Memorandum on the recent observations in the serum-therapy of plague in India. Submitted to the sanitary commissioner with the Government of India, September 1907 / by Khan Bahadur N. H. Choksy.

MEMORANDUM

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IN THE

SERUM-THERAPY OF PLAGUE IN INDIA.

Submitted to the Sanitary Commissioner with the Government of India, September 1907.

BY

KHAN BAHADUR N. H. CHOKSY, M.D.,

HON : CAUSÂ, FREIBURG, GERMANY.
CHEVALIER OF THE CROWN OF ITALY.
CORRESPONDING MEMBER OF THE IMPERIAL AND ROYAL SOCIETY OF PHYSICIANS OF VIENNA, OF THE MEDICAL SOCIETY OF MUNICH, AND OF THE MEDICO-PHYSICAL ACADEMY OF FLORENCE.
HONORARY MEMBER OF THE AMERICAN SOCIETY OF TROPICAL MEDICINE.
SPECIAL ASSISTANT HEALTH OFFICER, BOMBAY MUNICIPALITY IN CHARGE OF ARTHUR ROAD INFECTIOUS DISEASES AND MARATHA PLAGUE HOSPITALS.

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MEMORANDUM ON THE RECENT OBSERVATIONS IN THE SERUM-THERAPY OF PLAGUE IN INDIA.

In compliance with the desire of the Sanitary Commissioner with the Government of India, I have the honor to submit for his consideration the present memorandum on the results of further observations on the serum-treatment of plague in India. Before proceeding with the subject matter, I would venture to observe that scientific opinion, however pre-eminent, if "based on a priori reasoning," can scarcely be expected to counterbalance the weight of actual and demonstrable facts as elicited by long and laborious clinical observation. Nor is implicit reliance always to be placed upon "the results of laboratory experiments" conducted upon susceptible animals and their application, without any reservation, to the human being. How fallacious, not to say even mischievous, the inferences and conclusions so drawn may be, is well illustrated by a communication from Otto and Kolle* on a series of comparative tests made by them with various anti-plague serums. Whilst cautioning other observers against the application to man of experiences gained upon lower animals, the authors themselves fell into the very error and evolved a rather startling proposition to the effect that Lustig's serum should not be used in man! They were possibly not aware at the time, that the very serum they had condemned as unsafe for use in man, had been applied among 1550 patients and the benefit derived from its administration acknowledged by no less an authority than the Indian Plague Commission. † And lastly, that the volume of statistics available, when I submitted my representation to the Sanitary Commissioner in July 1906, was not greater. was to be regretted inasmuch as not more than 325 cases (222 hospital and 103 private) had been treated by then at Bombay. But the deficiency could have been readily supplemented by information available from Japan, Formosa, Hong-Kong, Mauritius, the Cape, Oporto, Glasgow, &c., where either Yersin-Roux serum from the Institut Pasteur de Paris or other serums prepared on the same principles elsewhere, had been largely utilised. Looking however to the volume of statistics now to be presented,

* Zeischrift für Hygiene und Infections Krankheiten IV Bd., 1902.
† Report of the Indian Plague Commission, page 317. para 565.

it is to be hoped that the necessity for going so far afield in search of further evidence would not arise.

PRELIMINARY CONSIDERATIONS.

In approaching the study of the serum-therapy of plague some preliminary considerations relating to the nature of the affection and the limitations they impose upon the successful application of the serum are worthy of attention. And no study could be held to be complete that either ignores their importance or fails to recognise the unfavourable influence they exert in every case of plague. They may be briefly summarised as under :—

(*a*) The complex nature of the disease.

(*b*) Its great virulence and high mortality.

(*c*) Early and grave septicæmia.

(*d*) Multiple foci of infection, and

(*e*) Its rapid course.

(*a*) *The Complex Nature of the Disease* :—

This involves as we are aware two distinct and separate processes—bacteriolytic and antitoxic—before recovery can take place. As this has been discussed fully elsewhere* it need not detain us here.

(*b*) *Its Great Virulence and High Mortality* :—

The vital statistics of Bombay from 1904 to 1907 show the virulence of the disease and the high rate of mortality that has hitherto characterised our epidemics :—

Years.	Attacks.	Deaths.	Case mortality rate per cent.
1904 ...	15,488 ...	13,538 ...	87.40
1905 ...	16,308 ...	14,198 ...	87.06
1906 ...	12,323 ...	10,830 ...	87.88
1907 (7 months) ...	6,850 ...	5,974 ...	87.21
	50,969 ...	44,540 ...	87.38

The foregoing statement exhibits an almost uniform mortality rate of over 87 per cent extending over four successive

* *Vide* the Treatment of Plague with Lustig's serum by the author :—Also the Representation submitted to the Sanitary Commissioner with the Government of India, July 1906.

epidemic seasons. The average rate of mortality was 87·38 per cent ; and if the hospital cases with a lower case mortality be excluded, it would stand at 89 per cent. In other words, it means that the disease is so virulent that only 11 individuals out of every 100 attacked, escape.

(*c*) *Early and Grave Septicæmia* :—

Blood examination of over 1400 patients at the Maratha and Arthur Road Hospitals as made by Drs. Alfons Mayr and Berestneff in 1901 and 1902 revealed that 617 that is—45 per cent—were septicæmic ; all these patients succumbed except four, two having only one or two colonies of plague bacilli, and two doubtful cases. Greig found septicæmia among 60 per cent of the cases he examined. The Plague Research Commission examined the blood of 94 patients during the epidemics of 1905 and 1906,* and found 55 septicæmic, *i.e.*, 58·5 per cent. All died except two and they owed their recovery to the application of Yersin-Roux serum. The extent of septicæmia varied very greatly—between 10 to 1,000 plague bacilli per c. c. of blood ; in some they exceeded 10,000, and in one case the number was 1,000,000. The gravity of this factor is self evident indicating as it does that 58 per cent of the hospital admissions are septicæmic and therefore practically beyond all hope.

(*d*) *Multiple Foci of Infection*:—

Unlike diphtheria, the foci of systemic infection are numerous. Not only is there rapid extension of the lymphatic infection, involving numerous glands, superficial and deep-contiguous as well as distal, but a constant stream of blood infection is kept up by direct communications between the lymphatics on the one hand, and the veins and even arteries on the other, in those regions where buboes mostly occur†. The constant infection and reinfection of the blood enhance the difficulties attendant upon the action of the serum.

