

ON RECENT PROGRESS IN THE SERUM-THERAPY OF PLAGUE.

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MEASURES for the prevention of plague have absorbed so much of the energy and attention of those concerned that the progress made in its clinical study and the application of newer methods of treatment have to a great extent been overlooked. The clinician, however, has not been idle, and his continuous study, now extending over eleven epidemics at Bombay, has enabled him to evolve something like a rational system of treatment. One of the means that science has placed at his disposal is the antiplague serums associated with the names of Yersin and Lustig. Too much, however, was expected of them. The virulence of plague and the unfavourable conditions existing in India were not taken into account. It is therefore not surprising that the results obtained by Yersin when he went to Bombay in 1897 caused great disappointment. The antiplague serum of Professor Lustig of Florence had a more extended trial, but after having been applied in 1,551 cases, was also abandoned for similar reasons, as well as on financial considerations, etc., that need not be entered into here.¹

Further trials were subsequently made with Yersin's serum improved by Roux, as also with Terni's (Milan), Brazil's, Tavel's (Berne), Haffkine's (Bombay), Palthau's (Vienna), and the Japanese serums. These observations were conducted from time to time, chiefly at the Arthur Road, Maratha and Modikhana Hospitals, Bombay, and may be tabulated as under :

Serums.	Number of Observations.	Case Mortality per Cent.
Lustig's	1,551	63.4
Yersin-Roux's	570	62.0
Terni's	112	81.2
Brazil's	70	82.8
Tavel's	28	64.2
Haffkine's	15*	73.3
Palthau's	8	50.0
Japanese... ..	4	25.0

* Haffkine had also made about 100 other observations at Poona on the "alternate system"; the exact results are not known, but the case mortality was found to be 14 per cent. higher in the serum than in the control cases.

These observations having been made prior to 1905, possess but an academic interest now. The results which I shall bring forward in the present paper have been obtained during the last two and a half years by thirty observers in different parts of India. They possess the advantage that all the cases were treated with one variety of serum—namely, Yersin-Roux serum from the Pasteur Institute of Paris.

PRELIMINARY CONSIDERATIONS.

It is requisite that for the adequate estimation of the results of serumtherapy in plague due account should be taken of certain unfavourable factors which militate against its successful application. These are :

(a) *The complex nature of the affection*, necessitating two distinct and separate processes—bacteriolytic and antitoxic—before recovery can ensue.

(b) *The great virulence and high mortality*, as demonstrated by a series of epidemics. The epidemic at Poona, in 1906, yielded a case mortality-rate of 93.5 per cent., while in Bombay 50,969 attacks, with 44,540 deaths, have been recorded within the last three years and seven months—equivalent to a mortality-rate of 87.38 per cent. If hospital cases were to be excluded from these the rate would be 89 per cent., which means that the natural expectation of recovery from plague in this city is but 11 out of every 100 attacked.

(c) *Early and grave septicaemia*, as noted by Mayr, Berestneff, the present writer, Greig, and the Plague Research Commission.* It has been estimated that from 55 to 60 per cent. of hospital admissions at Bombay are septicaemic and therefore practically not amenable to any treatment. Almost all succumb within forty-eight hours of admission; if any survive, the ultimate result is death from toxæmia and marasmus.

(d) *Multiple foci of infection* exist in the numerous buboes, superficial and deep, contiguous and distal, and owing to direct communication between the lymphatics on the one hand, and veins and even arteries on the other, a constant stream of blood infection is kept up.²

(e) *The rapid course of the disease and late treatment* carrying off the largest proportion of cases by the sixth day, with the period of maximum mortality from the third to the sixth day. As most of the hospital cases are admitted between the third and the sixth day of illness they are already too late for special treatment.

RECENT OBSERVATIONS (1905-7).

The recent observations now amount to 1,081 cases, distributed as follows: Bombay, 690; Poona, 118; Indore, 218; Karachi, 32; and Calcutta, 25.

Observations at Bombay.

The observations at Bombay were conducted at the Maratha Plague Hospital by the present writer, and concerned 438 cases; 243 cases were treated by him and others in private practice.†

The Method of Treatment.—Clinical experience having repeatedly demonstrated that the "alternate method" as hitherto applied was unsuited to an affection of the nature of plague, as also the fact that the 55 to 60 per cent. of hospital admissions already septicaemic do not respond to treatment by drugs or serum, the method adopted consisted in rejecting all those who appeared to have hardly any probability of benefiting by the serum treatment. Convalescent and semiconvalescent cases were further eliminated, as well as those in whom the illness had already lasted for six days or more. The latter were excluded since experience has shown that patients who are alive on the sixth day are either too far advanced for treatment or are just beginning to improve spontaneously. The observations were thus restricted to the most acute cases within the first five days of illness, and 238 cases were treated in this way. This method met with the approval of Professor C. J. Martin, of the Lister Institute (member of the Advisory Committee for Plague Investigation in India). He suggested that, after rejecting the unfit cases, every alternate case might be treated with the serum, so that those left untreated would serve as controls. This system of "rational alternation" for testing the utility of the serum in hospital practice, and thus obtaining an exact numerical demonstration of the benefit derived from its application, was adopted in a further series of 400 cases.

