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W. M. HAFFKINE, C.I.E.

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"On Preventive Inoculation."* By W. M. HAFFKINE, C.I.E. Communicated by LORD LISTER, P.R.S. Received June 5, —Read June 8, 1899.

My Lord and Gentlemen,—The most important modern methods of prophylactic treatment are based upon the fact that an attack of disease from which an individual recovers leaves in him a condition of relative immunity to another attack.

The method of turning this result to advantage for the protection of whole communities was first demonstrated to us by Mahomedan physicians, to whom the world thus owes what proved to be one of the most fertile principles of modern science.

The successes of Jenner and Pasteur, who utilised cultivated virus for preventive treatment, have led to a general conception that there is the possibility of creating artificial immunity to diseases by treating the organism with morbid virus rendered by some special means harmless.

This view involves a generalisation which led to a considerable

* The paper as published here, after final revision by the author, differs in some details from what has appeared in the 'Lancet' of June 24, and 'British Medical Journal,' of July 1, 1899, under the title of "A Discourse on Preventive Inoculation, delivered at the Royal Society, London, on June 8, 1899."

amount of disappointment, as the application of the principle in a number of instances did not give the expected results.

Derivatives from Microbic Virus and their Effect.

When we cultivate a pathogenic micro-organism in a liquid medium, two different elements are obtained mixed together : the bodies of the microbe and the liquid which it has modified, and into which it has secreted its own products.

A modification of the entire preparation, as represented by this mixture, can be first of all obtained by filtering and separating the two elements just mentioned, and considering each of them by itself.

Or else the two can be left together, and only the vitality of the microbe destroyed by some physical or chemical agent.

Or the constitution and the properties of each, or of both of these elements can be, to a desired degree, altered by the admixture of chemicals, or by subjecting them to physical processes.

Or, the vital and pathogenic properties of the microbe can be modified by artificial breeding, and then the microbe itself, or the products of such a modified microbe, used for treatment.

The immediate effect which a given virus or its derivate produces on an animal differs with the kind of virus taken, the process of modification to which it has been subjected, and the species of animals upon which it is used. The following instance may give an idea of these variations.

The ordinary Indian grey, as well as the brown, monkey are susceptible to the plague virus, and may contract a fatal disease from being simply pricked with an infected needle. The rabbit and guinea-pig are also susceptible to the disease. The horse, on the contrary, contracts no fatal disease after being infected even with large doses of the living virus.

If, however, a plague culture be heated and the microbes killed in it, the relative susceptibilities of the monkey and the horse seem to be reversed, the guinea-pig remains comparable with the monkey, while the susceptibility of the rabbit is now like that of the horse, and not, as previously, like that of the monkey.

It will require, according to several observers, a very large dose of virus so treated to produce in the monkey or in the guinea-pig any marked rise of temperature, or any alteration of the skin at the seat of injection ; while the horse answers to the injection by almost as brisk an attack of fever as if the virus were a living one, and at the seat of inoculation a tumour is produced which, if the dose be at all considerable, may lead to a complete mortification of the tissue. The rabbit similarly answers to the injection by an attack of fever and by the formation of a hard tumour at the seat of injection.

As varied as is the immediate effect of different forms of virus upon

different animals, so varied is the result of the application of such virus from the point of view of immunity conferred by it.

There are animals in whom the inoculation leaves no lasting effect whatever. In others a very temporary immunity is created, vanishing entirely in a few days. In other cases again, a condition appears that produces the impression that, after the treatment, the animal has become more susceptible to a subsequent infection than is a normal animal not so treated.

And lastly, there may be found animals in which the same virus will produce a firm and enduring immunity.

In general I believe it to be admissible that in the case of every disease, and with regard to every species of animal, a form of prophylactic treatment may be found that will produce immunity in that particular case; but that same method of treatment may or may not be applicable to another animal or to another disease affecting the same animal.

It is the failure of taking into account this variation of circumstances that, I believe, more than anything else has checked the success of a number of experimenters.

Immunity from Attack, and Resistance to actual Symptoms of Disease.

The study of the anti-cholera inoculation in India has revealed a new problem in the subject of prophylactic treatment.

The particular character of cholera epidemics, which appear unexpectedly, do not last, and in places where they are permanent, are spread and scattered over large areas, makes the study of that disease and the demonstration of the effect of a preventive treatment in its case a matter of much greater difficulty than is the case in localised contagious diseases, like smallpox, or in plague; and although a large amount of material has been collected already, it is desirable that further observations be still added to the present ones confirmatory of the results obtained.

The information collected permits, however, already of pointing out very important features in the working of the anti-cholera inoculation.

The most extended and continuous observations on the subject were organised by the Municipality of Calcutta, upon the enlightened initiative of Professor W. J. Simpson, late Health Officer, and under his continuous supervision, as well as my own. These observations refer to the cholera stricken suburbs of Calcutta, the so-called "busties" or groups of huts situated round the tanks, where rain-water is collected during the monsoon.