(*e*) *Its Rapid Course*:—

The disease runs a very rapid course, by far the largest proportion of cases succumbs from the third to the sixth day of illness. And as the time of admission into hospital coincides generally with the period of the maximum fatality, 55 to 60 per cent. of the deaths occur within 48 hours of admission. It would not be wrong therefore to assume, that practically all the septicæmic cases die off within this period ; we thus see that out

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* *Vide* the Journal of Hygiene, September 1906. I am indebted to the Plague Research Commission for the information on the subject in advance.

† *Vide* the Lancet 3rd March 1906—On the Relation of Blood to Lymphatic Vessels by Cecil H. Leaf M.B., also the Treatment of Plague with Lustig's Serum by the author.

of every 100 admissions, there exist only 42 who are likely to be influenced by any kind of treatment, and for statistical purposes 58 per cent. should be eliminated from the hospital records.

Such then are the circumstances and conditions under which the serum-treatment of plague has to be conducted in hospital practice in India, and such the adverse influence of the factors militating against its successful application. To any clinician familiar with the nature, course and progress of acute infective diseases, the barriers raised by them would appear to be simply insurmountable and the utter futility of expecting brilliant results sufficiently patent. The true explanation of the apparent want of success of serum-treatment and of the differences of opinion that it has raised among numerous observers is therefore to be found in them, and unless and until the results are looked into with due regard to these inhibitory factors, erroneous conclusions are apt to arise. The wonder is, not that we have been able to demonstrate such comparatively good results, but that any at all have been obtained under such unfavourable conditions.

THE RESULTS OF RECENT OBSERVATIONS.

I shall now discuss the results of the recent observations of the serum-treatment of plague as applied at Bombay, Poona, Indore, Calcutta and Karachi comprising 1081 cases.

Observations at Bombay 1905-1907.

The total number of observations at Bombay now amounts to 690 (upto 31st July 1907) and includes 438 patients treated at the Maratha Hospital, 9 at the Parsee Fever Hospital and 243 in private practice by various observers. I am personally responsible for 490 of the above total.

Maratha Hospital.

The observations at the Maratha Hospital extended over three epidemic seasons :—

1905	222	Cases
1906	48*	,,
1907	168	,,
Total	438	Cases.

The System of Treatment:—The rationale on which the present series of observations has been based is as follows :—

Clinical experience extending over several epidemics, subsequently supplemented and confirmed by blood examination having

* The number of cases treated was limited owing to the late arrival of the serum from Paris.

shown that 55 to 60% of hospital admissions being septicæmic are practically beyond any chances of recovery and that it would be merely wasting the serum if applied to all, either indiscriminately or even to half the number by the alternate method, the best course, which would not only obviate such waste, but allow of a larger number of observations and at the same time the least objectionable and well calculated to demonstrate the utility or otherwise of the serum, would be to reject all those who appeared clinically so far advanced as to indicate scarcely any chances of recovery. With this view, only such acute cases, the duration of whose illness did not exceed five days and the state of whose circulation indicated that there existed some hope, however feeble though it may be, of saving their life were subjected to the serum-treatment. All others in whom the cardio-vascular paresis had advanced so very far as to render the pulse thready and extremely quick or imperceptible and who had no reasonable probability of being influenced by any line of treatment, as also those actually moribund, were rejected ;—all however receiving the same general drug-treatment. And similarly all those whose period of illness had extended to six days and over (with but few exceptions) as also, all semi-convalescent and convalescent patients were rejected. The reasons for thus arbitrarily restricting the choice of patients for serum-treatment upto the fifth day of illness were the inefficacy of the serum beyond this stage of the disease as shown by past experience, as also the fact that after that period most of the cases are found actually in the dying state and that only a few who survive by then have a reasonable probability of recovering without the aid of the serum. The inclusion of the latter therefore would have favourably affected the results. The above procedure was adopted as the out-come of my long clinical experience, and that it was fully justified, will be borne out by the results as shown hereafter. It met with the approval of Prof. C. J. Martin of the Advisory Committee for Plague Investigation in India, who further suggested that after rejecting the unfit cases, every alternate case might be treated with the serum so that those left untreated would be controls for purposes of simultaneous comparison, and it was thus anticipated that it would be possible to obtain an exact numerical demonstration of the value of the serum treatment in hospital practice. This was accordingly adopted among 400 cases considered fit for treatment, 200 of whom were treated alternately with a similar number of control cases. The observations therefore divide themselves into two series.—(*a*) The first includes 238 cases considered fit for treatment and—(*b*) the second, 200 cases treated alternately as above.

The Results of Serum-Treatment :—(*a*) In the first series among 238 patients, there were 141 deaths and 97 recoveries equivalent to a case mortality rate of 59·2 per cent ;—

(*a*) *Cases fit for Serum-Treatment.*

No.	Died.	Recovered.	Case Mortality per cent.
238	141	97	59·2

(*b*) In the second series, the 200 control cases lost 148, and 52 recovered, the case mortality being 74·0 per cent whereas among the 200 serum cases, there were 127 deaths and 73 recoveries, equivalent to a case mortality rate of 63·5 per cent. The difference in favour of the serum cases was therefore 10.5%.

(*b*) *Cases fit for Serum treatment treated alternately with similar Cases as Controls.*

	No.	Died.	Recovered.	Case mortality per cent
Control Cases	200	148	52	74·0
Serum ,,	200	127	73	63·5
Difference in favour of Serum Cases				10 5%

This difference of 10·5% in favour of the serum cases should therefore be considered as the numerical demonstration of the value of the serum treatment in hospital practice obtained by the method of rational alternation of cases based upon clinical experience. That the difference has not been greater is not a matter for reproach, considering the unfavourable factors above described. But that it should almost equal the normal recovery rate from the disease (11 %) or in other words that the serum treatment should be capable of doubling the rate of natural recovery should be considered a matter for extreme satisfaction. In no other similar grave infective affection has such been the case. If the above series of cases are amalgamated and the results considered on the whole we see that

No.	Died.	Recovered.	Case Mortality per cent.
238	141	97	59.2
200	127	73	63.5
438	268	170	61.1

the case mortality rate of 438 cases is 61·1% as contrasted with 74% among the control cases, the difference in favour of the serum cases being therefore 12·9% or to put it in another way, whereas about 39 patients recover under the serum treatment among every 100 treated, only 26 recover under the ordinary drug treatment. The serum treatment thus increases the ratio of recovery by 33% among those who are amenable to any kind of treatment and not beyond all hope. Consider these results however as we may, we cannot but admit the beneficial influence of the serum treatment as an indisputable fact.

