an infectious agent of unexpected virulence, and such virus, on being transferred to a less resistant subject, produces a terrible attack, not infrequently leading to a fatal epidemic in the community. In view of this dangerous character the religious laws of the Hindus, by special regulations, restrict the practice, and the Government from time to time find themselves under the necessity of instituting legal proceedings against those who apply the method. As soon as Jenner discovered an attenuated virus, and showed the method of keeping it in the desired strength by passage through the calf, the practice became immediately safe and certain, and the Eastern method has been abandoned in the whole civilised world.

In the case of small-pox, however, as in the case of rabies or syphilis, the disease is communicated from individual to individual, and the morbid virus is cultivated exclusively in the animal body, under conditions varying little in their character. The modifying influences become infinitely greater when a virus can grow in a saprophytic form and is exposed, in the interval between visiting animal bodies, to the vicissitudes of nourishment, oxidation, light, temperature, which are to be found in the external world. Even microbes, like that of anthrax or tetanus, provided with protective spores do not escape this law, and one finds in Nature their specimens presenting a very large scale of modifications; but there appears to be no limit to variability in infectious virus leading a saprophytic life and deprived of the sporulating faculty. The microbe of cholera is one of the most striking examples of this phenomenon.

VARIABILITY OF THE CHOLERA MICROBE.

When the cholera bacillus was first discovered, eleven years ago, its properties were described with great precision, which helped in concentrating for a long time all studies on well-defined and carefully-chosen specimens. Little by little, as the field of investigation grew larger, a number of varieties have been found with characteristics differing so largely as to annihilate almost completely the original description. When we open the intestines of deceased cholera patients and investigate the microbes there, the adopted methods will bring to the surface vibrios in which the external form, instead of the characteristic comma or spirillum, will vary between a coccus and a straight thread; the number and disposition of the cilia, the secretion of acids, the form of growth in broth, will vary; instead of giving in gelatine a discrete and well-defined figure of liquefaction, the variation will extend from the complete loss of this property to a rapid dissolution of the whole of the medium; there will be varieties which grow luxuriantly in given media, and others which do not grow there at all; some will be phosphorescent in the dark, and others not; some will give the indol reaction, and others will be deprived of this property, and so on. The first thing to be done is carefully to select amongst these the most typical specimens, rejecting the others, and then we try their pathogenic power. We shall find such a divergence in strength that the extreme forms will not be believed to be of the cholera species. There will be commas deprived of any

virulence demonstrable on animals, and others which kill the most resistant species. Some will be fatal to a guinea-pig at a dose of $\frac{1}{100}$ of a culture tube, and others harmless in doses 500 times stronger. The average comma dies out when introduced under the skin to an adult animal; others will spread in the system and give a fatal septicæmia. The ordinary comma will be without effect on birds; but several specimens have been isolated, and believed to be typical, which easily killed pigeons by hypodermic or intramuscular injection. I believe to be of great value the method worked out by Pfeiffer for comparing all such varieties with one selected as typical, and which he employed for the preparation of an antitoxic serum. This method will be found of efficient help in distinguishing specimens of the greatest affinity with the average cholera comma. But once such specimens are selected and their particular properties studied, they begin to change from the first day they are introduced into the laboratory, and no calculation based on these studies is possible. In a case quoted by M. Metchnikoff, the proportion of initial power of the microbe, and the strength it showed at a later trial, was of 75 to 1, the microbe having gradually sunk to $\frac{1}{5}$ of its initial virulence. If, for producing a certain infectious, or preventive, or curative effect, we had to use, in the first days, 1 c.cm. of this culture, later on a dose smaller than 75 c.cm. would be without effect, and the changes of the microbe would certainly continue still further.

THE SYSTEM FOLLOWED IN INDIA.

In all operations on men done in India we used exclusively living cholera virus, for the reason that sterilised cultures or products of cultures, as a rule, produce an effect of a far shorter duration than living microbes. The symptoms in anticholera vaccination consist in localised swelling and pain in the side, at the seat of injection, and in an attack of fever. The pain is felt only on pressure, and its amount is such as to prevent a soldier from putting on his belt for a couple of days, and a coolie worker from doing work involving bending the body or stretching otherwise the interested tissues. But the intensity of the symptoms and their duration vary in direct proportion with the virulence of the cultures and the doses administered. On the other hand, in all forms of preventive treatment the amount of protection depends on the intensity of reaction produced in the subject. A small dose of a given virus, or else the same dose of a weakened virus, will produce less reaction and afford less protection; a higher dose of the same virus, or the same dose of a stronger virus, produces more reaction and affords a higher and, probably, more lasting protection.