Some 8000 people were inoculated in those localities, and for two years observations were made and the results collected as to the occurrences of cholera in the huts inhabited by the inoculated.

In the vast majority of cases there lived in the same families members who had not been inoculated, together with others inoculated, and the possibility thus presented itself of comparing the incidence of the disease in individuals of the same households, exposed as much as it is possible to the same chances of infection.

During the time under observation cases of cholera occurred in seventy-seven huts. The interval which elapsed between the application of inoculation in each particular hut and the occurrence of cholera in it was as follows :—

Among *uninoculated* members of the families cholera occurred—1, 2, 3, 4, 5, 6, 9, 12, 13, 15, 17, 22, 34, 37, 44, 57, 62, 63, 71, 95, 99, 109, 114, 118, 119, 120, 129, 132, 139, 143, 162, 189, 191, 203, 240, 251, 271, 281, 284, 300, 309, 318, 319, 334, 356, 359, 362, 370, 372, 378, 383, 384, 389, 391, 393, 394, 401, 404, 408, 416, 433, 446, 448, 453, 472, 493, 498, 673, 720, 723, 724, and 738 days after the inoculation of the other members of these families. Among the *inoculated* members of the families cholera occurred—0, 2, 3, 4, 219, 421, 459, 512, 688, 735, and 738 days after their inoculation.

Thus for a period of 738 days, cases of cholera occurred among the uninoculated, so to say, at all intervals after the date of inoculation ; whereas the figures referring to the inoculated showed a striking variation of the incidence when compared at various distances from the time of inoculation. Cases continued to occur among the inoculated for a period of four days after the treatment, and then for 416 days they practically remained free from the disease, only one death from cholera having occurred among them during that time. From the 421st day up to the end of the observations six cases occurred among them again.

The relative immunity in the inoculated considered separately during those three periods shows that during the first four days the inoculated had proportionately 1·86 times fewer deaths from cholera than the uninoculated.

During the period between the 5th and 420th days, *i.e.*, for a period of nearly fourteen months, the number of deaths among the inoculated was 22·62 times smaller than amongst the uninoculated. And for the rest of the time under observation the proportion in their favour fell to 1 to 1·54.* The plan has since been formed of trying the effect of larger doses and of stronger vaccines, in order to obtain a more lasting protection.

While thus the absolute number of cases and deaths from cholera appeared so strikingly influenced by inoculation, the peculiarity that became apparent from the observations in Calcutta as well as in other

* *Vide* Health Officer's Report to the Chairman of the Calcutta Municipal Corporation, reprinted in the 'Indian Medical Gazette,' vol. 31, No. 8, August, 1896.

places was that the proportion of deaths to cases was not changed by the treatment.

Thus, in the observations made in a camp of coolies of the Assam-Burmah Railway Survey, out of thirty-three attacked among the uninoculated portion of the camp twenty-nine died, and of four attacked among the inoculated all four died.

In the Durbhanga prison out of eleven uninoculated attacked all eleven died, while five inoculated attacked lost three.

In the Gaya gaol twenty uninoculated attacked lost ten, and eight inoculated attacked lost five.

In a group of tea plantations in Assam 154 cases in uninoculated had sixty deaths, fifteen cases in inoculated had four.

In the East Lancashire Regiment in Lucknow 120 uninoculated attacked had 79 deaths, and 18 inoculated attacked had 13.

This circumstance, the non-reduction of the case mortality by a treatment which influenced unmistakably the case incidence, appears an astonishing divergence from the result of small-pox vaccination, where both the number of attacks and their fatality are reduced by the treatment.

The new aspect of the problem of preventive inoculation which thus presented itself in these observations on human communities consisted in the possibility of a prophylactic treatment being directed separately towards the reduction of the number of attacks, leaving the fatality of the disease unchecked, and towards the mitigating of the character of the disease and the reduction of the case mortality in those who get attacked.

Possible relation between Immunity from Attack and Resistance to actual Symptoms of Disease.

In analysing the nature of this particular result, the following two facts well known in laboratory practice presented themselves to me as of essential significance.

In patients who recover from an infectious disease the pathogenic microbe does not disappear from their body for a considerable time after their recovery. It does not do them harm any longer, though when transferred to another animal it may still cause a fatal attack. Similarly, as in the case, for instance, of a guinea-pig inoculated with the bacillus of chicken cholera, a naturally immune animal can breed for weeks, in an abscess, microbes of an intense virulence without in the least suffering in its own general health.

A condition seems to set in in the convalescent patient, or to exist in naturally immune animals, by virtue of which they do not suffer from the results of activity of a pathogenic microbe, *i.e.*, from its morbid products; and from that time the presence of the microbe in the system, even in

the tissues, becomes innocuous. Immunity against morbid symptoms generated by the products of microbes does not seem to imply necessarily the ridding of the system of such microbes. It is known now, since the discoveries of Behring and Kitasato, that such a resistance to these products can be originated artificially, by gradually treating the system with increasing quantities of toxines. The system reacts by developing anti-toxines tending to neutralise the effect of the toxines.