Analysis of Serum and Control Cases—In my former communication to the Sanitary Commissioner with the Government of India, I had pointed out how practically impossible it was to obtain *control cases strictly comparable with those receiving the serum* in any method of alternate treatment adopted for purposes of comparison. I had further indicated that the chief determining factor was the condition of the circulation, and that if it was not *approximately comparable* among those cases—as it can never be strictly so—no two sets of cases however apparently similar in other respects would be worth comparing. It should be remembered here that in the present series of cases, no attempt has been made to argue that the serum treated cases were *strictly comparable* to the control. All that is intended to convey is that they were *only approximately* so, in so far as the state of the circulation was concerned. And the following details of analysis bear this out. The period of the duration of illness as given by hospital patients is always an indefinite and unreliable factor, and it is only by the course of events and the progress of the case that it could be determined with anything like accuracy:—

Analysis according to Duration of Illness

Duration of Illness.	Serum Cases.				Control Cases,			
	No.	Died.	Recovered	Case mortality per cent,	No,	Died.	Recovered.	Case mortality per cent.
1st Day	11	7	4	63·6	8	4	4	50·0
2nd ,, ...	73	46	27	63·0	66	48	18	72·7
3rd ,, ...	68	43	25	63·2	71	53	18	74·6
4th ,, ...	30	20	10	66·6	28	25	3	89·3
5th ,, ...	15	10	5	66·6	16	8	8	50·0
6th ,, ...	3	1	2	33·3	11	10	1	90·0
	200	127	73	63·5	200	148	52	74·0

The foregoing statement shows that the distribution of cases between the serum and control groups was not exactly equal, though fairly so and that the numbers were not sufficiently large among the first, fifth and sixth-day cases to indicate any striking differences in the results. We have therefore to fall back upon the second, third and fourth-day cases, and they indicate that whilst in the control group the rate of mortality advanced from 72·7% to 74·6% and to 89·3% respectively, it was 63·0, 63·2 and 66·6% in the serum group. The mortality rate appears to have been practically equal in the serum group, among the first, second and third-day cases which is rather unusual and is probably due to faulty information of the duration of illness. Plague unfortunately is not a science of arithmetic or mere numerals, otherwise we should not have to encounter such discrepancies which are not capable of explanation. But such apparent irregularities are found not infrequently to right themselves when statistics in larger numbers are considered. One important point in this connection should not be overlooked *viz.*, that among the above 400 cases the proportion of first-day cases was just 4·7% which shows, how precious time is wasted in resorting to hospitals and how the latter are thus handicapped in their fight against such a virulent infection.

Analysis according to Location of Buboes.

The following statement shows that the serum and control cases approximated more closely as regards the distribution of buboes than in the previous instance:—

Location of Buboes.	Serum Cases.				Control cases.			
	No.	Died.	Recovered.	Case mortality per cent.	No.	Died.	Recovered.	Case mortality per cent.
Femoral Inguinal and Iliac	131	84	47	64·1	136	99	37	72·7
Cervical ...	8	5	3	62·5	7	5	2	71·4
Axillary ...	46	28	18	60·8	40	29	11	72·5
Multiple: — (contiguous and distal).	15	10	5	66·6	17	15	2	88·2
Total ...	200	127	73	63·5	200	148	52	74·0

The buboes have been classified into four main divisions according to the frequency of their prevalence and their gravity and it will be seen that among multiple buboes the serum cases were better off by 21·5% than the control, and similarly among axillary cases, the difference in their favour was 12·3%. Among the two other divisions it was between 8 and 9 %. It thus ap-

pears, that corresponding with an almost approximate distribution of cases, the serum cases gave better results in every group. There was also lesser suppuration of the buboes among the patients who recovered. They were absorbed in 58·9 % of serum cases as against 48·0 % among the control; convalescence was therefore hastened to that extent among the former.

Analysis according to Complications—From the unequal distribution of the grave complications of plague among these two groups of cases, we see that the control cases had a distinct advantage over the serum, as in this respect they were *not even approximately comparable* with the latter. Whilst the control had 6 fewer complications of a certain class, the serum cases had 27 more of another :—

	Serum Cases.			Control Cases.		
	No.	Died.	Recovered.	No.	Died.	Recovered.
Coffee-Ground Vomiting	2	2	...	5	5	...
Hæmatemesis	2	...	2	1	1	...
Hæmaturia	1	...	1	3	2	1
Melæna	1	...	1	...	...	...
Secondary Pneumónia	11	10	1	6	6	...
Grave Icterus	1	1	...	...	...	...
Mesenteric Infection (grave)	7	4	3	4	2	2
Tympanites (grave)	6	4	2	1	1	...
Marasmus	18	16	2	7	5	2
Pest Pyæmia	2	2	...	...	...	...
Glosso-labio-pharyngeal Paralysis ...	1	1	...	...	...	...
General Convulsions	...	...	...	1	1	...
Meningitis	1	...	1	2	2	...
Epilepsy	...	...	...	1	...	1
Tetanus	1	1	...	...	...	...
Keratitis	2	2	...	4	4	...
Sub-Conjunctival Hæmorrhage ...	2	2	...	1	1	...
Cellulo-Cutaneous Plague (Necroses) ...	5	3	2	16	9	7

Three complications in the above list require a passing reference. Secondary pneumonia existed among 17 cases in all with but a single recovery and that in the serum group—a striking enough testimony of its gravity. Marasmus accounted for 18 among the serum cases with but 2 recoveries, as against 7 with 2 recoveries among the control. The reasons for this are sufficiently obvious and have been fully set forth in my report on serum-treatment for 1905. Cases of Cellulo-cutaneous plague with necroses that form by itself

a distinct and comparatively benign type of plague numbered five only among the serum cases as against 16 among control. The one and only inference to be drawn from the above analysis is that whatever comparative method of treatment we may adopt, it is practically impossible to ensure such distribution of cases as to have *control cases strictly comparable with those treated with the serum.* And plague being what it is, the above system is the best adapted to the circumstances, least open to objection, sound from clinical experience and best calculated to bring out fair results.

