

for their performance a profound narcosis in order to prevent reflex movement, retching, or other incidents which might embarrass the surgeon or prejudicially affect the success of the operation. The laryngeal, peritoneal, rectal, vesical, and ocular reflexes are amongst the latest to disappear, so that in operations upon these parts full narcosis is usually necessary. The local application of cocaine is a most useful adjunct to chloroform anæsthesia in intra-laryngeal operations, for it enables the anæsthetist to work with a somewhat lighter chloroform anæsthesia than would otherwise be necessary. One of the greatest problems of the modern anæsthetist is the maintenance of deep anæsthesia during certain intra-abdominal manipulations. Whilst there can be no doubt that such an anæsthesia is convenient, and in some cases almost essential to the surgeon, it certainly cannot always be obtained in horizontally placed patients under chloroform without directly subjecting them to the risk of surgical shock of a circulatory type. When this profound anæsthesia is desired it is often wise, therefore, to employ ether. In some cases the administration of morphine before or during chloroform anæsthesia is very useful. When muscular relaxation is essential, as in the reduction of dislocations, abdominal examinations, &c., deep anæsthesia must also be obtained, but great care is necessary not to exceed the limits of safety. On the other hand, most operations within and about the upper air-passages, and particularly those in which hæmorrhage is profuse, require only a moderate anæsthesia; and the same may be said of most operations upon the lungs and pleuræ. It is a mistake, for example, to keep up a very deep chloroform anæsthesia for operations upon the thyroid gland, for those involving the deep structures of the neck, and for operations upon the brain and spinal cord, and the same may be said of those intra-abdominal cases which admit of being conducted during moderate anæsthesia. Another factor in the adjustment of the strength of vapour is the particular stage of the operation in hand. We have already seen that deep anæsthesia should, as a rule, be secured before the operation commences, and that from this point onwards a slight trace of corneal reflex should, if possible, be preserved. There is a point in many administrations which may be called the "critical juncture," and at this point great care is always necessary lest the anæsthesia be too profound. It occurs in abdominal cases just when the abdomen is being opened or just afterwards; in cases of nephrectomy when the pedicle is being pulled upon; in prostatectomy when the urethra is being torn through; and in hysterectomy when traction is at its height. In order to prevent reflex movement at the moment of the skin incision and abdominal rigidity subsequently, the anæsthetist is often tempted in abdominal surgery to push the anæsthetic unduly at the commencement, and if chloroform be the agent in use two risks are thereby incurred—that of overdosage and that of circulatory shock when the abdominal manipulation commences. Contrary to time-honoured doctrines, I would submit to you that at all these junctures the anæsthesia, though deep, should not be too profound. In operations within and about the throat and nose, attended by free hæmorrhage, there is also a critical juncture. It arises at the beginning of the operation—i.e., before the larynx has taken on, and has become practised in, its new function—that of preventing (by swallowing and coughing) the entry of blood into its cavity. In these cases great care must be exercised at the point indicated. There are many operations in surgery in which the manipulations of the surgeon successively involve organs or regions differing widely in their sensibility, and it is often necessary, therefore, to vary the strength of anæsthetic vapour *pari passu* with these manipulations. Sometimes, of course, it is quite impossible to reduce the strength of anæsthetic at the desired moment owing to the surgeon requiring complete muscular relaxation, and it is under such conditions that a change from chloroform to ether is advisable. Profuse or protracted hæmorrhage during any operation should generally be taken to indicate a lessening of the depth of anæsthesia; and the same may be said of cases in which circulatory shock has occurred, and of those in which unavoidable intercurrent asphyxia is present. Considerable practice is necessary in the adjustment of these different strengths of anæsthetic vapour, particularly if no regulating apparatus be used. At the same time such adjustments have their great advantages not only in the direction of providing the surgeon with the anæsthesia required, but also in the direction of ensuring satisfactory recovery.

The Croonian Lectures

ON

PLAGUE.

Delivered before the Royal College of Physicians of London
on June 18th, 20th, 25th, and 27th, 1907,

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OF PLAGUE IN HONG-KONG, 1902, ETC.

LECTURE III.¹

Delivered on June 25th.

IMMUNISATION AGAINST DISEASE.

MR. PRESIDENT AND FELLOWS,—The next question from a preventive aspect is whether there is a prophylactic against plague similar to that of vaccination against small-pox, and if so what is its value. The question naturally leads to a consideration of Haffkine's prophylactic against plague and of methods of artificial immunisation. Jenner's great discovery lay in the fact that he ascertained that the passage of the small-pox virus through the cow fixed its properties in such a manner that the immunising effects of the small-pox virus were retained while its power of producing the disease was destroyed. The defects of inoculation with the small-pox virus consisted in the danger to the inoculated which sometimes attended the operation and in the risk of infection which sometimes spread from the inoculated to other persons. Notwithstanding these disadvantages inoculation was practised as the lesser evil because in the majority of cases its effects were comparatively mild and it conferred a very high protection. Inoculation against disease is thus a very old method of protection. In some of the ancient shastras written contemporaneously with the works of Menoo inoculation is mentioned as being practised as a preventive or modifier of small-pox. Even inoculation against plague has been practised among the Turks.