On the other hand, Gamaleia first drew attention to the fact that it is possible to create in an animal resistance to lethal doses of virulent microbes without that animal acquiring any resistance to a dose of the products prepared from the same microbes in the laboratory.

One seems justified therefore in considering separately two kinds of immunity: One against the living microbe, which would prevent it from entering the system and causing an attack; and another against the fatality of the symptoms of the disease caused by the products of the microbe when the latter overcomes the initial resistance and does invade the system.

In the inoculation against cholera, which is done with the bodies of microbes, the first result alone is obtained.

These considerations were confirmed by a set of laboratory experiments by Pfeiffer and Kolle, intended to verify our Indian results, and in the course of which they detected in the serum of men inoculated with only one dose of cholera vaccine an extremely high protective power, equal to that which, in goats for instance, could be created only after a very prolonged treatment, extending over five or six months, and including injections with gigantic doses of cholera vaccine.

On analysing, however, in detail the properties of that serum they found that it possessed an intense power of destroying the cholera microbes, but exhibited no antitoxic properties capable of neutralising the effect of the products of those microbes.

The Plan of Anti-plague Inoculation.

When, in 1896, I was confronted with the problem of working out a prophylactic treatment against the plague, I determined to put to test the ideas originated by the observations on our cholera patients, and to attempt, in the new preventive inoculation, to obtain at once a lowering of the susceptibility to the disease, and a reduction of the case mortality.

This I resolved to obtain by treating the system with a combination of the actual bodies of microbes and of the concentrated products of their activity.

In presenting the above considerations, I beg that they may be considered as provisional, subject to modification or to complete refutation.

There may exist already facts unknown to me, which are opposed to the guesses implied in them. It was those guesses which led to the results obtained in the plague inoculation; but, in giving the reasoning which I passed through while working out the method, I am yielding only to a demand expressed to me to that effect, as I considered that part of my communication unnecessary; the more so that the theoretical conjectures above enumerated are not shared even by very eminent experimenters, such as Pfeiffer himself, to whose results I owe some of my premises; and the correctness of the composition of the plague prophylactic, with regard to the extracellular toxines which I have added to it, the so-called supernatant fluid of the plague prophylactic has been the subject of an animated dispute.

It is certain that no theoretical views conceived by one experimenter are binding, or need even be interesting, to others. What is obligatory is the acceptance of the results obtained.

The Plague Prophylactic.

In order to accumulate for the plague prophylactic a large amount of extra-cellular toxines, the bacilli are cultivated on the surface of a liquid medium where they are suspended by means of drops of clarified butter or of cocoanut oil.

The bacilli grow down in long threads into the depth of the liquid, and produce what I have termed a stalactite growth in broth, an appearance quite peculiar to this microbe, and which, I hope, will be accepted as the specific diagnostic feature of this microbe.

The products of their vital exchange—the toxines—are secreted by the stalactites into the liquid and accumulate there.

The growth is periodically shaken off the surface of the broth, after which a new crop appears underneath that surface.

Thus a large quantity of the bodies of microbes is collected at the bottom of the cultivation vessel, and the liquid itself gets gradually permeated with increasing quantities of toxines.

The process is continued for a period of five to six weeks, at the end of which the bodies of the microbes become extremely deteriorated.

It will be seen from this that, in my eagerness to put to test our ability to influence the case mortality I may have, perhaps, paid less attention than I might have done to the problem of reducing the number of attacks; and I have now sketched out a simple plan whereby to test this circumstance, and to try to improve our results from this point of view.

In order to render harmless the inoculation of the virus above described, I determined to kill the microbes by heating the material up to 65 to 70° C. The virus so treated, differing from what is observed in some other instances, loses at once, for the animals susceptible to the

disease, almost all its pathogenic power; and it was a question to determine, whether it contained the qualities that were sought for, viz., the power of creating *in man* a useful degree of resistance to plague.

The plan has been contested by a number of experimenters who tried a material similarly prepared on different animals and failed to detect in it any immunising properties.

Among other forms of plague virus which were tested by us, and by other experimenters, a large number were found to be too dangerous to use; in other instances the mode of application was inadmissible in the case of men; in others, again, the effect appeared too transient to be of practical use.

The Properties of the Plague Prophylactic.

The immunising effect of the plague prophylactic, as above described, was worked out on domestic rabbits, and its actual efficiency was verified and confirmed by a number of investigators who experimented on the infection with virulent plague of protected and unprotected rabbits.

Comparing the rabbit with other laboratory animals, such as the rat, the guinea pig, the mouse, the monkey, one may consider the rabbit as the one that perhaps required the least amount of protection, as its natural resistance to plague is relatively high. The most altered virus, *i.e.*, such as was rendered the most harmless of all, was found to confer on the rabbit a very considerable degree of immunity, enabling it in a few days to resist ten or fifteen-fold lethal doses of virulent plague microbes. The same treatment applied to animals of a more susceptible nature would, on the contrary, in many instances fail.

The Questions which were to be solved by Experiments on Human Beings.