Influence of Prophylactic Inoculation.—The control patients included three recently inoculated cases, of whom two recovered and one died : among the serum cases there was one only who recovered.*

Prolongation of Life under Serum-Treatment.

That apart from saving more lives, the serum prolongs life as well is well demonstrated by the following tabulation of the time of death after admission into hospital :—

	Within 1 day.	Within 2 days.	Within 3 days.	Percentage of deaths within 4 days to total mortality.
Control cases	21·6 %	28·3 %	16·2 %	79·0 %
Serum cases	14·9 %	19·6 %	8·6 %	58·2 %

It will be noted that whilst among the control cases 79 per cent of all deaths occurred within 4 days of admission, the ratio was 58·2 per cent among the serum and examining the figures from day to day we see the same striking differences. Would that it were possible to carry the serum-treated patients over two days longer, and thus ensure recovery in larger numbers.

The Rejected Cases.

The real test of the soundness or otherwise of the system of serum-treatment adopted in these observations, lies in the statistics of the cases rejected as unfit ; it must stand or fall by the results among them. If the results indicate that the elimination was judicious and careful, it would mean, that it was justifiable and that the system adopted was rational as based on clinical experience and therefore the only one applicable to plague. Should it be otherwise, then it must necessarily convey the impression, and rightly so, that cases that would have been influenced by the

* Among the whole series of 438 cases there were 6 recently inoculated, of whom 5 recovered and one died. Of 6 other cases (3 among control and 3 among rejected—because of too recent inoculation) two died and four recovered : there were thus 12 inoculated cases with 3 deaths and 9 recoveries.

serum had been unwarrantedly excluded from its benefit. Simultaneously with the 438 cases treated with the serum and 200 taken as control, that is 638 cases in all, the large total of 557 cases was rejected as unfit as under :—

Duration of Illness.	Rejected cases during the Alternate system.			Other Rejected cases simultaneously with serum-treatment.		
	No.	Died.	Recovered.	No.	Died.	Recovered.
1st to 5th day	243	234	9	143	142	1
6th to 9th ,, ...	81	43	38	35	28	7
10 days and over ...	27	7	20	21	8	13
Pestis Ambulans ...	4	.....	4	.....	.....	.....
Too Recently Inoculated.	3	1	2	.....	.....	.....
Total.	358	285	73	199	178	21

Excluding the few recently inoculated cases, and cases of pestis minor, it will be observed that there were 386 cases, the duration of whose illness was between the first and fifth days. There were only 10 recoveries among them, equivalent to a recovery rate of 2·6 per cent. The margin of error therefore, in clinically determining, from the state of the circulation that the patients were not likely to be influenced by the serum-treatment, was thus 2·6 per cent ! Who would deny under these circumstaces that the rejection was not judicious or discriminate so far as human foresight could prevail.

The following tabulation contrasts, these three groups of cases and further confirms the above view:—

Acute cases between the first and fifth days of Illness.	No.	Died.	Recovered.	Case Mortality per cent.
Rejected Cases*	386	376	10	97·4
Control Cases	189	138	51	73·0
Serum Cases	428	261	167	60·9

* The Plague Research Commission examined some of these cases for Septicæmia and found 67 to be septicæmic, all of whom succumbed.

The above figures need hardly any comment, and strengthen the conviction that we were fully justified from clinical experience in adopting the system we did. Just imagine for a moment, what an enormous quantity of serum would have been wasted, had we attempted to treat the above 386 patients and how many who would otherwise have been benefitted by it, deprived of its aid. Apart from justifying the rejection of these cases, the previous tabulation lends further support to our contentions about the rejection of the cases that had gone over the period of five days as discussed in one of the opening sections. It shows that cases who survive over this period are either dying or just beginning to improve. The former can under no circumstances be saved and the latter do not require the help of serum as nature has by the time elaborated sufficient antibactericidal and antitoxic substances to ensure recovery. And although some of those who survive over 9 days die from complications, the recovery rate among them is as high as 69%.

Rejected cases.	No.	Died.	Recovered.	Case mortality per cent.
From 6 to 9 days	116	71	45	61·2
10 Days and over	48	15	33	31·2

Deaths among the above cases cannot be averted, nor can they be influenced by any serum, as they are due to toxæmia, the grave results of the combination of the toxins with the tissue cells of the body.

We may thus reasonably claim that the above statistics have fully justified the position we have hitherto maintained with regard to the method of testing the utility of the serum treatment. They have further substantiated our contention that not all the patients whom we receive in our hospitals are amenable to this treatment. That the hospital treatment of plague is thus greatly handicapped by a large proportion of unsuitable cases and that comparative methods of treatment are unsuitable to plague and, if adopted, possess but an approximately relative value.

CASES TREATED IN PRIVATE PRACTICE AT BOMBAY 1904-1907.

The observations in private practice at Bombay now amount to 243* with 144 recoveries and 99 deaths, equivalent to a case mortality rate of 40·7%. They may be tabulated as under :—

Observers.	No.	Died.	Recovered.	Case mortality per cent.
Dr. B. Pais	128	52	76	40·6
„ M. A. de Heredia	55	21	34	38·1
„ N. H. Choksy	52	22	30	42·3
„ Alfons Mayr	6	3	3	50·0
„ K. S. Engineer...	1	...	1	...
Lieut. Col. L. F. Childe, I.M.S. ...	1	1	...	100·0
Total	243	99	144	40·7

It will be recognised from the foregoing figures that the case mortality rate among these cases is lower by 20·4 % as compared with hospital cases and that the variation between the results of three observers who treated the largest number of cases, does not exceed 4·2%. To what causes is the difference of 20·4% between the private and hospital cases to be attributed, naturally suggests itself. The answer to that is—Chiefly to the overwhelming preponderance of first-day cases among the former :—the proportion to total treated was 47·0% as against 8·4% among the latter. The subjoined tabulation shows at a glance the distribution of hospital and private patients according to duration of illness at time of treatment and contrasts their mortality :—