The Brahmins who performed the inoculations against small-pox in India instituted certain procedures to avoid the defects as much as possible. They made it a point to inoculate if possible all the children in the village at the same time so as to prevent natural infection; they selected the virus from a discrete case and they usually kept it several days before inoculating it into individuals, for they found by experience that it produced a milder disease when thus kept than when directly transmitted from person to person. In later times such precautions were often relaxed with results not nearly so satisfactory. In China the inoculations against small-pox were often practised by ignorant men and instead of the small-pox virus being inoculated through the skin, which generally gives a mild attack, it was not infrequently placed in the nostrils and a very severe attack of the disease usually followed. When in China I came across an instance of this kind where some 17 persons had been inoculated in this manner and where the results were serious.

The older methods of inoculation, whether for small-pox or plague, depended on the employment of crude material containing the living germs of the disease and over these there was little or no control. Sometimes the material was efficacious and harmless, at other times it was dangerous. There was also risk of the method, while protecting the individual inoculated, spreading the disease to healthy persons. The discoveries of Jenner, Pasteur, and Haffkine have introduced new methods by which the material employed is fixed in strength, protective and harmless to the individual, does not spread the disease, and is fully under control.

HAFFKINE'S CHOLERA VACCINATION.

There is a difference between the cholera and plague inoculations introduced by Haffkine. In cholera a living vaccine is employed; in plague a devitalised or chemical vaccine is used. The cholera vaccine needs to be fixed in its strength in order that the microbe shall behave constantly in the same manner when injected alive into man. It was the non-recognition of this fundamental principle which led to

¹ Lectures I. and II. were published in THE LANCET of June 29th p. 1757) and July 13th (p. 73), 1907, respectively.

Ferran's failure in Spain. He practised inoculation against cholera on the same principle as the old inoculations against small-pox. The crude microbe isolated from a cholera patient was employed without fixing its strength. In Haffkine's method of inoculation against cholera there are two vaccines. The cholera microbe is first fixed at a high stage of virulence by passing through animals and is maintained at its high strength by the same process. It is necessary to mention that the cholera microbe requires air for its life and accordingly in the process of passing it through a succession of animals it is necessary to alternate this procedure with aeration of the microbe for some hours, otherwise it will die. It is in this way that the strong vaccine is obtained. But as this vaccine when injected under the skin of animals is apt to produce a slough, an attenuated microbe is used as a first vaccine. The attenuation is attained by a prolonged aeration and exposure to a continuous high temperature.

The advantage derived from using a living vaccine is that the immunity is higher and of longer duration. The disadvantage is that it has always to be prepared afresh by a bacteriologist and consequently difficulties arise in its preparation and distribution over large and numerous areas, whereas a devitalised or chemical vaccine can be preserved for a considerable time and sent out to great distances and administered by any physician who knows how to employ it aseptically.

Toussaint was the first to introduce chemical vaccines. He employed a vaccine of this kind against anthrax prepared from the heated defibrinated blood of dead animals. The method worked well as long as there were no spores in the blood. The heat to which the blood could be subjected without being coagulated—viz., 57° C.—would not destroy spores, so that if these were present and animals were inoculated the result was the death of the animals and the danger of spread of anthrax to other animals.

Many experiments were tried on similar lines by others with different kinds of microbes and on different animals, but the immunity obtained by such chemical vaccines was so short-lived that the methods could not be used for practical purposes, and so it happened that up to the time of the cholera inoculations inclusive all vaccinations were done with living vaccines.

HAFKINE'S PLAGUE INOCULATION.

When the problem of preparing a vaccine against plague presented itself Haffkine with his experience of the cholera vaccine quickly realised the importance of endeavouring to discover a chemical preparation of practical utility. The reason for this was the distribution of the plague in numerous villages and small towns and the impossibility of obtaining a sufficiently large number of bacteriologists to prepare and use a living vaccine. With these facts in front of him Haffkine pursued several lines of research. One of these was to vary the microbial preparation and to study the effect on each of them of different processes of sterilisation. Artificial cultures of the microbe, the blood and exudation of animals dead from plague, and the pulp of their different organs were taken and subjected to heating, drying, chloroform, carbolic acid, lactic acid, or essential oils.

Inoculation with the dried powder of pulverised organs and blood of animals dead from plague was found to be by far the most effective. A few years ago Dr. Klein made a very careful investigation in this direction and was successful in preparing a powder possessing very high immunising properties. In India, however, dying animals are rapidly invaded with intestinal vibrios and bacilli and the heating and drying which were employed to devitalise the plague microbe were not sufficient to kill the spores of these extraneous microbes, so that the same difficulty met with by Toussaint recurred here in another form. Sometimes also the powder appeared sterile in culture but when injected into an animal killed it, plague bacilli being present in its blood; at other times the animal died apparently from toxins, no microbes being found. When the animal did survive it was very thoroughly vaccinated but for the reasons mentioned this method was set aside.

The most practical method of preparation was to use artificial cultures and sterilise them by heat, but it was found that the animals naturally susceptible to plague, such as rats, guinea-pigs, and monkeys, could not be vaccinated by this preparation or required many injections extending over several weeks before any immunity was established.

Experiments, however, showed that an animal not naturally susceptible to plague—viz., the rabbit, which possesses a relatively high degree of resistance even to injected plague—could be rendered immune with this chemical vaccine. Influenced by this circumstance and not deterred by the other Haffkine determined to ascertain whether man could not be immunised in a similar way to the rabbit.

On a *priori* reasoning it seemed improbable but the experiment first made in the outbreak of plague in His Majesty's House of Correction at Byculla in Bombay proved the possibility of such immunisation. This epidemic only lasted a week after the inoculations but still it seemed to show that during that short time benefit had accrued from the use of the prophylactic. The result obtained at the Byculla jail was subsequently confirmed by many experiments made under varied conditions and on a larger scale, and finally, it has been established that the immunity in man is not only real and of a satisfactorily high degree but lasts for a considerable time.