At the end of our laboratory experiments a set of questions stood before us that were to be solved by direct experiment on human beings. Those questions were:—

1. Would man behave with regard to the prophylactic like the animals upon which its protective power had been worked out?
2. If it so happens that the answer is affirmative, what would the dose of the prophylactic, and the method of administering it be; and would not the dose required be so high, and the reaction to be produced so severe, or the number of inoculations to be repeated so great, as to render the treatment inapplicable to men, or impracticable?
3. How many days counting from the date of inoculation would it take to produce in man a useful degree of immunity?
4. How long would that immunity last?

And lastly, there followed two questions, to which my experience of the anti-cholera inoculation entitled me to give a reassuring answer, but the correctness of which it was necessary to demonstrate afresh in the case of plague, viz. :

5. During the period of reactionary fever and all the other symptoms produced by inoculation, will the resistance of the inoculated exposed to plague be, for the time being, reduced, or remain the same, or be increased ? *i.e.*, would it constitute a danger to apply the inoculation in localities actually affected with plague ? and

6. When a man who happens to be incubating the plague, or to have initial symptoms of the disease already, chances to be inoculated, would it aggravate his condition, or have no effect, or on the contrary, help him ?

Demonstration of the Harmlessness of the Treatment.

The perfect harmlessness of the inoculation was first of all demonstrated by the officers of the Laboratory, the Principal and Professors of the Grant Medical College, a large number of leading European and native gentlemen of Bombay, and their families and households, being inoculated. And then, in the last week of January, 1897, when the plague broke out in Her Majesty's House of Correction at Byculla, in Bombay, the option of inoculation was offered to the prisoners.

The Experiment in Her Majesty's Byculla House of Correction, Bombay.

The Byculla House of Correction is a long-term prison. There are no children, nor very young people among the inmates, there being in Bombay a separate establishment, the Sassoon Reformatory, where minor criminals are sent.

The prisoners of the House of Correction present a well-fed, well clad, regularly worked, and almost as uniform a set of people as can be seen in a regiment, amongst whom one could scarcely see a single infirm or very aged individual.

At the appearance of plague the prisoners numbered 346 souls.

The inoculation was introduced after nine cases of plague had already occurred, five subsequently ending fatally; there remained thus 337 individuals to be dealt with. Of these, 154 only volunteered for inoculation, and 183 remained uninoculated.

On the 30th January, in the forenoon, before the inoculation was applied, six more cases occurred, of which three afterwards proved fatal. The inoculation was applied in the afternoon, and afterwards it was discovered that one more prisoner had already a bubo on him when inoculated, while two prisoners developed buboes the same evening after their inoculation. These three cases, attacked on the day of inoculation, proved also fatal.

After that, the difference which was observed in the fate of the two groups, the inoculated and uninoculated, is seen from the subjoined table :—*

Date of occurrence of plague.	Occurrences in uninoculated.			Occurrences in inoculated.		
	Number of uninoculated present.	Cases.	Fatal.	Number of inoculated present.	Cases.	Fatal.
1897. 23rd to 29th January, previous to the day of inoculation.	..	9	5			
30.1.97, the day of inoculation. Forenoon, before inoculation	..	6	3			
30.1.97, the day of inoculation. Afternoon, after inoculation	..	..	..	..	3	3
1st day after inoculation, 31.1.97.....	177	2	1	151	1	
2nd day after inoculation, 1.2.97.....	172	1	1	150		
3rd day after inoculation, 2.2.97.....	173	1	1	146		
5th day after inoculation, 4.2.97.....	171	1	1	146		
6th day after inoculation, 5.2.97.....	169	2	1	146		
7th day after inoculation, 6.2.97.....	169	5	1	146	1	
Total after the day of inoculation	172 uninoculated, average daily strength.	12 cases.	6 deaths.	147 inoculated, average daily strength.	2 cases.	No deaths.

* During the time under observation the number of *uninoculated* was reduced on the second, fifth, and sixth day after inoculation by three, one, and one discharged prisoners, whose terms of confinement expired on those days; and it was increased on the third and seventh day by two and two prisoners newly admitted into the jail. The number of *inoculated* was reduced on the third day after inoculation by four released prisoners.

No information as to the subsequent history of these few released (uninoculated and inoculated) prisoners reached the authorities or the officers of the Laboratory, but the question had no interest for the experiment, since their conditions of life and their exposure to plague ceased to be comparable from the time the prisoners were discharged into a large city, with various chances of infection, different in its different quarters. The observations referred only to the prisoners who remained exposed to plague under the conditions of the jail.

With the exception of the fourth day, cases of plague continued to occur among the uninoculated group for seven days after inoculation, their average daily strength throughout the week being 173; altogether twelve cases occurred among them with six deaths; while in the 148 inoculated there was one case on the next day after inoculation, who rapidly recovered, and one on the last day of the epidemic, who recovered also.

Analysis of the Results of the Byculla Jail Experiment.

A glance at the above table will show the progress which was made in our information by that initial experiment, and how far it carried us ahead from the state of uncertainty which surrounded the question originally.