Table Showing Results of Serum Treatment.

	Number.	Died.	Re-covered.	Case Mortality per Cent.	
Serum cases	238	141	97	59.2	
Alter-nate series.	Control cases... ..	200	148	52	74.0
	Serum cases	200	127	73	63.5
	Difference in favour of the serum cases	—	—	—	10.5
Total of serum cases ...	438	268	170	61.1	

In the first series of 238 cases the case mortality-rate was 59.2 per cent., and among the 200 cases treated alternately with 200 controls, it was 63.5 as contrasted with 74.5 among the latter. There was thus a difference of 10.5 per cent. in favour of the serum cases, which is

* The ratio arrived at by the Plague Research Commission was 58.5 per cent. among 94 patients examined; vide also the *Journal of Hygiene*, September, 1906.

† The remaining 9 patients were treated at the Parsee Fever Hospital, of whom 4 died and 5 recovered.

indicative of the present limit of the usefulness of the serum treatment as applied to suitable cases under the by no means favourable conditions of Indian hospital practice. The foregoing figures, therefore, demonstrate that if applied to such cases as are likely to be benefited by it, the serum treatment is capable of increasing the ratio of recovery by 33 per cent. as compared with ordinary drug treatment in hospital practice. The limit of its usefulness does not end here, for apart from this, it prolongs life. By comparing the time of death after admission between the serum and control cases, it was found that whereas 79 per cent. of all deaths among controls occurred within four days after admission, the proportion was 58.2 per cent. among the serum cases, a difference of nearly 21 per cent. Such prolongation of life is of great importance where patients have to settle their worldly affairs, and it is no uncommon occurrence to find an unconscious patient so far improved after one or two injections of the serum as to be in his perfect senses and able to execute his will.

The Rejected Cases.—Upon the ultimate fate of the cases eliminated from the above observations rests the real test of the soundness or otherwise of the method of treatment now adopted.

Table of Cases Rejected as Unfit for Serum Treatment or Controls (557).

Rejected Cases : Duration of Illness.	No.	Died.	Re-covered.	Case Mortality per Cent.
Between first and fifth day ..	386*	376	10	97.4
Between sixth and ninth day ..	116	71	45	61.2
Ten days and over ..	48	15	33	31.2
Pestis ambulans† ...	4	—	4	—
Too recently inoculated with Haffkine's prophylactic‡ ..	3	1	2	33.3

* The Plague Research Commission found from blood examination of only a few of these cases that 67 were septicaemic, all of whom succumbed.

† These cases were rejected because they are extremely mild and always end in recovery.

‡ Inoculated within a week of illness, during the period of incubation.

A glance at the above figures shows that the exclusion of the 386 acute cases, within the first five days of illness, was fully justified, inasmuch as only 10 recovered, although the same remedial measures were used, except, of course, the serum. Similarly, the exclusion of cases of over six days' duration and those over ten days' (semiconvalescent or convalescent) was equally justified by their larger ratio of recoveries without the aid of the serum.

Nature and Gravity of the Cases Treated with the Serum.—With the exception of 20 cases of septicaemic plague and 10 of pneumonic plague among the rejected cases, all the patients suffered from the bubonic type of plague. Each patient received the same general drug treatment,³ without alcohol in any shape, and all were placed under practically identical conditions.⁴ The treatment was carried out during the greater part of two severe epidemics and a part of the third. As the serum was applied under the same conditions to all the patients, whether treated alternately or not, both the series of cases have been grouped together for purposes of comparison with the control cases. The serum cases exhibited a lower mortality-rate than the control, the difference varying between 7.8 per cent. in the cervical form of buboes and 27.7 per cent. among the multiple form. As regards the grave complications and sequelae of plague, it was found that they preponderated largely in the control group. Haemorrhages and terminal pneumonia existed in almost double the frequency among the serum cases; and so also marasmus due to the rapid bacteriolysis induced by the serum, and consequent surcharging of the system with the toxins thus set free, and their combination with the tissue cells of the body. Here it is that the want of a purely antitoxic serum is badly felt which alone could avert the fatal issue in such cases. Early treatment is by far the most important point in serumtherapy. The proportion of first-day cases treated with the serum was only 8.4 per cent. For this reason the results in hospital have not been so encouraging as those gained in private practice.