These two circumstances demonstrated for the first time the practicability of immunisation by a chemical vaccine. The success of the method encouraged a trial of immunisation on similar lines against typhoid fever, and this also appears to have been attended with successful results.

Experience of the effect produced by the cholera vaccines in India from 1893 to 1896 demonstrated that immunity was obtained against attacks of cholera, but when the inoculation failed and the person inoculated was subsequently attacked the fatality was practically the same as among those not inoculated. This result pointed to antimicrobial immunity being obtained but not to antitoxic immunity, and appeared to be related to the fact that the cholera vaccine consisted of the bodies of living bacilli obtained by cultivation on solid media. Haffkine realised that the defect attaching to the cholera vaccines should, if possible, be remedied in the production of the plague prophylactic and endeavoured to prepare a material which would give, not only an immunity against attack, but also at the same time diminish fatality when an attack occurred.

In the case of microbes producing extra cellular toxins, such as diphtheria, antitoxic properties are obtained in animals by injection of the toxins. Plague cultures in fluid media do not show the presence of any appreciable toxins in the filtrate, but Haffkine observed that when he injected into animals sterilised old fluid cultures of the plague bacillus he obtained a reaction which he could not obtain to the same extent when using the microbes and the filtrate separately. This appeared to indicate that the fluid possessed properties of its own. It encouraged him to try the combination of the microbes and the fluid which later was proved to be a success. The method adopted was to use old cultures rich in bacilli and their secretions. A suitable medium for obtaining such cultures was peptone broth to which were added a few drops of butter or oil. By the end of six weeks the culture is ripe for use and its purity is ascertained by drawing off a small quantity and subjecting it to the tests already described in the first lecture. The culture is then heated at from 55° to 60° C. for 20 minutes, with the result that the microbe is devitalised. The prophylactic then becomes a chemical drug with fixed properties and can be used in measured doses like other drugs. The preliminary fixation of the biological and pathogenic properties of the microbe is under such conditions not an essential process as in the case of cholera and small-pox, where living vaccines are introduced into the system.

The dosage of the prophylactic was determined by careful observation of its effects on man, which led to the adoption of the principle gathered from the study of the results of the cholera inoculations in India. This principle consists in regulating the dose with the view of producing an average temperature of 101° F. The same dose in different individuals gives rise to different ranges of temperature. Following the above standard it is generally observed that in one-third of the inoculated the temperature may rise to 102° F. and above. This proportion should not be exceeded. The thermometer is thus used as the indicator of the reaction. There is no testing of the blood in plague or cholera inoculation for the purpose of ascertaining what dose shall be given. The information obtained by the thermometer has been found to be a reliable guide and supplies a very simple and practical method of regulating the dose. It is a notable fact that in cholera and plague inoculations no instance has been observed of the inoculated groups having been rendered

by the inoculation at any time more susceptible to these diseases than the uninoculated.

THE RESULTS OF THE USE OF THE PROPHYLACTIC.

The harmlessness of the prophylactic was first established by the inoculation of several hundred volunteers, European and Indian. Then its protective effect was ascertained for the first time at the height of an outbreak of plague at the Byculla jail and certain facts were observed by Haffkine which enabled him to arrive at some very important conclusions. These were: (1) that one injection of three cubic centimetres of the prophylactic was sufficient to protect during an existing epidemic; (2) that inoculation was powerless to arrest the disease in those in whom the symptoms have already appeared or develop in a few hours

to the disease and recommended that no "contacts" or persons exposed to infection should be inoculated. The Indian Plague Commission of 1889, though not endorsing this view, was of opinion that inoculation was not likely to effect any protection for the first five days and was against Haffkine's conclusion as to the benefit of the inoculation in the incubation period. Subsequent study of the subject, however, induced Sir Almroth E. Wright to adopt Haffkine's views, and it is in conformity with the results obtained by Haffkine's inoculation in the incubation stage of plague that he based his opsonic method of treating with vaccines patients suffering from furunculosis, sycosis, acne, and other bacterial infections. The fact of the prophylactic immunising so rapidly and being beneficial in the incubation stage not only excludes the danger that was

CLASS I.—TABLE A.

OBSERVATIONS ON THE WORKING OF HAFFKINE'S SYSTEM ON A SMALL SCALE, SPECIAL OBSERVATIONS BEING CARRIED OUT ON RESTRICTED COMMUNITIES.