In the first period of my work in India I adopted $\frac{1}{20}$ of a standard culture, of a given strength, as a dose for an adult person. The reduction of this dose by a small fraction is sufficient not to produce in the subject any noticeable reaction at all. Later on, after the first series of observations was collected, I was induced to apply a treatment by increased doses of a stronger vaccine. A series of experiments and observations, for which I am especially indebted to Dr. Arthur Powell in Cachár, have been instituted with this object. It has been

found that with the increase of the doses the amount of local pain, and especially that of general discomfort, was proportionately increasing, the fever was of a more severe type, and lasted longer, disabling the men for work for four, five, and more days. In Dr. Powell's mind there remained no room for doubt that with the increase of the doses the operation would become fatal to man. The limit of the doses adopted for the strength of the vaccines we used was between $\frac{1}{2}$ and $\frac{1}{3}$ of a culture.

From this it will be seen that it is a matter of vital importance, a *sine qua non*, in order not to exceed or fall below the intended reaction, to have a method of fixing the properties of this modifiable microbial virus, to keep it at the same degree of activity, and to know exactly the amount of power contained in a given dose.

The general method worked out for that purpose consists in finding out an animal susceptible to the given virus, and discovering the conditions in which the virus can be transplanted from animal to animal without interruption and without having recourse to artificial media. Jenner's method in its essential features remains intact, and our proceedings correspond exactly to the cultivation of vaccinia from calf to calf, or from vaccinated man to man. The particular difficulties which were connected with the diseases for which vaccines have been worked out, have been treated in the technical literature, and I believe there is no room for dealing with the matter in the present lecture. The terms virus and vaccine are still used in the same sense as they were used in regard to small-pox. The infectious substance from a subject who naturally fell ill from a disease—a small-pox patient, a rabid dog, a person affected by cholera—is a virus; the Eastern practice of inoculating small-pox virus against small-pox is variolisation. On the other hand, the substance cultivated under conditions intended to keep the morbid agent at a given and fixed state of virulence, permitting the use of it with safety and sure measurement, such as Jenner's calf lymph, or Pasteur's rabies emulsions, is a vaccine, and the application of such substances for preventive treatment is called—following the suggestion of Pasteur and in honour of Jenner who first used the term—vaccination.

The method which I worked out for the preparation of two cholera vaccines, one weakened and a second one strengthened, has been described in my previous lecture delivered in this hall three years ago.

It is the difference between vaccination and variolisation that distinguishes the method which I have applied in India from that tried in Spain by Dr. Jaime Ferran in 1885. Ferran's operations consisted in inoculating vibrios collected from cholera patients. The method employed in India consists in inoculating a vaccine worked out following the proceedings of Jenner and Pasteur.

The difference between the two operations is such that Jenner's method has survived criticism and the test of a century's daily application, and has been vastly generalised; the other method, imitating the inoculation of small-pox virus against small-pox, had to be abandoned on every occasion where attempts to apply it were made. At present there is not a single practice, in therapeutics or in preventive medicine, where the use of living virus taken directly from infectious persons, is allowed, whether on individual