Duration of Illness.	1905-1906-1907. Maratha Plague Hospital.				1904-1905-1906-1907. Patients in Private Practice.			
	No.	Died.	Recovered.	Case Mortality per cent.	No.	Died	Recovered.	Case Mortality per cent.
1st Day	37	17	20	45·9	116	33	83	28·4
2nd „	138	85	53	61·5	77	33	44	42·8
3rd „	145	97	48	66·8	37	25	12	67·5
4th „	72	41	31	56·9	5	2	3	40·0
5th „	36	21	15	58·3	7	5	2	71·4
6th „	7	4	3	57.1	1	1	...	100·0
7th „	3	3	...	100·0	...	...	...	...
Total ...	438	268	170	61·1	243	99	144	40·7

* A few more cases have been treated, the particulars of which are unfortunately not available.

As a corollary to the numerical superiority of the first-day cases among private patients, we observe great differences in results between them and hospital cases. The same is also noticeable among the second-day cases. It is possible that this was partly due to the better social condition of the former, but not invariably so, as we shall have to notice hereafter. It is principally *to early treatment and early treatment alone* that the better results should be ascribed. This view is considerably strengthened by the mortality rate among the third-day cases, which is equal—nay even higher by a fraction, among both the groups, indicating as it does, that the virulence of the affection is extremely great at the time and that social conditions, however apparently favourable, do not alter the essential characteristics of plague infection. And the mortality rate is thus found to more than double itself by the third day as compared with that on the first.

The racial distribution of hospital and private cases and the incidence of case mortality among them was as under :—

Races.	Hospital Patients.				Private Patients.			
	No.	Died.	Recovered.	Case Mortality per cent.	No.	Died.	Recovered.	Case Mortality per cent.
Europeans... ...	...	...	...	.....	3	1	2	33·3
Eurasians	...	...	...	.....	1	1	...	100·0
Christians (Goans)	69	32	37	46·5	129	57	72	44·1
Hindoos	275	184	91	66·9	58	22	36	37·9
Mahomedans ...	53	30	23	56·6	16	7	9	43·7
Parsees	38	21	17	55·2	34	10	24	29·4
Chinese	...	...	...	.....	1	...	1	.....
Jews	2	1	1	50·0	1	1	...	100·0
Japanese	1	...	1	.....	...	...	...	.....
Total...	438	268	170	61·1	243	99	144	40·7

The first point that strikes us in the above statement is the uniform reduction in mortality among Christians, Hindoos, Mahomedans and Parsees treated in private practice. But whilst the three latter communities show a difference of 29·0%, 12·9% and 25·8% respectively in their favour, it is but 2·4% among Christians although a much larger number happened to be treated with the serum. That was because most of them belonged to the Goan community, mostly poor, treated in their shops or clubs,

usually without any nursing and amidst surroundings the least calculated to favour success. Is it then to be wondered at, that they did not respond so well to the treatment as the other communities ?

Owing to the difficulty of obtaining the detailed particulars of all the patients treated in private practice, a complete analysis of the complications, &c., that existed in them is not available, but from the few data at hand, it appears that plague is no respector of persons or social status inasmuch as the virulence of the affection was just as well marked among them as among the hospital cases:—

Fatal Cases :—Among the fatal cases, 20 were septicæmic when the treatment was begun ; one was suffering from pneumonic plague, three were pregnant, one of them being a Hindu girl of 18 in the fourth month of her third pregnancy. One patient was over 80 years. The serum injections were prematurely stopped among four. Two cases were too far advanced for serum treatment, but had to be treated at the solicitations of friends. In septicæmic cases, life was prolonged for 12, 15 and 30 days, the quantity of serum used being 1280, 1520 and 1900 c. c. respectively. In one of them plague bacilli and streptococci were found in the blood on the twentieth day of illness, after 1500 c. c. had been injected. In another case, the temperature rose to 108° after reaching to normal after the first injection of serum and remained so for eight hours ; subsequent injections had no influence on the course of the disease.

Successful Cases :—One was a case of mixed infection—plague and measles—the latter supervening on the third day of illness, although slight coryza and watering of the eye s were present from the first day of fever, together with femoral and inguinal buboes. One Chinaman, who recovered, had 1220 c. c. of the serum in nineteen injections. He had a succession of buboes, and after each fresh injection, they disappeared from one part to appear at another. A Parsi patient had plague and pyæmic infection with suppuration of both the tunica vaginalis and cold abscesses ; pyæmia developed after the plague symptoms had been well controlled by the serum: antistreptococcus serum was used and he made a tardy recovery. The buboes became absorbed in 7 5 per cent of patients who recovered ; their convalescence was therefore very rapid.

The above particulars illustrate the limitations and difficulties encountered in the use of serum in private practice and indicate that the serum was not applied invariably under the most favourable conditions, as it might at first sight appear. The results therefore should be considered all the more encouraging.

OBERVATIONS AT POONA—1906.

The serum treatment of plague came into vogue at Poona during the epidemic of 1906 after one patient had been successfully treated by Lieut.-Col. Burke, I. M. S., and Dr. Erasmus Dias in consultation with myself. It was readily taken up by the profession, official as well as non-official, and was also used at the General Plague Hospital. In spite of the fact that in several instances the treatment was adopted among patients scarcely suitable, the results were found to be satisfactory and coincided with those obtained at Bombay. Dr. Anklesaria treated 56 patients at the General Hospital, of whom 34 died and 22 recovered, the case mortality being therefore 60·71% as compared with 61.1% among 438 cases treated at the Maratha Hospital Bombay. Major G. Thomson, I. M. S., Capt. Sylvester Bradley, R. A. M. C., Drs. Modi, · Bilpodiwalla, Gokhale, Dias, Bharucha, Shikhare and Sunderlal Modi treated altogether 62 patients, all of whom were private cases with the exception of 11 treated by the first two in the regimental and cantonment hospitals. There were 24 deaths and 38 recoveries among them, equivalent to a case mortality rate of 38·7% as compared with 40·7% among 243 private cases at Bombay. The results in both the series of cases exhibited a remarkable coincidence. Tho treatment was conducted on the lines laid down in my report for 1905 with the exceptions noted below. The results of the cases treated by each observer will be found in the summary.