Name of locality.	Non-inoculated.						Inoculated.							
	Non-inoculated.	Cases.	Percentage of cases to population.	Deaths.	Percentage of deaths to population.	Proportion per cent. of deaths to cases.	Inoculated.	Cases.	Percentage of cases to population.	Deaths.	Percentage of deaths to population.	Proportion per cent. of deaths to cases.	Percentage of saving in cases.	Percentage of saving in deaths.
1. Byculla jail	172	12	7.0	6	3.5	50.0	147	2	1.4	—	0	0	80.0	100.0
2. Umerkhadi jail... ..	127	10	7.9	6	4.7	60.0	147	3	2.0	—	0	0	74.1	100.0
3. Undhera village (plague infected houses)	64	27	42.2	26	40.6	96.3	71	8	11.3	3	4.2	37.5	73.3	89.6
4. Hubli (mill)	75	—	—	20	26.66	—	1098	—	—	30	2.7	—	—	89.7
5. Hubli (employees of Southern Maratha Railway)	760	35	4.6	21	2.7	60.0	1260	11	0.9	2	0.2	18.2	81.03	94.1
6. Dharwar jail *	—	—	—	—	—	—	374	—	—	—	—	0	—	100.0
7. Broach (Parsee population) ...	763	9	1.2	5	0.6	55.6	1080	2	0.2	1	0.1	50	83.3	85.7
8. Broach (tailors' camp)	135	10	7.4	6	4.4	60.0	90	—	0	—	0	0	100.0	100.0
9. Belgaum† (49th Battery R.F.A. Native followers)	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10. Belgaum (Army Hospital Corps, 1897)	3	2	66.7	2	66.7	100.0	80	—	0	—	0	0	100.0	100.0
Ditto, 1899	5	1	20.0	1	20.0	100.0	79	2	2.5	2	2.5	100.0	87.3	87.3
11. Major Forman's servants	2	1	50.0	1	50.0	100.0	28	—	0	—	0	0	100.0	100.0
12. Bulsar Shanchis (oil pressers) ...	35	4	11.4	4	11.4	100.0	261	7	2.7	4	1.5	57.1	76.6	86.6
13. Colaba ward (Chawl), Bombay ...	32	19	59.4	12	37.5	63.2	21	1	4.8	—	0	0	99.0	100.0
14. Poona, Yerowda jail. †	—	—	—	—	—	—	—	1	0.06	0	0	0	—	—
15. Aden—Jewish community. (31 households infected.)	179	44	24.6	29	16.2	65.9	246	19	7.7	8	3.3	31.2	68.3	79.5
16. Aden (special prison)§	2	2	100.0	1	50.0	50.0	—	0	0	—	0	0	100.0	100.0
17. Aden (Crater Plague Hospital) ...	—	263¶	—	163	—	61.9	—	21¶	7.0	—	33.3	—	—	—
18. Kirkee, near Poona, 1906	12	6	50.0	3	25.0	50.0	1300	5	0.4	1	0.1	20.0	99.2	99.7

* Four deaths occurred among the prisoners before inoculation. The entire population was inoculated. One case occurred two days after inoculation, which recovered.

† Population 334. Plague continued for 37 days and 23 cases and 17 deaths occurred. Gradually the whole population was inoculated and none of those inoculated were attacked.

‡ Population 1661. Plague continued for 13 days and three cases and three deaths occurred in those who had not been inoculated. 1658 were inoculated by the thirteenth day; of these one was attacked but recovered. There were no further cases.

§ All the prisoners were inoculated excepting two; these two were attacked, one of whom recovered. When inoculation completed no cases, although rats were dying from plague.

¶ Admissions.

These observations were made in places where non-inoculated people had between 1.2 and 100 per cent. of cases and between 0.6 and 66.7 per cent. of deaths, with a proportion of deaths to cases varying between 50 and 100 per cent. The inoculated people of the same places had between 0 and 11.3 per cent. of cases and between 0 and 4.2 per cent. of deaths, with a proportion of deaths to cases varying between 0 and 57.1 per cent. The number of cases among the inoculated was reduced by between 68.3 and 100 per cent., and the number of deaths by between 79.5 and 100 per cent., as compared to the incidence of attacks and deaths among the non-inoculated people of the same place.

after inoculation; (3) that the inoculation mitigated or aborted the disease in those who were in the incubation stage and had been infected three or four days previously; and (4) that the prophylactic, unlike the vaccines for cholera, rabies, anthrax, or small-pox, exercised its protective effect in less than 24 hours, acting in this respect with a rapidity which was only known in antitoxic sera.

Of these deductions that relating to the effect of the vaccine on individuals in the incubation stage and its power of arresting the development of infection or mitigating the disease appears to be the most incredible, particularly in view of the shortness of the incubation period in plague. Calmette and his co-workers as well as other bacteriologists asserted that an individual inoculated not only in the incubation period but also a short time before infection would succumb

feared but allows of the application of the prophylactic in infected houses and localities, and generally during the prevalence of an epidemic.

Later observations have fully confirmed Haffkine's conclusions which stand to-day without modification. It is not from observations on animals but from observations on man that the question as to the action of Haffkine's prophylactic has to be worked out and has to be judged. This test has now been applied in many places and under various conditions and always with the same successful result. The observations are divisible into two classes—viz., those that have been made on a small scale in restricted communities living under special administrative and medical control, and those made on a large scale. Owing to the circumstances in which the first class, conducted on a small scale, were carried

out and which permitted of the results being carefully watched and thoroughly checked, they possess a special value on account of their exactness and precision.

The subjoined Table A shows the incidence of plague cases and plague deaths in some 18 small communities under careful control where a part of the inhabitants were inoculated and a part remained not inoculated; most of them are taken from the reports of Colonel W. B. Bannerman, I.M.S. The table shows their comparative liability to attack and death and the percentage of saving in cases and deaths among the inoculated as compared with the not inoculated.

In the Byculla jail, out of 172 not inoculated there were 12 cases of plague, six of which proved fatal, while among 147 inoculated there were only two cases and no deaths—that is, among the non-inoculated 7 per cent. of the population were attacked and 3·5 per cent. of the population died, and the proportion of deaths to cases was 50 per cent., whereas among the inoculated only 1·4 per cent. of the population

with two deaths—that is, among the non-inoculated 4·6 per cent. of the population were attacked and 2·7 per cent. of the population died with the proportion of 60 per cent. of deaths to cases, whereas among the inoculated there was 0·9 per cent. of cases to the inoculated population and 0·2 per cent. of deaths with a proportion of deaths to cases of 18·2 per cent. The percentage of saving in cases amounted to 81·03 per cent. and of saving in deaths to 94·1 per cent.