subjects, or, still less, in application to whole populations. The attempts made by Toussaint, previously to Pasteur's operations, of inoculating anthrax virus against anthrax, died out without the slightest possibility of practical application. In the treatment against anthrax by Pasteur's method, an excessive attenuation of the first anthrax vaccine, which was permitted to fall below the desired amount of virulence, caused on some occasions serious accidents. The neglect to make strict distinction between vaccine and virus was responsible for a disaster which occurred in the inoculation of sheep against anthrax in the south of Russia. The misadventure led to a prolonged suspension of all anthrax inoculations in that country, and partly in Austria-Hungary, and Italy; but one shudders to think of any similar accident occurring, instead of a flock of sheep, in a regiment of men. The attempts at inoculating cholera virus against cholera by Ferran had to be stopped by the Spanish Government, and was disapproved by all commissions sent out to investigate these operations by the Governments of Spain, Great Britain, France, Russia, Belgium, a result which was used as one of the arguments, seven years later, by the Government Committee in Russia, in refusing to admit the trial of my method of protection against cholera. On the other hand, *vaccination* against rabies has been going on these ten years with a marvellous precision, and has been already applied to about 15,000 people in France alone; innumerable flocks of domestic animals are vaccinated yearly in different parts of the world, against anthrax and pig-measles. And now we come to record the results of upwards of 70,000 injections of living bacteria, performed on 42,179 people, without having to record a single instance of mishap or accident of any description produced by our vaccines.

INDIAN EXPERIENCES.

My actual work in India lasted twenty-nine months, between the beginning of April, 1893, and the end of July, 1895. During this period the anticholera vaccination has been applied to 294 British officers, 3,206 British soldiers, 6,629 native soldiers, 869 civil Europeans, 125 Eurasians, and 31,056 natives of India. The inoculated people belonged to 98 localities in the North-West Provinces and Oudh, in the Punjab, in Lower Bengal and Behar, in the Brahmaputra valley and in Lower Assam. No official pressure has been brought on the population, and only those have been vaccinated who could be induced to do so by free persuasion. In every locality efforts were made to apply the operation on parts of large bodies of people living together, under identical conditions, in order to compare their resistance in outbreaks of cholera with that of not-inoculated people belonging to the same unit of population. This object has been obtained in 64 British and native regiments, in 9 gaols, in 45 tea estates, in the fixed agricultural population of the villages parallel to Hardwar pilgrim road, in the *bustees* of Calcutta, in a certain number of boarding schools where the parents agreed to the inoculation of their children, in orphanages, etc. The vast majority of inoculated people lived thus under direct observation of the sanitary and medical authorities of India.

Cholera broke out in the inoculated localities from 1 to 459 days after the operation, and careful statistics of occurrences were immediately collected by the corresponding civil and

military and medical authorities, as well as by myself. The whole number of observations made, as they were at the time when I left India, may be grouped in three categories: (I) the first, containing unsuccessful results, or such in which no conclusion was possible; (II) the second, with results slightly favourable to the method; and (III) the third with results satisfactory.

I. To the first category belong observations made on a series of tea estates in Assam. The coolie workers on these plantations live in well-defined isolated bodies, distant from the villages, and not mixed with outside population. The inoculated individuals were scattered among the non-inoculated, and shared with them food, water supply, and all other conditions of life. In all instances belonging to this category the people had undergone only one part of the preventive treatment—namely, were inoculated with first attenuated anti-cholera vaccine given in maximal doses; the second inoculation, with the final vaccine, was applied after the cholera season had ceased. The disease occurred from one to six months after the first inoculation with the following results.

ADAM TILA.

657 non-vaccinated had no cases.
318 vaccinated had 2 cases (0.63 per cent.) with 1 death (0.31 per cent.).

KALACHERRA.

520 non-vaccinated had 4 cases { 0.77 per ct. } with 3 deaths { 0.58 per ct. }
211 vaccinated had 1 case { 0.47 per ct. } with 1 death { 0.47 per ct. }

CHARGOLA.

1,007 non-vaccinated had 3 cases (0.30 per cent.) with 1 death (0.10 per cent).
291 vaccinated had no cases.

PALLARPUND.

1,170 non-vaccinated had 2 cases (0.17 per cent.) with 2 deaths (0.17 per ct.).
451 vaccinated had no cases.

LUNGLA.

2,050 non-vaccinated had 3 cases (0.15 per cent.) with 3 deaths (0.15 per ct.).
421 inoculated had no cases.

BURNIE-BRAES, LOOBACHERRA, KALAINCHERRA, AND SANDHURA.

Number of non-vaccinated not stated; had 11 cases with 5 deaths
677 vaccinated had no cases.

II. To the second category, with results slightly favourable, belong (a) two observations made on people inoculated with maximal doses of the first vaccine only, cholera occurring a short time after the inoculation, and (b) two observations on people inoculated with weak doses of both vaccines, cholera occurring thirteen to fifteen months after vaccination had been applied.