Remarks:—From the details kindly furnished by the above observers, it appears that in clinical effects, as well as in other particulars the action of the serum was found to be similar to what was noted at Bombay. Among 60 patients who recovered, the buboes did not suppurate in 30, a somewhat lower average than at Bombay. The "serum disease" (erythema and arthritis) was not so evident at Poona, as the majority of patients were strict vegetarians, in whom these complications do not appear with much frequency. About 15 patients only suffered from it. Secondary pneumonia was observed in 6 patients, five of whom recovered and one died. Two patients who had been inoculated with Haffkine's prophylactic six and ten days previous to the attack were treated with the serum and both recovered.

Among the fatal cases two were septicæmic and one of pneumonic plague. The serum was prematurely stopped in four cases. Five had practically no care or nursing. One patient was pregnant and succumbed after premature labour. Another died from marasmus and meningeal symptoms after 2 months. One patient wa unconscious, but recovered conciousness after the first injection, and was able to make her will, but succumbed thereafter. One was a case of second attack of plague after an interval of four years.

Dr. Anklesaria laboured under similar disadvantages as regards early cases as we do at Bombay. The quantity of serum used

per patient at the hospital was somewhat less than our average ; it was however more liberally administered among the private cases in the city. Although the average mortality rate in the city was 93·5%, it was 65% among 17 7 patients under ordinary treatment at the hospital. This was probably due to the most serious cases having died off before removal to the hospital or perhaps to a somewhat better class of patients than those generally coming under treatment at Bombay. Had the serum been used somewhat more freely than it was, under the above comparatively favourable circumstances, the results would have been better still. Major G. Thomson, I. M. S., was rather more favourably situated with regard to his patients as they were all first-day cases, but he appears to have used too small doses. Seven of his patients were privates from his regiment (104th Marathas N. I.) and as they were all seen within a few hours of illness, he could have obtained better results, instead of only 2 recoveries among 7 cases, had he used the serum more liberally.

OBSERVATIONS AT INDORE 1903—06.

Dr. G. R. Tambe, State Surgeon at Indore, first used the serum in 1903-04 and treated about 25 patients of whom 13 recovered. During 1906, at the Indore Plague Hospital, 92 patients were treated, of whom 39 died and 53 recovered, the case mortality rate being 42·3%. Among 101 private cases treated by Dr. Tambe and other observers, as will be found in the summary, there were 27 deaths and 74 recoveries, equivalent to a case mortality rate of 26·7%. These results appear to be extremely favourable inasmuch as nowhere anything approaching to them has been recorded.

They could be accounted for either by the comparatively lesser virulence of the disease or by early treatment or by the greater efficacy of the serum. Dr. Tambe states that "the recoveries amongst general patients in the city,—not to mention those treated at the plague hospitals or registered as out-patients in the city were not less than 1553 out of between 6000 to 7000 attacks." The average case mortality rate would therefore work out at 74·1% or 77·8% respectively, *i. e.* much lower than what obtained at Bombay and Poona, 89% and 93·5% respectively. From the data kindly placed at my disposal by Dr. Tambe, it appears that both as regards the lesser virulence of the epidemic and the greater preponderance of first-day cases he was exceptionally better situated than us. Apart from the general mortality rate indicating the same, the hospital mortality confirms this view as it was 61·1% only among the non-serum cases as contrasted with 65·0% and 75·2% at Poona and Bombay respectively. And whereas the proportion of first-day cases among hospital and private patients combined was 21% at Poona and 22·4% at Bombay, it was 64%

at Indore, These data are conclusive as to the extremely favourable circumstances under which the serum treatment was applied at Indore. The results shown under the serum treatment still further support this view. The case mortality rate among first-day hospital cases at Bombay was 45·9%, whereas among the Indore cases it was 31·7% and similarly among private cases at the former place it was 28·4% against 25·2% at the latter. There was thus a difference of 14·2% in favour of the hospital cases and 3·1% in favour of private cases at Indore.

As regards the greater efficacy of the serum there could have been no difference excepting in so far that the milder type of the disease required a correspondingly smaller dose. But looking to the doses employed and the limited number of injections given (114 patients had only one injection of less than 40 c.c. each. 51 received two injections aggregating 52 c.c. each. 24 had 87 c.c. each; and 4, 112 c.c. each) the mildness of the disease is even more prominently brought into view than by the previous figures. Our experience at Bombay with small doses has been so unfavourable, both on account of the virulence of the disease and its rapid extension within a few hours of its onset, that the small doses as used at Indore or the delay of 24 hours between two injections as practised by Dr. Tambe, would be fatal. We must conclude therefore that no comparison between the Bombay cases and those at Indore would be of any value. The only cases with which they could be at all compared and to which they approach in results are those among the European patients treated at Oporto by Calmette and Salimbini. But at the same time we have to note that whilst the average city mortality was between 74 per cent. and 78 per cent. it became reduced to 42 per cent. in hospital cases and 26 per cent. in private cases, a striking difference and greater than that noted at Oporto, but which is not capable of any explanation. Another point that appears rather puzzling is the difference in the results between hospital and private serum cases :—

	Case mortality rate of Hospital serum cases.	Case mortality rate of private serum cases.	Difference in favou of private cases per cent.
Bombay	61·1	40·7	20·4
Poona	60·71	38·7	22·0
Indore	42·3	26·7	15·6

With epidemics of a more virulent type the results at Bombay and Poona show almost approximate differences between the hospital and private cases, and yet strange as it may appear, the results at Indore instead of being better, are lower by 6 per cent.

After making due allowances for everything that favoured the serum cases at Indore, it becomes evident that certain points remain inexplicable and neither Dr. Tambe's report, nor his subsequent communications to me throw any light on them. The Indore results must therefore be judged on their merits as they stand.

Observations at Calcutta 1904-05.