Among these 18 observations there are several where the whole community was inoculated with the result that the plague was arrested. Thus in the Yerowda Jail, Poona, plague appeared and in 13 days caused three cases which were fatal. By the thirteenth day the whole of the jail consisting of 1658 persons were inoculated, one of whom was attacked, but recovered, and there were no further cases. In the Aden Prison all the prisoners were inoculated except two; these two were attacked with plague and one recovered.

CLASS II.—TABLE B.

OBSERVATIONS OF THE WORKING OF THE SYSTEM ON A LARGE SCALE.

Name of locality.	Non-inoculated.						Inoculated.							
	Non-inoculated.	Cases.	Percentage of cases to population.	Deaths.	Percentage of deaths to population.	Proportion per cent. of deaths to cases.	Inoculated.	Cases.	Percentage.	Deaths.	Percentage.	Proportion per cent. of deaths to cases.	Percentage of saving in cases.	Percentage of saving in deaths.
Mora	580 (about)	26	4·5 (about)	24	4·1 (about)	92·3	419	7	1·7	—	0	0	62·7 (ab't)	100·0
Damaun	6,033 (about)	—	—	1482	24·6	—	2,197	—	—	36	1·6	—	—	93·4 (ab't)
Lanowli	377	78	20·7	57	15·1	73·1	323	14	4·3	7	2·2	50·0	79·1	85·7
Kirkee, in 1897	859	143	16·6	98	11·4	68·5	671	32	4·8	17	2·5	53·1	71·4	77·9
Undhera village, whole population...	437	27	6·2	26	5·9	96·3	513	8	1·6	3	0·6	37·5	74·8	90·2
Khoja community in Bombay, 1898	9,516 (about)	—	—	77	0·8 (about)	—	3,814	—	—	3	0·08	—	—	90·3 (ab't)
Hubli	17,786	—	—	2348	13·2	—	24,631	—	—	338	1·3	—	—	89·6
Dharwar (tov.n)	16,848	1,100	6·5	889	5·3	80·8	4,231	129	3·04	54	1·3	41·8	52·2	75·7
Gadag (town)	4,163	278	6·6	216	5·2	77·7	13,004	193	1·5	83	0·6	43·0	77·7	87·6
Belgaum (cantonment)...	4,558	506	11·1	346	7·59	68·4	4,842	78	1·6	40	0·83	51·3	83·8	89·1
Ahmednager (district)	8,794	563	6·4	415	4·7	73·7	2,493	70	2·8	31	1·2	44·3	56·2	77·0
Aden (Jewish community)...	982	83	8·4	65	6·6	78·3	1,190	23	1·9	8	0·6	34·7	77·0	89·7
The Punjab:														
1897-1900	—	—	—	—	—	60·99	306,730	—	—	—	—	36·55	—	—
1900-1901	—	—	—	—	—	60·59	197,278	—	—	—	—	36·50	—	—
1901-1902	3,909,326	266,700	6·8	173,732	4·4	65·14	235,776*	881	0·4	209	0·1	35·07	94·5	97·1
1902-1903	—	—	—	—	—	60·1	505,849	—	—	—	—	30·47	—	—
Re 1 portion of the inoculated in 1902-03	639,630	49,433	7·7	29,723	4·6	60·1	186,797	3399	1·8	817	0·7	23·9	76·5	90·6
Aden, 1905... ..	1052	368	34·9	294	27·9	78·6	898	37	4·1	14	1·6	37·8	88·2	94·4

* Besides 32,789 in Punjab native states.

These observations refer to places where the non-inoculated part of the population had between 4·3 and 34·9 per cent. of cases and between 0·8 and 27·9 per cent. of deaths, with a proportion of deaths to cases varying between 60·1 and 96·3 per cent. The inoculated part of the population had between 0·4 and 4·8 per cent. of cases and between 0 and 2·5 per cent. of deaths, with a proportion of deaths to cases varying between 0 and 53·1 per cent. The number of cases among those inoculated was reduced by between 52·2 and 94·5 per cent. and the number of deaths by between 75·7 and 100 per cent., as compared to the incidence of attacks and deaths among the non-inoculated inhabitants of the same localities. The results observed in the inoculations made on a large scale were therefore substantially the same as those obtained in special observations made for study in restricted numbers of people living under special administrative and medical control.

were attacked and there were no deaths. The percentage of saving in cases was accordingly 80 per cent. and in deaths 100 per cent.

Again, in Umerkhadi jail, out of 127 persons not inoculated there were ten cases with six deaths, whereas among the inoculated there were three cases and no deaths—that is, among the non-inoculated 7·9 per cent. of the population were attacked and 4·7 per cent. of the population died, with the proportion of deaths to cases of 60 per cent., whereas among the inoculated there were only 2 per cent. of the population attacked and none died. The percentage of saving in cases amounted to 74 per cent. and in deaths to 100 per cent.

The results given in these first two practically represent the results in the others; for instance, if the employees of the Southern Maratha railway be taken it will be observed that out of 760 not inoculated 35 cases occurred with 21 deaths, whereas out of 1260 inoculated 11 cases occurred

When inoculation was completed no cases occurred although rats were dying from plague.