The dose of prophylactic administered to the prisoners was 3 c.c.

They all had the customary attack of fever from the operation, with the discomfort accompanying that condition,—a headache in many cases, nausea, loss of appetite for a couple of days, a feeling of fatigue and lassitude, recalling a mild attack of influenza, with swelling and pain in the inoculated side. Did, however, all this make them more susceptible to the disease than were their non-inoculated fellow inmates? It is certain that the results testify unmistakably to an opposite effect.

Further, the incubation period in plague appears to be on the average five days, extending, however, not unfrequently up to ten.

As to the few newly admitted (uninoculated) prisoners mentioned above, none were subsequently attacked, and the cases of plague stated in the table refer all to old residents, who were present in the jail on the day, and long before the day, of inoculation. Had a case of plague occurred in any of the uninoculated new-comers, it would not have been included in the comparison with the occurrences among the inoculated inmates, since such new-comer had been exposed outside the jail to conditions of infection other than those which existed inside the jail. Notwithstanding this, it was permitted that the number of the uninoculated new-comers should be added by the jail authorities to the strength of the uninoculated as quoted in the table, since this tended to weaken, and not to exaggerate, the proportion of immunity obtained by inoculation.

In a similar way, in the outbreak of plague in the second (Umerkadi) Bombay jail, described below, one of the three attacks among inoculated persons, as reported by the jail authorities, namely in a man named Sital Vary, prisoner No. 7542, occurred after he had been set at liberty in the city. Had it been an attack in an uninoculated person, it would not have been admitted into the comparison with the inoculated, for the reason mentioned above, *i.e.*, because the conditions of infection outside the jail were not comparable with those in the jail. But as this was a case in an inoculated subject, and tended to present the results in a less favourable light, it was included in the record.

Every prisoner attacked with plague and taken away to the isolation or plague hospital was excluded on the subsequent day from the strength of those who remained in the jail and were still liable to an attack.

Of the twelve prisoners in the uninoculated group who developed plague during the next few days after the date of inoculation a large proportion, if not all, must have been already incubating the disease on that day; and seeing the perfect similarity of conditions under which the inoculated and the uninoculated, who belonged to the same crowd of people, were living, one could infer safely that a similar group of individuals incubating plague was present among the inoculated also at the time when the inoculation was performed on them.

The inoculation, however, did not aggravate their condition, as the number of inoculated who developed plague, counting from the first twelve hours of inoculation, was proportionately five times smaller than the corresponding number among the uninoculated; and the two cases that appeared among the inoculated, one on the very next morning after inoculation, both ended in recovery.

As far as that first experiment went, therefore, men behaved like the laboratory animals upon which the prophylactic properties of the drug had been worked out.

For communicating that protection one injection of prophylactic appeared sufficient, with a dose of 3 c.c., which dose, however, in our subsequent operations was further reduced to $2\frac{1}{2}$ c.c.

The difference in favour of the inoculated appeared within some twelve hours after the operation; but the man who was inoculated with plague on him, and the two who developed clear symptoms of plague the same evening, did not benefit by the operation.

This completed the first information gathered with regard to five of the six questions enumerated above. No answer could be given as to the final duration of the effect of inoculation, except that the operation appeared to be useful in a localised already existing epidemic, extending over seven days.

The Experiment in the Umerkadi Common Jail, Bombay.

In the next case the strictness of the conditions of the last experiment was enhanced further. This was in the second Bombay jail, the Umerkadi Common Jail.

The plague broke out there at the end of December, 1897, and by the 1st of January three prisoners were attacked and all of them subsequently died.

In the interval between the operations in the two jails, some 8000 people in the free population of Bombay had already availed themselves of the inoculation.

This time the whole of the prisoners, numbering 401, appeared willing to undergo the preventive treatment. In view of the novelty of the operation, however, and of our responsibilities before the government and the public, and the necessity of demonstrating clearly the effect of

inoculation, the prisoners were not allowed to undergo the treatment in a body, and it was resolved that only one half of them should be permitted to do so.

The manner in which that half was selected guaranteed the elimination of all possible errors usually inherent to observations on human communities.

The population of a jail in India is gathered into several groups, the largest being the ordinary convicts divided into simple prisoners and hard labour convicts; then there is a group of civil prisoners, debtors; a group of under-trial prisoners, of convict warders, of cooks, bakers, men employed in the infirmary, &c.; and a separate group of female prisoners.

On the morning of the 1st of January, 1898, in the presence of Major Collie, I.M.S., and Dr. Leon, medical officers, Mr. Mackenzie, the superintendent, and of all the officials of the jail, the above groups were brought one after the other into the jail-yard, and asked to seat themselves in rows; and after all were seated, every second man without further distinction was inoculated, excepting two of them, who did not volunteer for the treatment.

From this moment the even numbers, the inoculated, were left to live with the uninoculated, under conditions identical with those under which they were living before. They had the same food and drink, the same hours of work and of rest, shared with them the same yards and buildings, &c.