(a) The 2nd Battalion Manchester Regiment at Dinapore 2 to 6 days after injection of first vaccine only:

729 non-inoculated had 6 cases (0.82 per cent.) with 3 deaths (0.41 per cent.).

193 inoculated, no cases.

Degubber Tea Estate, 3½ months after inoculation of first vaccine only:

228 non-inoculated had 2 cases (0.88 per cent.) with 1 death (0.44 per cent.).

387 inoculated, no cases.

(b) The British troops in Cawnpore, 13 months after inoculation with small doses of both vaccines:

797 non-inoculated had 19 cases (2.38 per cent.) with 13 deaths (1.63 per cent.).

75 inoculated, no cases.

The East Lancashire Regiment in Lucknow, 14 to 15 months after inoculation with small doses of both vaccines:

640 non-vaccinated had 120 cases { 18.75 p. ct. } with 79 deaths { 12.34 p. ct. }
133 vaccinated had 18 cases { 13.53 p. ct. } with 13 deaths { 9.77 p. ct. }

III. To the third category, with results satisfactory, belong (a) observations on maximal doses of first (mild) vaccine made

on the Karkurie and Kalain Tea Estates, one to three months after inoculation; (b) observations on small doses of both vaccines, made on the prisoners of the Gaya Gaol inoculated during an epidemic; (c) observations on middle doses of one and of both vaccines in the *bustees* in Calcutta, collected during a period of 459 days, and finally, (d) the observation made quite lately on the Kassia Hill coolies, from the survey party of the Assam-Burmah Railway.

(a) Karkurie Tea Estate, 2 to 3 months after inoculation with strong doses of first vaccine only:

203 non-inoculated had 5 cases (2.46 per cent.) with 2 deaths (0.98 per cent.).

409 inoculated had 1 doubtful case (0.24 per cent.) with 1 death (0.24 per cent.).

Kalain Tea Estate, 1 to 3 months after inoculation with strong doses of first vaccine only:

1,375 non-inoculated had 23 cases (1.67 per cent.) with 11 deaths (0.8 per cent.).

681 inoculated had 2 cases (0.29 per cent.) with 1 death (0.15 per cent.).

(b) In the Gaya Gaol the inoculations were for the first time applied in a prevalent epidemic, and very weak doses of relatively weak vaccines have been used. The gaol contained over 400 inmates. After 6 cases with 5 deaths had occurred, a half of the prisoners, including aged and young people, women, children, patients from the hospital, and people affected with premonitory diarrhoea, was inoculated; the other half, of an exactly similar composition, was left uninoculated. The result was a gradual disappearance of cases and deaths among the inoculated, the difference in susceptibility having gradually increased during the period of 10 days necessary for the two vaccines to produce their full effect.

During the first period of 5 days necessary for the 1st inoculation:

210 non-vaccinated had 7 cases } 3.33 per ct. } with 5 deaths } 2.38 per ct. }

212 vaccinated had 5 cases } 2.36 per ct. } with 4 deaths } 1.89 per ct. }

During the second period of 5 days necessary for the 2nd inoculation:

197 non-vaccinated had 9 cases } 4.57 per ct. } with 4 deaths } 2.03 per ct. }

206 vaccinated had 3 cases } 1.46 per ct. } with 1 death } 0.48 per ct. }

During the last 4 days of the epidemic:

192 non-vaccinated had 3 cases (1.56 per cent.) with 1 death (0.52 per cent.).

201 vaccinated had no cases.

The total results are as follows:

The non-vaccinated half had } 9.90 p.c. } of cases with } 4.95 p.c. } of deaths.

The vaccinated half had } 3.86 p.c. } of cases with } 2.41 p.c. } of deaths.

The treated prisoners showed a reduction of 2.56 times of cases, and of 2.05 times of deaths. I wish to call your attention to the fact that the inoculations had been applied in this instance not before the epidemic, but a week after it had actually broken out, in order to arrest it, and to cure, so to say, the community from the disease. The reduction of deaths by one half will therefore justify the application of the method in all similar conditions, there being up to now no other method known in medicine by which such an effect could be obtained. We shall see directly an instance of the same kind when far higher results have been obtained by an application of stronger doses.