Summing up these experiments as a whole, they were made in places where the non-inoculated people had between 1·2 and 100 per cent. of cases and between 0·6 and 66·7 per cent. of deaths, with a proportion of deaths to cases varying between 50 and 100 per cent. The inoculated people of the same places had between 0 and 11·3 per cent. of cases and between 0 and 4·2 per cent. of deaths, with a proportion of deaths to cases varying between 0 and 57 per cent. The number of cases among the inoculated was reduced by between 68·3 and 100 per cent. and the number of deaths among the inoculated was reduced by between 79·5 and 100 per cent., as compared to the incidence of attack and deaths among the non-inoculated people of the same places.

The conclusions derived from these observations will be more clearly followed if the comparative results are given in a graphic form and the smaller numbers excluded.

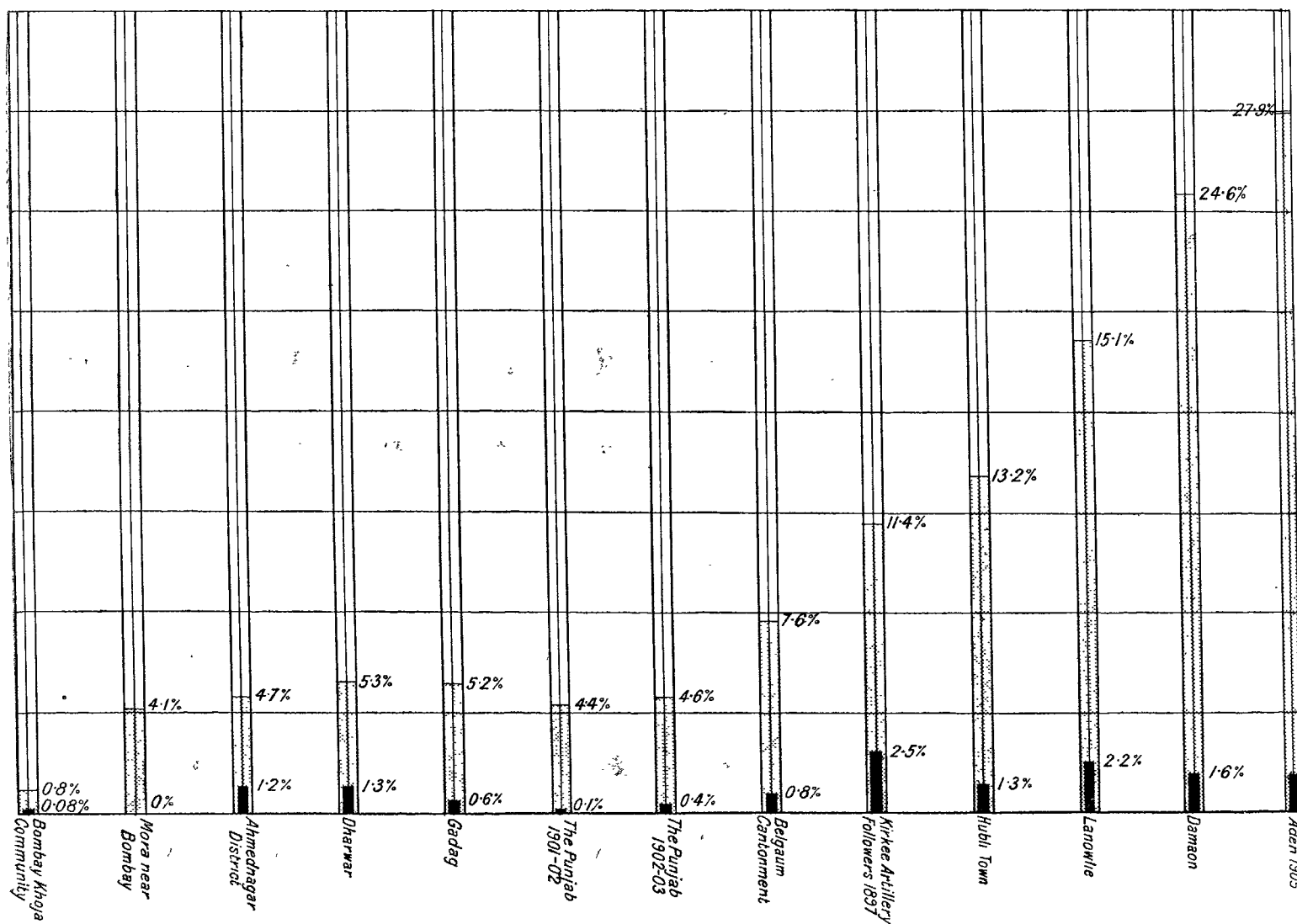
[Professor Simpson here showed upon the screen several diagrams dealing graphically with these figures. In Diagram I. A the most instructive epidemics had been taken which illustrated different degrees of severity on the population, the incidence of plague varying from 1.2 to 59.4 per cent. of the population. The columns were formed on the principle of each column representing 100 inhabitants inoculated or not inoculated.

Diagram I. A showed that the observations were made in epidemics in which the incidence of attack in the non-inoculated varied from 1.2 to 59.4. The incidence of attack among the inoculated varied from 0 to 11.3. In general the incidence of attack on the inoculated corresponds to the severity of the epidemic, but this is not uniformly the case, for in a few the inoculated show a striking immunity in the midst of very severe epidemics.