The mortality-rate was lowest among the patients treated on the first day; it increased by 15.6 per cent. on the second day, and by 20.9 per cent. on the third. The control cases also behaved similarly.

Recovery of Septicaemic Cases under Treatment.—The fact that in the earlier observations no amount of serum injected either intravenously or subcutaneously had been effective in septicaemic cases led the investigators to believe that this type of disease was necessarily hopeless. The investigations of the Plague Research Commission, however, have shown that this is not invariably the case. Among the cases examined by them, seven which were under the serum treatment were found to be septicaemic, and two of these recovered, one of them having no fewer than 500 to 600 plague bacilli per c.c.m. of blood. This patient, a child of 7, had received 270 c.c.m. of the serum in six injections from the second day to the sixth day of illness. The other patient, a female aged 25, had received 420 c.c.m. in six injections between the third and seventh days.

The Influence of Serum Treatment among those Protected by Haffkine's Prophylactic Inoculation.—Among the cases under serum treatment 6 were inoculated by Haffkine's method, of whom 5 recovered and 1 died. Of 6 other inoculated cases (3 among controls and 3 among the rejected cases) 2 died and 4 recovered. The application of the serum thus appears to be more beneficial after protective inoculation.*

Observations in Private Practice at Bombay.

Three out of the six observers who applied the serum treatment in private practice were responsible for 235 out of the 243 cases. The results show that 99 died and 144 recovered; this is equivalent to a case mortality-rate of 40.7 per cent., as contrasted with 61.1 per cent. among hospital patients. The reduction in the mortality was chiefly due to the larger proportion of first-day cases—namely, 47 per cent. as against 8.4 per cent. Better social conditions might account for a small proportion of this gain. The mortality of the private practice cases treated on the third day, however, was practically the same as that of the hospital patients treated on the same day.

Table showing Results in Private Cases.

Duration of Illness.	Hospital Cases.		Cases in Private Practice.	
	Number.	Case Mortality per Cent.	Number.	Case Mortality per Cent.
First day ...	37	45.9	116	28.4
Second ..	138	61.5	77	42.8
Third ..	145	66.8	37	67.5
Fourth ..	72	56.9	5	40.0
Fifth ..	36	58.3	7	71.4
Sixth ..	7	57.1	1	100.0
Seventh ..	3	100.0	1	100.0
Total ...	438	61.1	243	40.7

Observations at Poona.

It was during the severe visitation of plague at Poona, in 1906, that the serum treatment was tried for the first time. At the General Plague Hospital Dr. Anklesaria submitted 56 patients to the treatment, of whom 34 died and 22 recovered, the case mortality-rate being, therefore, 60.7 per cent. (cf. the 438 cases at Bombay with 61.1 per cent.) Nine other observers treated 62 patients (51 in private practice and 11 in the regimental and cantonment hospitals); there were 24 deaths and 38 recoveries, equivalent to a mortality-rate of 38.7 per cent. (cf. the 243 cases similarly treated with 40.7 per cent. mortality). The epidemic at Poona was of great virulence, the case mortality for the city being 93.5 per cent.; the mortality-rate at the General Plague Hospital among the patients under the ordinary drug treatment was 65.2 per cent. No first or second day cases were treated with the serum at the hospital. There was no material difference in gravity

* At Poona two patients who had been inoculated six and ten days previous to attack, recovered under the serum treatment.

between the cases treated in Poona and those treated in Bombay.

Observations at Indore.

Dr. Tambe reports on 92 cases treated at the Indore Plague Hospital with 39 deaths and 53 recoveries, equivalent to a case mortality-rate of 42.3 per cent. Among 101 cases treated in private practice by him and others there were 27 deaths and 74 recoveries, the mortality-rate thus being 26.7 per cent. The epidemic at Indore (1906) was of lesser virulence than that at Bombay or Poona, as indicated by the general case-mortality rate, which varied from 74 to 78 per cent., as compared with 89 per cent. at Bombay and 93.5 per cent. at Poona; the mortality-rate among patients under the usual drug treatment was 61.1 per cent., as compared with 65.0 at Poona and 75.2 per cent. at Bombay. The proportion of first-day cases treated with the serum (hospital and private) was 64 per cent., as against 21 per cent. at Poona and 22.4 per cent. at Bombay. The above facts go to show that the serum treatment was applied under far more favourable circumstances at Indore.

Observations at Calcutta.

Only 20 cases were treated at Calcutta, 6 of whom were practically moribund at the time of treatment. The serum was generally injected late, the doses employed too small, and in more than half the number of cases only one injection was administered. The mortality-rate was 65 per cent. as compared with 78 per cent. among hospital cases under the usual drug treatment.