Lieut-Col. Dutt, I.M.S., Dr. M. Banerjee and others have used the serum at Calcutta on a rather limited scale and from the data supplied by them to Dr. Frederick Pearse, the Special Health Officer for Plague, it appears that during the year ending 30th June 1905, particulars of only 20 cases so treated could be obtained. Six of them were moribund or nearly so when injected. The treatment in almost all the cases was adopted late, the doses employed were small, and in nearly half the cases one injection only was administered. Marked and rapid change for the better was observed in six cases. The mortality rate among all the serum cases was 65% as against 78% in hospital cases.

Observations at Karachi.

Dr. Nazareth has treated 27 cases with 15 deaths and 12 recoveries and Dr. K. D. Contractor, F.R.C.S., Edin., 5, of whom 3 recovered and 2 died.

SUMMARY.

The observations discussed in the preceding pages may now be fitly summarised here and the results considered on the whole. I have endeavoured in the following statement to furnish as complete a list as possible of the observations made with Yersin-Roux serum upto 31st July 1907, and with the exceptions noted above, it may be taken so far as complete :—

Observations from 1898-1904.

Observers.	No.	Died.	Recovered.	Case mortality per cent.
1898—1904.				
Yersin, Simond, Mason, the German, Russian and Indian Plague Commissions, Drs. Alfons Mayr, West and Dr. Choksy (at Bombay, Bangalore, Karad, Karachi, Mandvi, &c.)	570	358	212	62·0
Total ...	570	358	212	62·0

Observations from 1905-1907.

Observers.	No.	Died.	Recovered.	Case Mortality per. cent.
1905 and 1907.				
BOMBAY.				
Dr. N. H. Choksy— at the Maratha Plague Hospital...	438	268	170	61·1
Dr. S. K. Nariman— at the Parsee Fever Hospital ...	9	4	5	44·4
In Private Practice:—				
Dr. B. Pais	128	52	76	40·6
Dr. M. A. de Heredia	55	21	34	38·1
Dr. N. H. Choksy	52	22	36	42·3
Dr. Alfons Mayr	6	3	3	50·0
Dr. K. S. Engineer	1	...	1	...
Lieut.-Col. L. F. Childe, I.M.S. ...	1	1	...	100·0
Total ...	243	99	144	40·7
1905 and 1906.				
INDORE.				
Dr. G. R. Tambe	25	12	13	48·0
Do. do.	61	12	49	19·1
Plague Hospital staff	92	39	53	42·3
Dr. S. N. Deo.	4	1	3	25·0
„ Bhandarkar	1	...	1	...
„ Atmaram	5	1	4	20·0
„ Sarangpani	19	12	7	63·8
„ Golvelkar	1	...	1	...
Tookojirao Hospital staff	7	...	7	...
Dr. Surujparsad	2	...	2	...
Mr. Lohokre	1	1	...	100·0
Total ...	218	78	140	35·7

Observers.	No.	Died.	Recovered.	Case Mortality per cent.
1906.				
POONA.				
Dr. B. K. Anklesaria—				
at the General Plague Hospital...	56	34	22	60·7
Dr Erasmus Dias	17	8	9	47·0
,, S. H. Modi	16	3	13	18·7
Major G Thomson, I. M. S. ...	8	5	3	62·5
Dr. Erach S. Bharucha	6	3	3	50·0
,, D S Bilpodiwalla	4	...	4	...
Capt Sylvester Bradley, R.A.M.C. .	3	...	3	...
Dr. P.V. Shikhare	3	2	1	66·6
,, Soonderlal N. Modi	3	2	1	66·6
,, V. C. Gokhale	2	1	1	50·0
Total ...	118	58	60	49·1
1904—1905.				
CALCUTTA.				
Dr. M. Banerjee	3	1	2	33·3
Other Practitioners	20	12	8	60·0
Total ...	23	13	10	56·5
1907.				
KARACHI.				
Dr. Nazareth	27	15	12	55·5
,, K. D. Contractor	5	2	3	40·0
Total ...	32	17	15	53·1
Total of Observations from 1905—1907	1081	537	544	49·6
Grand Total ...	1651	895	756	54·2

The foregoing statement shows a total of 1651 cases treated with the serum with a mortality rate of 54·2 per cent. If the

observations made during the last two and a half years are separated from those of the previous years we note as under :—

	No.	Died.	Recovered.	Case mortality per cent.
Observations up to and including 1904	570	358	212	62·0
Observations during 1905-1907 ...	1081	537	544	49·6
Total	1651	895	756	54·2

The later observations number 1081 against 570 during the previous years. While the latter comprise but isolated observations, conducted by different observers in small numbers at various centres, under varying conditions, and distributed over a period of seven years, the latter have the advantage not only of more systematic observation, but of having been conducted during three epidemics at but three places. And further whilst the previous ones laboured under the disadvantages incidental to all new lines of treatment, the latter have gained by the experience obtained in the serum-therapy of plague with other serums be sides the one under consideration. Greater confidence in its utili ty and boldness on the part of observers would therefore expla in the better results of the later observations.

Another point that the above statement brings into view is the disparity in the results between hospital and private cases owing to the greater preponderance of first and second-day cases among the latter, apart from their better social condition :—

	No.	Died.	Recovered.	Case mortality per cent.
Hospital Cases	613	350	263	57·0
Private Cases	468	187	281	39·9
Total	1081	537	544	49·6

The difference of 17·1 per cent. between the two is a striking testimony of the advantages of early treatment which is still better demonstrated by the following tabulation of 1037* patients

* Particulars of 44 patients are not obtainable.

according to the duration of illness when they came under treatment :—

Duration of Illness.	No.	Died.	Recovered.	Case Mortality per cent.
1st Day	316	96	220	30·3
2nd ,,	300	158	142	52·6
3rd ,,	246	155	91	63·0
4th ,,	105	60	45	57·1
5th ,,	52	32	20	61·5
6th ,,	14	8	6	57·1
7th ,,	4	4	.....	100·0

The above table shows that the lowest mortality was observed among patients treated on the first day of illness, that it increased from 30.3 % to 52·6% among those treated on the second day and that it more than doubled itself among those treated on the third day. Thereafter some irregularity is noticeable, but that is due to various causes such as the comparative smallness in the number of observations on the later days, &c.