In this case fatal attacks continued to occur in the jail for thirty days, during which time an almost equal number of prisoners, inoculated and uninoculated, were discharged from jail, and thus excluded from further observation.

The average daily strength of the uninoculated who remained in the jail up to the end exposed to the plague was 127; and of the inoculated, 147.

In the smaller uninoculated number, ten cases of plague occurred, six of them proving fatal; while the larger inoculated number produced three cases, of whom all recovered.

In these three cases, however, in the inoculated, the character of the disease was so much mitigated that the authorities of the Government hospital at Parel, Bombay, where they were sent, hesitated to return them as plague, and the Director-General of the Indian Medical Service, who examined two of them, diagnosed them as mumps. They were returned as cases of plague in order that no possibility of error in favour of the inoculation should be admitted.

The Experiment in the Dharwar Jail.

On the third and last occasion, when the plague broke out in a jail, the authorities did not feel justified in withholding the inoculation

from any of the inmates, and all were permitted to be inoculated. This was in Dharwar, at the end of October and the beginning of November, 1898, during the terrible outbreak of plague in that town and district, the news of which must have reached you even here.

Five cases of plague, of which one was imported, and four in old residents of the jail, occurred, all five ending fatally.

The prisoners, then numbering 373, submitted in a body to inoculation, and only one case followed, in a man attacked two days after inoculation, and he recovered, the only one of the six.

The Experiment of Undhera, in a Free Population.

The most carefully planned out and precise demonstration of the working of the prophylactic system among a free population, exposed to a great amount of infection, was that made in the village of Undhera, six miles from Baroda.

The following was the mode of operation adopted :—

A detailed census was made by the authorities of all the inhabitants of the place, and on the 12th February, 1898, when a committee of British and native officers arrived to carry out the inoculation, the people were paraded in the streets, in four wards, family by family.

Major Bannerman, I.M.S., of the Madras Medical Establishment, and myself, accompanied by the Baroda officials, went from one household to another, and, within each, inoculated half the number of the male members, half that of the females, and half that of the children, compensating for odd figures that happened to be in one family by odd figures in another. I, personally, and the officers who were with me, directed special attention to distributing the few sick in the two groups of inoculated and uninoculated as equally as our judgment permitted us to do.

The plague, which had carried off, before inoculation, seventy-nine victims, continued afterwards in this instance for forty-two days and appeared in twenty-eight families, in which the aggregate number of uninoculated was sixty-four, and of inoculated seventy-one.

The total number of attacks in those families was thirty-five, and they were distributed as follows :—

The 64 uninoculated had 27 cases with 26 deaths ;
The 71 inoculated „ 8 „ 3 „ ,

thus showing 89·65 per cent. of deaths fewer in the inoculated members of the families than in the uninoculated.

There were no deaths from other causes in the inoculated of the village, while among the uninoculated there were three deaths attributed to causes other than plague.

The subjoined figures show the number of days which elapsed

between the date of inoculation and the occurrence of a death from plague in the families. The first row of figures refers to occurrences in uninoculated members, the second to occurrences in inoculated, while the small figures show the number of deaths which occurred in each group on those days:—

Deaths from plague occurred in uninoculated—
3^2 4^1 5^3 7^2 8^3—10^3 11^3 12^1———— 15^1 16^1 19^1 20^1 21^1 24^1 32^1 and 42^1,
and in inoculated
———— 9^1———— 12^1 and 14^1 ————————————————
days after date of inoculation.

There had elapsed therefore eight days, during which eleven deaths from plague occurred among the uninoculated members of the families, before the first death took place in an inoculated case. The inoculation has again acted, so to say, immediately; or, to use the mode of expression which we have adopted, has exercised its protective effect within the time necessary for the subsidence of the *general* reactionary symptoms produced by the inoculation.

The investigation in this village was carried out by Surgeon-General Harvey, the Director-General of the Indian Medical Service, and a committee of British and native officials. Every member of the family who survived was seen, his particulars verified from the documents, and every detail was confirmed from the registers kept at the time, and from the testimony of the whole of the villagers, who were present throughout the inquiry.

Experiments on a Large Scale. Average of the Results obtained.

I have dwelt so long upon the description of the above experiments not because they were the largest in volume or the most striking which were made, but because they were the most precise of all, and, so far as I am aware, free from any possible loophole of mistake.

I made prolonged and detailed observations in very severely affected communities of Lanowlie, in a population of 700 people, and among the followers of the artillery at Kirkee, numbering at the time 1530. Very complete data were collected by Professor Robert Koch and Professor Gaffky, of the German Government Plague Commission, by Major Lyons, I.M.S., of the Bombay Medical Establishment, and by myself, in the Portuguese colony of Damaon, in a population of 8230 individuals, during a frightful outbreak of plague there, which lasted more than four months, in 1897. A minute investigation extending over four months, was made by me in the Khoja Mussulman community of Bombay, numbering some 12,000 people, where about half of the total number were inoculated under the auspices of His Highness the Aga Khan. A most comprehensive inoculation campaign, and with widely

reaching and most satisfactory results, was carried out, under Mr. Cappel, late Collector of Dharwar, by Captain Leumann, I.M.S., Dr. (Miss) Corthorn, Dr. Hornabrook, Dr. Foy, Dr. Chenai, and others, in three adjacent small towns of Hubli, Dharwar, and Gadag, where 80,000 people were inoculated. The latter was the most magnificent piece of work done, from the point of view of practical application of the method, and of the testing of its general efficiency.