Diagram I. D represented the percentages of plague attacks averted by inoculation. Each column represented 100 attacks which occurred among the uninoculated population; the

143 cases with 98 deaths, and the proportion of deaths to cases was 68.5 per cent. Out of 671 inoculated there were 32 cases with 17 deaths and the proportion of deaths to cases was 53.1 per cent. Thus the incidence of attack on the not inoculated was 16.6 per cent. and of deaths 11.4 per cent., whereas the incidence of attack on the inoculated was 4.8 per cent. and of deaths 2.2 per cent. Or, in other words, there was among the inoculated a percentage of saving in cases of 71.4 and of deaths of 77.9, as compared with the not inoculated.] He went on to say:—

Undhera village may also be taken as another example. In this village more than half the population was inoculated, 513 being inoculated and 437 not being inoculated. Out of the 437 not inoculated there were 27 cases of plague with 26 deaths, the proportion of deaths to cases being 96.5 per cent. Out of the 513 inoculated there were eight cases with three deaths, the proportion of deaths to cases being 37.5 per cent. The incidence of attack among the not inoculated was 6.2 per cent. and of deaths 5.2 per cent., while among the



Inoculation on a large scale. Percentage of plague deaths to population. The stippled portions of the columns represent the percentage of deaths in the non-inoculated. The black portions represent the percentage of deaths among the same number of inoculated.

upper shaded portion of the columns represented the number of attacks which occurred in an equal number of the inoculated population. The remaining blank portion of the column shows the percentage of attacks averted by inoculation; the saving in attacks varies from 58.3 to 100 per cent. In the Jewish community in Aden against each 100 attacks among the non-inoculated there were 31.7 in the inoculated and the saving in cases was 68.3, whereas in the tailors' camp at Broach the inoculated escaped attack altogether and the saving was 100 per cent.

The second class of observations, which represented observations of the working of the system on a large scale, furnished results similar to those obtained on the smaller scale. Table B gave those results. Of these Professor Simpson specially referred to the observations at Kirkee in 1897, because he had the opportunity, along with Haffkine, of checking the results on the spot. Of the community on which the experiment was made, 859 were not inoculated and 671 were inoculated. Out of the 859 not inoculated there occurred

inoculated the incidence of attack was 1.6 per cent. and of deaths 0.6 per cent. So that among the inoculated the percentage of saving in cases was 74.8 and in deaths 90.2, as compared with the not inoculated.

Considering the observations as a whole in the different places recorded the results show that the non-inoculated part of the population had between 4.3 and 34.9 per cent. of cases and between 0.8 and 27.9 per cent. of deaths, with a proportion of deaths to cases varying between 60.1 and 96.3 per cent., while the inoculated part of the population had been 0.4 and 4.8 per cent. of cases and between 0 and 2.5 per cent. of deaths, with a proportion of deaths to cases varying between 0 and 53.1 per cent. The number of cases among those inoculated was reduced by between 52.2 and 94 per cent., and the number of deaths between 75.7 and 100 per cent., as compared to the incidence of attacks and deaths among the non-inoculated inhabitants of the same localities.

The following diagrams refer to the observations on large

communities and they are constructed on the same principle as those relating to the smaller communities.

Diagram II. B (a copy of which we print) illustrates epidemics of different degrees of severity and the relative incidence of the disease among the not inoculated and the inoculated. The whole column represents 100 inhabitants inoculated or not inoculated, the shaded portion shows the percentage of deaths among the not inoculated, and among the inoculated. The incidence of deaths in the non-inoculated population varied between 0·8 and 27·9 per cent., whereas among the inoculated it varied between 0 and 2·5 per cent.

[*Diagram II. E* showed the saving in the number of deaths among the inoculated compared to the non-inoculated. Each column represented 100 deaths which occurred among the uninoculated population. The shaded portion of the column represented the number of deaths which occurred in an equal number of the inoculated population. The remaining blank portion of the column showed the percentage of deaths averted by inoculation. The saving in the number of deaths effected by the inoculations varied between 75·7 and 100 per cent.]

These diagrams bring out in a very clear manner the great value of the inoculation. Stated generally, the average reduction amounts to three times fewer attacks among the inoculated and should the inoculated take plague the chances of death are reduced at least twice. Accordingly, the chances of escape from death are 6 to 1 in favour of the inoculated compared to the uninoculated. In many cases they are at least 10 to 1 in favour of the inoculated—that is, out of 1,000,000 deaths among a non-inoculated population, if that population had been inoculated and exposed to the same infection, 900,000 lives would have been saved.

There are numerous other observations that might be quoted showing the value of Haffkine's prophylactic as a protective against plague. I shall content myself, however, by giving two further examples, one recorded by Dr. J. A. Turner, health officer of Bombay, and the other by Lieutenant-Colonel J. A. Cunningham, I.M.S. The first relates to the municipal employees under Dr. Turner. 7182 were inoculated and 418 were not inoculated. Out of the 7182 inoculated there were 14 attacked with plague and 13 died, being a percentage of 0·19 of attacks and 0·18 of deaths, whereas among the 418 not inoculated there were 28 attacked and 26 deaths, equal to a percentage of 6·7 attacks and 6·2 deaths. If the inoculated had suffered to the same extent as the non-inoculated they would have furnished 481 attacks with 446 deaths, instead of 14 and 13 respectively. The second refers to a small plague-stricken village in the Umballa district of the Punjab, where Lieutenant-Colonel Cunningham inoculated nearly half the population. Lieutenant-Colonel Cunningham describes the circumstances connected with the inoculations as follows:—

The village is Chamaru, about nine miles from Umballa city, situated in Thana Ganour in the Patiala State, the population of which was 783 souls. Narain Singh, a Lambardar of the village, brought in batches to the civil hospital, Umballa, between 21st and 27th March, 1907, 312 people, comprising men, women, and children of all classes, and these were inoculated with plague prophylactic serum by Captain Ross, I.M.S., assistant plague medical officer. The Lambardar, to whom great praise is due, took this action because rats were dying of plague in the village. On the 22nd March, the day following the first batch of inoculations, cases of plague were observed amongst the people of the village, and between this date and the 14th May 64 people contracted the disease, 38 dying.