(c) In the *bustees* situated round the tanks in Calcutta, where cholera exists in a permanent state, the disease occurred in 36 houses with inoculated people. In each of these houses there was one part of the family inoculated and another not. The observations were continued for 459 days, with the following results:

During the first period of 5 days subsequent to the inoculation with first vaccine cholera occurred in 8 houses:

75 non-inoculated had 5 cases (6.66 per cent.), with 3 deaths (4 per cent).

52 inoculated had 3 cases (5.77 per cent.), with 3 deaths (5.77 per cent).

During the second period of 5 days subsequent to the second inoculation cholera occurred in 2 houses:

8 non-inoculated had 2 cases (25 per cent.), with 2 deaths (25 per cent.).

17 inoculated, no cases.

After the 10 days necessary for the preventive treatment had expired, and up to the 459th day, the disease visited 26 houses, with the following results:

263 non-inoculated had 38 cases (14.45 per cent.), with 34 deaths (12.93 per cent.)

137 inoculated had 1 case (0.75 per cent.), with 1 death (0.75 per cent), in a child that had not been brought up for the second inoculation.

Thus, after the expiration of the first 10 days, the inoculated members of the affected houses had 17.24 times fewer deaths and 19.27 times fewer cases than the non-inoculated inhabitants of the same houses, and this proportion was maintained up to the 459th day after vaccination.

(d) The last observation comes from the Brahmaputra valley, where Surgeon-Captain Hare, of the Indian Medical Service, my co-worker during the last eight months of my stay in India, is continuing now the work of inoculation for the Assam Government. Dr. Hare's full account of this observation has not yet reached me, but from a communication of the Health Officer of Calcutta, and from the Indian papers, it appears that 350 Khassia Hill coolies had been collected for the survey party of the Assam-Burmah Railway and put under the escort of a detachment of Goorkhas, when cholera broke out amongst them. The largest part of the coolies immediately submitted to the preventive inoculation, the rest remained uninoculated. The result was that among the not inoculated minority there were 34 cases, with 30 deaths; whereas the inoculated had 4 fatal cases. In this instance, also, the inoculation appears to be applied not as a preventive but as a curative for an existing epidemic, and the result, if the information is complete, has been the reduction of the mortality of more than seven times.

SUMMARY.

The following seems to be a summary of the results observed up to now:

1. In all those instances where cholera has made a large number of victims, that is to say, where it had spread sufficiently to make it probable that the whole population, inoculated and uninoculated, were equally exposed to the infection, in all those places the results appeared invariably favourable to inoculation.

2. The treatment applied after an epidemic actually breaks out tends to reduce the mortality even during the time which is claimed for producing the full effect of the operation. In the Gaya Gaol, where weak doses of a relatively weak vaccine had been applied, this reduction was to half of the number of deaths; in the coolies of the Assam-Burmah survey party, where, as far as I can gather from my preliminary information, strong doses have been applied, the number of deaths was reduced to one-seventh. This fact would justify the application of the method independently of the question as to the exact length of time during which the effect of this vaccination lasts.

3. In Lucknow, where the experiment was made on small doses of weak vaccines, a difference in cases and deaths was

still noticeable in favour of the inoculated fourteen to fifteen months after vaccination, in an epidemic of exceptional virulence. This makes it probable that a protective effect could be obtained even for long periods of time if stronger doses of a stronger vaccine are used.

4. The best results seem to be obtained from application of middle doses of both anticholera vaccines, the second one being kept at the highest degree of virulence obtainable.

5. The most prolonged observations on the effect of such middle doses were made in Calcutta, where the mortality from the 11th up to the 459th day after vaccination was, among the inoculated, 17.24 times smaller, and the number of cases 19.27 times smaller than among the not inoculated.

RESULTS OF ANTICHOLERA INOCULATION.

The evidence accumulated up to now is decidedly in favour of the anticholera vaccination, and my own conviction in the matter is more and more strengthened. The special responsibility, however, which lies on me in this subject forces me to point out that the number of observations is not yet very large, and that it is most desirable that the results obtained should be further confirmed by new and more ample information. At the same time, you will find it, I hope, pardonable on my part if, before finishing the review of the results, I cite the opinion expressed on the subject by the scientist who himself accomplished the first and the most difficult part of the cholera problem, and whose discovery was the starting point of the whole of the modern researches on cholera.