With the extension of the number of inoculated the exactitude and precision of observation certainly suffer. A number of questions and objections arise with regard to points of detail, which it is not always possible to answer with certainty. Such wholesale observations are, however, required to enable us to judge whether the application of the method as a general measure answers to the expectations formed; whereas the exact extent of the results is only to be gathered from mathematically precise experiments, imitating the conditions of laboratory practice, such as were those which I have detailed above.

The difference in the mortality from plague in inoculated and uninoculated sections of communities was estimated to average over 80 per cent., approaching often 90, as was the case in Undhera described above. The lowest proportion ever observed in the experiments which I made personally was 77·9 per cent.; this was at Kirkee.

Effect on the Case Mortality.

A very accurate set of data were collected in almost all the larger hospitals where inoculated plague cases were admitted, upon the fatality of the disease in inoculated. These were to the effect that the case mortality among them was some 50 per cent. lower than among uninoculated plague cases. A number of documents on this point has been collected by the Indian Plague Commission and will, I trust, appear in their records.

Minimum Duration of the Effect of the Plague Inoculation.

As to the duration of the effect of the plague inoculation, the only statement which can be made for the present is that it lasts at least for the duration of one epidemic, which, on the average, extends over four to six months of the year.

The Government of India have recognised the inoculation certificates, entitling the holder to exemption from plague rules, as being valid for a period of six months; on the understanding that if accurate data are forthcoming as to the effect lasting longer, the holders will be permitted to renew their certificates for another period, without being reinoculated.

The further Problems pursued in the Bombay Plague Research Laboratory.

The task which lies now before the Plague Laboratory in connection with prophylactic inoculation comprises the following problems :—

The perfecting of processes for turning out large and uniform quantities of material, and avoiding the variations due to the character of the plague microbe, and to the differences in the composition of the cultivation media ;

The further investigation of the different constituents of the plague prophylactic, with a view of intensifying those which produce definite and beneficial results ;

The possible mitigation of the reactionary symptoms after inoculation ; and

The study of the effect of antiseptics used for preserving the prophylactic ;

while the most important general problems concerning plague relate to the study of the curative treatment and to the life-history of the plague microbes in nature.

The Typhoid Inoculation.

The inoculations against cholera and plague, which are the outcome of the work of Jenner, Pasteur, and Koch, and their admirable succession of pupils, contain in their turn a promise of development and success, which, I trust, will be only enhanced at every subsequent step, and which, it seems to me, already warrants the application of the same kind of effort to other diseases and epidemics.

In this order of ideas permit me to enter a plea in favour of a new inoculation campaign, which has been inaugurated already, and which I hope will be carried out successfully, for the benefit of a large number of soldiers of this country residing in India, and of white men in general in all tropical countries.

The problem of typhoid inoculation has quite a special interest for Europeans, as much as cholera has for the natives of India. Typhoid proved to be a more difficult disease to eradicate from military cantonments than cholera. It is possible that the explanation of this lies in what is already known of the character of the microbes of these diseases.

The typhoid bacillus when subjected to different chemical and physical agents, such as acids or antiseptics, or a high temperature, or desiccation, or the admixture of other microbes, appears far more resistant than the cholera microbe.

Such a character would ensure for the typhoid bacillus an existence in more varied media, under more various climates, and a greater inde-

pendence from seasonal or local changes, than is the case with the cholera microbe.

Outside the endemic area cholera remains in one and the same place but for a few weeks, and in any given part of a town often for a few days only. It is rare that it visits the same barrack more than once in five, sometimes ten years, and when it occurs, a temporary evacuation of the place puts a stop to the disease.

The typhoid virus, on the contrary, sticks to an infected locality for years, and causes a continuous incidence of the disease for which occasionally nothing short of a complete desertion of the station is effective.

At the same time, while the cholera infection seems to be almost exclusively confined to the water supply, in typhoid the improvement of the water appears to leave intact a large number of other sources of danger which up to the present have escaped detection.

While thus differing in their life-history in nature, the bacilli of cholera and typhoid present important common features in the manner in which they behave in the human and animal body.

The chief centre of infection in both instances is the intestinal canal, the circulatory system remaining free from invasion. When inoculated into animals, both microbes admit of the same kind of transformation by passages from animal to animal; and against both immunity can be created in laboratory animals by the same preparation of virus as used in the inoculations for cholera; while, when examining the tissues of immunised animals, the same modifications are detected in them as those observed after the anti-cholera inoculation.