Finally, the racial distribution of the patients and their incidence of mortality are indicated by the following analysis of 1051* cases :—

Races.	No.	Died.	Recovered.	Case mortality per cent
Europeans	15	5	10	33·3
Parsees	115	46	69	40·0
Mahomedans	151	67	84	44·3
Native Christians (mostly Goans)	217	97	120	44·7
Hindus	547	301	246	55·0
Japanese	1	...	1	...
Chinese	1	...	1	...
Jews	3	2	1	66·6
Eurasians	1	1	...	100·0

* Particulars of 30 patients are not obtainable.

The incidence of mortality was lowest—33·3 per cent—among the European patients, but the number treated was too small; of the other communities, Parsees stand next to Europeans with the mortality rate of 40·0 per cent. and then Mahomedans with 44·3 per cent. followed by Native Christians with 44·7% and lastly by Hindus with the higest rate of 55·0%. These results bear a corresponding relation to the natural mortality from plague among these races.*

Concluding Remarks.

A careful and impartial survey of the facts discussed in this Memorandum, having regard to the limitations imposed by the nature of the affection, should lead to only one conclusion *viz.*, *that the treatment of plague by Serum is the only treatment capable of saving a larger proportion of lives in a certain class of patients.* That it cannot favourably influence all types of plague, or even the malignant forms of bubonic plague, must be recognised. As also the fact, that in hospital practice, where more than half the number of admissions are found to be septicæmic and consequently not amenable to any specific treatment, it must be of comparatively limited value. In every case of plague, there is constant disintegration and reproduction of the plague bacilli. Should the system be not capable of producing enough antitoxin to neutralise the toxins so liberated, they combine with the tissue-cells, a combination that is fatal to the individual. Greater success is possible only in those instances, where such combination could be forestalled and that only happens where early treatment is resorted to. This unfortunately is not available in hospital patients. And again the great disparity in the results of treatment between the first and second-day cases should not be overlooked, indicating as it does the extreme gravity of witholding the serum even for a few hours. Under such circumstances, is it to be wondered at, that in hospital practice we have not been able to achieve more than we have done? The results, be it remembered, have been obtained in a disease that carries off about 89 persons on an average out of every 100 attacked. From my long and intimate connection with plague and its serum-therapy, I am inclined to conclude that for the present at least the above must be considered to be the limit of our success. So long, however, as we have to work under conditions as hitherto obtainable, I do not think better results are possible, unless indeed it be that we obtain a serum combining both antitoxic and antibactericidal properties. To expect miraculous cures or brilliant results in a disease like plague is simply futile, and hardly in accord with our knowledge and experience, as well as, our successes and failures in the treatment of other grave infections.

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* *Vide* the Treatment of Plague with Prof. Lustig's serum by the author P. 11.

The whole aspect of plague serum-therapy, however, becomes altered when applied under different, and in most cases, more favourable circumstances—that is, in private practice. Here the patients belong to a better class of society, are better housed and better fed. They come under observation early, and unless there is gross carelessness or the symptoms masked, plague is recognised early and treated equally early. That the disease does not become altered, or its characteristics change, because the patient happens to be in a better social position is demonstrated by the great disparity between the results of the first-day cases, as compared with those of the second and third-day, and once again it emphasises the cardinal fact that if good results are to be obtained from serum-therapy the patients must be treated on the first day of illness or even within a few hours of the onset of the symptoms.

I therefore consider the results obtained among both classes of patients as extremely satisfatory. They are capable of further improvement, if one could sufficiently impress upon the people that it is only by treatment on the first day, that the patient has the best chance of getting over the disease. That time and education are in its favour is shown by the more extended use of the serum treatment and the greater confidence of the profession, as well as of the people in its usefulness and efficacy.

Finally, it is a source of gratification to me that my humble efforts in the cause of serum-therapy of plague have been the means of arousing interest in the subject, and an incentive to its study and adoption, with the consequent saving of many a useful life that would have ended otherwise but for the timely application of the serum.

Appendix.

Extract from Prof. S. Kitasato's Paper on "Fighting Plague in Japan" read at the Annual Meeting of the American Society of Tropical Medicine, March 1906:—

"For treatment of plague patients two methods may be recommended, the one requiring operation or extirpation of buboes, and the other inoculation of the serum. Efficiency of the treatment depends on the stage of plague developed; when performed at an early stage a favourable turn may be expected, but in the later stage, especially when the patient develops septicæmia, the treatment becomes futile. Hence it is important for physicians to diagnosticate patients at the earliest stage possible. *The good result to be obtained from the serum-treatment admits of no dispute.* During the first outbreak in Osaka, Yersin's serum was used for inoculation, but owing to the scarcity of the supply results fell short of expectations. Since 1900 our institute commenced the preparation of the serum to meet the constant demand. For the patients actually suffering from the plague a comparatively large quantity (200

to 240 c. c.) of the serum ought to be used. Although we are not in a position to ascribe to the pest serum such absolute effectiveness as the diphtheria serum has, we have no doubts as to the value of the former remedy. The following fact illustrates most closely the value :

A series of experiments was conducted in an isolating hospital in Tainan, Formosa, with a view of comparing the results of serum inoculation with those of extirpation of buboes and systematic treatment. Of the fifty-six patients operated on, thirty-five (62·5 pe-cent.) died, while out of the same number of patients treated with the serum, the death-rate was 34 per cent. From these experiments it is seen that the power of the serum reduced the death-rate considerably.

That the most effective way to save the patients is to resort to both serum inoculation and extirpation of buboes *at as early a stage as possible* has been demonstrated by the experiences so far obtained during the epidemics in Japan."

Prof. Kitasato's opinion on the utility of the serum treatment is thus in perfect accord with our Indian experience. He, too, lays particular stress upon early diagnosis and early treatment. His recommendation about the simultaneous extirpation of buboes, though sound in principle, and based upon rational grounds, is scarcely adapted to the conditions obtainable in this country, where any such surgical interference would be resented, even by the educated classes. The ignorant and the illiterate, who constitute the bulk of our patients, are in constant dread of any operative measures, their invariable request on admission being " malà kápu nako " (pray don't cut me). Hence, any resort to extirpation, apart from seriously interfering with the popularity of the hospitals, would be of doubtful benefit to the patients themselves, inasmuch as most of them are admitted so late in the course of the disease as the third day and thereafter, when such measures are of little avail."

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