When recapitulating with Professor Koch the data of my report to the Government of India, I said that, in my idea, the results tend to prove the efficacy of the method, but that I feel necessary to do all in my power in order to confirm them by new observations, I was most happy to learn that, for Professor Koch, the demonstration was already complete; that he believes the protective power of the method to be established finally by the observations collected in India up to now; that further perfections and simplifications may be possible, but that the main question at issue, the chief part of the problem, is solved by the facts recorded in the above report. Professor Koch gave his kind permission to quote these decisive conclusions in this Hall and to use the very terms I used, and he added that, in his conviction, the chief struggle against cholera must certainly take place on the banks of the Ganges, in the home of the disease; that this struggle is to be effected by preventive inoculation, and that he sees in the application of this method the way in which, by gradually restricting the area of the extension of the disease, it shall be brought to such a limit when it will become possible to control its prevalence by simple measures of a sanitary police.

PROGRAMME FOR NEXT OPERATIONS.

Allow me now to consider the question whether the new facts brought to light during my absence in India ought to be incorporated into my method of anticholera vaccination. The treatment by antitoxic serum, which by now may be considered as having proved a decided success in diphtheria, could not, unfortunately, be substituted for a preventive vaccination, its effect being rapidly worn out by the system. According to the observations made up to now, neither the

antidiphtheritic nor an anticholera serum could be used for protecting a population against an epidemic lasting more than a few days, not to speak of an endemic prevalence of the disease. The question stands otherwise as regards the possibility of treatment in individuals actually affected with cholera. Although in this particular disease we have against us the great rapidity with which the symptoms take hold of the system, the antitoxic serum has accomplished in other instances such excellent results that there is every possibility of its being beneficial in the case of cholera also. I intend, therefore, on my return to India, to give, in connection with the physicians of the country and with the help of Professor Pfeiffer from Berlin—who most kindly put at my disposal all his experience in the matter, as well as a supply of a very active antitoxic serum—an extensive trial to this method.

In case a simple application of the antitoxin serum proves to be insufficient to stop the rapid course of the symptoms, I intend to combine it with intravenous saline injections and to prolong in this way the period left for treatment. And if in this case also the attempt should fail, I shall try to utilise the new therapeutic for accelerating the effect of my vaccines in a manner which I will characterise in a few words. We have seen up to now that in the places where anticholera vaccination has been applied in a prevalent epidemic, the total number of deaths was reduced from two to seven times in comparison with the deaths in the non-inoculated, but the effect of the treatment was *nil* in the first four or five days after the first inoculation. There is the possibility that, by injecting a mixture of my vaccines with a powerful antitoxic serum, the mortality may be reduced also in the first days after the treatment, the serum arresting the disease for the time necessary for the vaccines to produce their full effect. The admixture of antitoxic serum with the vaccines may mitigate the vaccinal reaction, as has been suggested to me by Professor Wright from Netley, and this reduction of reaction may possibly reduce the amount of active protection conferred by the vaccines. A series of experiments have therefore been undertaken in the Netley bacteriological laboratory in order to investigate this important question.

Mr. Chairman and Gentlemen,—On the day when I came back from my expedition to India, I found my former chief, M. Pasteur, lying on his bed of death. Whatever might have been his appreciation of the work done in India, there can be only one desire on my part, that all the honour for the results which may possibly come out of my efforts, should be referred to him, to his sacred memory.

To the Government of India, the gentlemen of the Indian and Army Medical Staff in India, to Professor Hankin in Agra, Dr. Powell, and especially to Dr. Simpson, the eminent health officer of Calcutta, I address my hearty expressions of gratitude for the assistance they have given me in carrying out my work. I beg these gentlemen, if my present words are destined to reach them, to accept this public acknowledgment that without their most efficient help I would have never been able, with all my individual powers, to accomplish in India the smallest part of the work which has been done.

I also beg the Chairman and the organisers of the present meeting to accept my best thanks for having given me this opportunity of making the present communication.