Observations at Karachi.

Two observers have treated 32 cases, with 17 deaths and 15 recoveries, equivalent to a case mortality-rate of 53.1 per cent.

GENERAL SUMMARY.

A general survey of the observations related in the preceding pages shows that out of 1,081 patients subjected to the serum treatment, 537 died and 544 recovered; the mortality-rate was 49.6 per cent. 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, is shown below:

Table showing General Results in Hospital and Private Cases.

	Number.	Died.	Recovered.	Case Mortality per Cent.
Hospital cases	613	350	263	57.0
Private cases	468	187	281	39.9
Total	1,081	537	544	49.6

The difference of 17 per cent. between the two is a striking testimony to the advantage of early treatment, which is still better demonstrated by the following tabulation of 1,037* patients, according to the duration of illness when they came under treatment:

Table of Results according to Duration of Illness before Treatment.

Duration of Illness.	No.	Died.	Re-covered.	Case Mortality per Cent.
First day	316	96	220	30.3
Second ,,	300	153	142	52.6
Third ,,	246	155	91	63.0
Fourth ,,	105	60	45	57.1
Fifth ,,	52	32	20	61.5
Sixth ,,	14	8	6	57.1
Seventh ,,	4	4	—	100.0

This 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 per cent. among those treated

* Particulars of 44 patients are not obtainable.

on the second day, and that it more than doubled itself among those treated on the third day.

Finally, the racial distribution of the patients and the death-rate for each group are indicated by the following analysis of 1,051* cases:

Table showing Racial Distribution of Cases.

Races.	No.	Died.	Re-covered.	Case Mortality per Cent.
Europeans	15	5	10	33.3
Parsees	115	46	69	40.0
Mohammedans	151	67	84	44.3
Native Christians (Most 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

The mortality was lowest among European patients, but as the number treated was small, much importance cannot be attached to this. Of the other communities, Parsees stand next to Europeans, with the mortality-rate of 40 per cent.; then Mohammedans, with 44.3 per cent.; followed by native Christians, with 44.7 per cent.; and, lastly, by Hindus, with a mortality of 55 per cent. These results bear a corresponding relation to the natural mortality from plague among these races.⁵

CONCLUSION.

The main conclusion to be deduced from the study of the foregoing facts is that in Yersin-Roux antiplague serum we possess a useful and efficacious remedy against plague. The absence of all antitoxic action is responsible for its limited utility. It must, however, be pointed out that a disease like plague, with a mortality of 89.9 per cent., is not likely to yield to serumtherapeutics as well as diphtheria has done. Professors Simpson⁶ and Kitasato⁷ both realized the limited but at the same time undoubted action of the serum. The whole secret of the treatment lies in applying the serum very early. Among patients subjected to the treatment within the first few or even twenty-four hours, it is noticed that the whole course of the disease becomes altered, the normal duration of eight to ten days is reduced to four to five; serious complications of the nervous, circulatory, and other systems are averted, the buboes get absorbed, and convalescence is rapid. If applied between twenty-four and forty-eight hours, its action is not so well marked; and after the expiration of forty-eight hours it does not appear to influence the course perceptibly. Comparatively small as these gains would appear to the enthusiast, they are by no means to be despised in a disease of the virulence of plague.

REFERENCES.

¹ The Treatment of Plague with Professor Lustig's Serum, by N. H. Choksy, M.D. Bombay: The Eagle Printing Office, 1903. ² The Treatment of Plague with Professor Lustig's Serum, by the writer. Also the Lancet, March 2nd, 1901, On the Relation of Blood to Lymphatic Vessels, by Cecil H. Leaf, M.B. ³ The Serum Therapy of Plague in India, by N. H. Choksy, M.D. Bombay: Akhbari-Sondagar Press, 1907. ⁴ See the Indian Medical Gazette, Calcutta, April, 1905, and February, 1907, for articles by N. H. Choksy, M.D., On Cardiac Failure in Plague and its Treatment and Further Observations on the Use of Adrenalin in Plague respectively. ⁵ The Treatment of Plague with Professor Lustig's Serum, by N. H. Choksy, M.D. p. 11. ⁶ The Fourth Croonian Lecture, the Lancet, July 27th, 1907. ⁷ Fighting Plague in Japan, New York Medical Journal, July 7th, 1908, and Transactions of the American Society of Tropical Medicine, 1906.

* Particulars of 30 patients are not obtainable.

A SOCIALIST medical fellowship society is to be organized at a meeting to be held in London on June 25th. The object of the promoters is to afford members of the medical profession who are socialists an opportunity of acting together to enlighten the profession and the public on the questions with which the medical profession is more essentially concerned, especially the nationalization of the medical profession and the socialization of medical education.