These considerations have led us to expect from the typhoid inoculation in man a similar protective effect to that observed in the inoculation against cholera; and seeing that the period of life during which the newcomers to India remain susceptible to typhoid extends only over a few years, it would seem that the application of the system, when properly organised, is likely to prove of a very high practical value.

Inoculation and General Sanitary Measures.

The anti-cholera inoculation, the inoculation against plague, and that against typhoid thus came to put themselves on the same line as vaccination, and represent attempts at dealing with epidemics on a plan differing from measures of general sanitation. During the last few years the question has, therefore, been frequently debated as to the relation in which the two stand to each other.

It is scarcely necessary to say that inoculation cannot be substituted for a good water supply, the draining, cleansing, or improvements in the building of cities, or for the admission of a larger amount of light and air into over-crowded localities, for all those measures to which the

nations owe the marked improvement in health which has taken place during the present century.

Only, injustice would be done to the sanitarian by calling him in when a patient lies already on his sick-bed, or when an epidemic actually breaks out in a community, and by asking him to stay the sickness, or the epidemic, to improve the health of the population, so to say, while you wait.

To be dealt with, epidemics, like individual diseases, require specifics, promptly administrable remedies, and measures of general sanitation can be no more advised for arresting a sharp outbreak of cholera or plague than an individual patient be directed to build for himself a new house, or to dry up the marshy lands or to cut down the jungle round his habitation when he requires a dose of quinine to arrest an attack of ague.

The part of vaccination and of preventive inoculation in combating epidemics stands in the same relation to general sanitary measures as therapeutics and the art of the healing physician stand to domestic hygiene and sanitation. It is certain that neither of these can ever be substituted for the other.

Inoculation and the Segregation-Disinfection Method.

A comparison of another kind now very actively discussed is that between the methods of combating epidemics by separation of sick and healthy, and disinfection, on the one hand, and by preventive inoculation of the people, on the other.

From this point of view the following distinction between infectious diseases is to be made:—

When we take some affected tissue from a leper, or a pustule from a small-pox patient, or virulent saliva from a rabid animal, or some syphilitic matter, and throw it into milk, broth, or any organic substance such as is to be found in the ordinary surroundings of men, it produces no modification in the medium, and in the course of time loses its infective properties and dies out. When, on the other hand, we repeat the experiment with cholera, or plague, or typhoid products, instead of dying out, the contagion begins to grow and multiply, spreads in the medium and soon transforms the whole of it into one mass of infectious matter.

It is evident that such a distinction—the strictly parasitic nature of one microbe and the capacity of the other to lead both a parasitic and saprophytic life—must influence most directly the ways in which these diseases spread and assume epidemic forms, and also the measures which are likely to be effective in combating them.

In the first instance the infection must remain confined entirely, or almost so, to the body of the patient, and the disease can be propagated

only directly from individual to individual, or by means of their immediate belongings. It is the inability of a virus to grow in lifeless nature that communicates to that disease a strictly contagious character.

In the second case, provided the surrounding conditions be favourable to it, the virus will spread widely around the original focus, and the sources from which infection reaches fresh individuals will grow in number rapidly.

From the point of view of preventive measures, therefore, in diseases like rabies, or syphilis, or small-pox, or leprosy, where infection is to be found in the patient alone, precautions of isolation taken with regard to the sick and their immediate surroundings, must affect directly the prevalence and propagation of the disease; whereas in typhoid, cholera, or plague, where the patient is only one, and proportionately a limited, source of danger, his isolation, and the destruction of his belongings, leaves unaffected the vast cultivations of infection which are going on in nature besides. Measures taken for circumscribing the prevalence of an epidemic by isolating and destroying the foci of infection are less likely to succeed in this category of diseases; attempts at eradicating an epidemic or at protecting individuals by ways which appear effective in merely contagious diseases will be in this case easily eluded; and the necessity of personal protection by means of a prophylactic treatment will soon be urgently felt and acknowledged.

Conclusion. The Officers who assisted in the Bacteriological Investigation in India.

My Lord and Gentlemen—Permit me, before I leave this place, to pay a tribute of gratitude for assistance and co-operation in the investigation work in India to the Officers of the Indian and Bombay Governments, to the Director-General of the Indian Medical Service, to Lieut.-Colonel Owen, Major Bannerman, Major Lyons, Major Herbert, Captain Thorold, Captain Hare, Captain James, Captain Vaughan, Captain Maynard, Captain Earle, Captain Stevens, Captain Green, Captain Clarkson, Captain Milne, Captain Leumann, of the Indian Medical Service, to Dr. (Miss) Corthorn, Dr. Gibson, Dr. Marsh, Dr. Balfour Stewart, Dr. Ransome, as well as to Dr. W. J. Simpson, Dr. Powell, Dr. Mayr, Dr. Surveyor, Dr. Paymaster, Mr. E. H. Hankin, the distinguished bacteriologist of the North-West Provinces of India, to His Highness the Aga Khan, and to a number of other European as well as Indian gentlemen, happily far too numerous to permit of my mentioning them all.

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