We can now compare the results (which I had carefully verified on the spot by a medical officer) between the 312 inoculated people and the 471 uninoculated similarly situated in all respects, except for the difference in inoculation. Out of 312 inoculated, 13 contracted plague and four died, whilst amongst 471 uninoculated people 51 got plague and 34 died. The percentage works out for inoculated, attacks 4·13 per cent. and deaths 1·25 per cent.; whereas for uninoculated the figures are: attacks 10·8 per cent. and deaths 7·2 per cent.

For comparison I had the results ascertained in another village, Rampur, population 484, situated two miles from Chamaru in the Patiala State, where no inoculation had taken place. Here there were 74 attacks and 32 deaths, the disease occurring simultaneously with that at Chamaru between 14th March and 14th May; the percentages here are: attacks about 15·2 per cent. and deaths 6·6 per cent. of the population. Of the four who died in Chamaru amongst the inoculated two of them showed signs of the disease the day following the inoculation, and in their case it is safe to assume that their fate was sealed by previous infection before the protective effect of the inoculation came into operation.

It is, I think, a fair assumption that the inoculation of these 312 people saved the lives of 19 and saved 21 others from an attack of a very serious disease. If we could conceive a relative amount of immunity from death and plague throughout the Punjab, what a difference it would make in the experience of thousands of families, and in the population of the province. Even if this Umballa district, with its population of about 763,250 had been thoroughly inoculated, these figures show that about 20,000 of the 26,551 deaths from plague this season might have been averted. This and previous experience would

justify the revival of an extensive inoculation campaign throughout the country.

DURATION OF IMMUNITY.

Observations in Hubli, Dharwar, and Gadag, three towns in the Southern Mahratta country where a large number of inoculations were done in 1898, tend to show that the effects lasted for several years (weekly reports of collector of Dharwar). The annual reports of the Parsee community in Bombay and the general report issued by them in 1902 seem to indicate that the effect of the inoculations lasted four or five years, though gradually it diminishes. Certain indications in a similar direction were obtained in the Punjab in observations made in 20 villages.

THE MULKOWAL ACCIDENT.

The inoculations have been going on for ten years in India, and several millions of people have undergone the operation. In these ten years there has been only one serious accident, and this was due to a departure from the technique or rules prescribed by the laboratory when opening a bottle of prophylactic in a village in the Punjab in 1902, in other words, to a faulty application of the prophylactic and not to a fault in its preparation. This accident is an important event in the history of plague operations and as the inquiry into it is of great scientific interest it is desirable briefly to record the salient facts connected with it. These facts have been gathered by a special commission of inquiry in India. Briefly, they are that the bottle was one of five filled from the same cultivation flask, and four were used without any ill effects, proving that the laboratory flask was not contaminated; further the bottle had been issued from the laboratory 26 days before being opened and when opened had no smell. This absence of smell is proof that no culture, even of a few days old, of the tetanus bacillus was present. A number of other facts confirm this conclusion. Thus the period of incubation and the duration of the disease were prolonged, which would not have been the case with an injection of a ready-made culture and toxin. It was found that the Mulkowal tetanus bacillus when experimentally introduced into a bottle of water agar prophylactic for a few days produced a very rich and extraordinarily toxic culture; 1½ cubic centimetres of this mixture of toxins and microbes would represent an infection such as never occurs in nature. The disease should therefore have been of the most fulminating character ever observed clinically; whereas, on the contrary, it was of an average character with a relatively long incubation period and duration of the disease. The syringe, moreover, with which the injections were made did not convey tetanus to those inoculated from other bottles which would have been the case if it had been infected with a rich culture of tetanus, notwithstanding a soakage for a few minutes in a carbolic solution of 1 in 20. The dregs of the bottle showed some aerobic microbes and only a poor and weak culture of tetanus such as would develop under aerobic conditions, subsequently to the emptying of the bottle. The actual contamination of the bottle was rendered possible by the local authorities having abolished the laboratory instructions of sterilisation by heat and having substituted for them momentary dipping in carbolic acid. In the opening of the bottle the cork and neck were not sterilised by passing through the flame and for withdrawing the cork soiled forceps were used which had fallen to the ground and were applied to the mouth of the bottle without sterilisation. The fact that no accident occurred while the proper technique was unaltered proves the high degree of safety with which operations on a large scale can be carried out in India.

ASSOCIATION OF SCOTTISH MEDICAL DIPLOMATES.

—The annual general meeting of this association was held on June 19th at 11, Chandos-street, Cavendish-square, W. The report of the council was unanimously adopted. The retiring President, Mr. C. St. Aubyn-Farrer, was made an honorary vice-president. Dr. David Walsh was elected President for the year 1907-08, that post being tenable for one year only without break. Mr. Sydney Stephenson was re-elected honorary treasurer and Dr. Arthur J. Harries was appointed honorary secretary. Mr. Skene Keith and Mr. Charles Ryall were elected to vacancies on the council. We are requested to state that Dr. Alexander Morison, Dr. C. O. Hawthorne, and Dr. T. N. Kelynack have resigned their position as members of the council of the society.