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Recent Trends in the Treatment and Control of Plague¹.

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Treatment of bubonic plague.

The favorable initial results obtained in the treatment of bubonic plague with sulfonamides have been fully confirmed through further observations (1) as exemplified by the following recently published data:

	<i>SULFATHIAZOLE</i>			<i>SULFADIAZINE</i>			<i>SULFAMERAZINE</i>		
	Cases	Deaths	Mortality per cent	Cases	Deaths	Mortality per cent	Cases	Deaths	Mortality per cent
Simeons and Chhatre (1946, 1947)	<i>All cases:</i>								
	142	26	18.31	858	154	17.95	700	98	14.0
	<i>Moribunds excluded:</i>								
	131	15	11.45	765	61	7.97	?	?	7.2
Sokhey and Wagle (1948)	<i>All cases:</i>			47	2	4.2	67	4	5.9
	<i>Pts. admitted with septicemia only:</i>			11	2	18.1	12	4	33.3
Datt Gupta (1948)							<i>SULFAMEZATHINE</i>		
				71	7	9.86	37	4	10.81

As will be noted, trials have been made recently with sulfamerazine and sulfamezathine but up to now sulfathiazole and sulfadiazine are mainly used for plague treatment. Whenever the two last mentioned drugs were compared, results with sulfadiazine were better but most observers considered the differences as statistically insignificant. General agreement exists, however, that sulfadiazine produces fewer toxic reactions than sulfathiazole. The lessened toxicity of the former drug and also of sulfamerazine facilitated intravenous administration of their sodium salts—a procedure recommended for the initial treatment of seriously affected patients by SOKHEY and WAGLE (1946) and routinely used by SIMEONS and CHHATRE in the early stages of medication.

Quite satisfactory results were obtained with administration of antiplague serum prepared through immunisation of horses, specially if the product was used in combination with sulfa drugs.

¹ The opinions expressed in this article merely represent the personal views of the author.

However, the comparatively high price of the serum, the impossibility of storing it in fluid form for prolonged periods, the difficulties of administering it properly and the reactions apt to follow its application, all militate against wholesale use of this therapeutic agent. SOKHEY and WAGLE (1946) as well as GIRARD (2) pointed out, however, that anti-plague serum is an effective means to control toxemia.

Apparently it was not possible thus far to utilise the stable concentrated and purified rabbit immune serum introduced by MEYER for the treatment of bubonic patients. There can be no doubt that it will prove superior to the Yersin type sera.

As with the sulfa drugs, so also in the case of streptomycin encouraging results obtained when treating small groups of patients (3) have been confirmed through more extensive observations. SOKHEY and WAGLE (1948) lost only 4 out of a total of 118 patients treated with the antibiotic and only 3 out of the 28 sufferers who showed secondary septicemia when treatment was started. DATT GUPTA (1) reported that 7 out of 24 treated with streptomycin in the Campbell Hospital at Calcutta died but added that severely affected patients had been selected for this type of treatment, two of them dying within 12 hours from admission.

Treatment of Pneumonic Plague.

Recent successes in the treatment of pneumonic plague may thus be summarised:

Kind of Treatment	Number of Cures
Yersin type immune serum (4)	2
Sulfa drugs only (5)	8
Sulfa drugs and Yersin type serum (6)	3
Sulfa drugs and rabbit immune serum (7)	1
Streptomycin (7, 8) ²	5
	19

Though in a number of instances treatment with Yersin type serum and/or with sulfa drugs proved successful, our experiences in China indicate that cures of this kind are fortunate exceptions rather than the rule. Presumably, however, it will be possible to obtain more consistently good results with rabbit immune serum or perhaps better still with streptomycin as indicated by the excel-

² Usually in combination with sulfa drugs, in one case (7) also with rabbit immune serum.

lent success of experiments recently reported by MEYER and his collaborators (9).

It has to be added that TIEH and collaborators (5) had good results when giving sulfadiazine to four apparently healthy contacts showing plague bacilli in throat swabs. Identical success had been obtained in 1939 by GIRARD (10) in three instances with sulfa-pyridine. However, administration of this drug was of no avail in 1940, all 13 contacts found by GIRARD to harbor plague bacilli in their throat or saliva falling afterwards ill with fatal pneumonic plague.

Personal Prophylaxis in Pneumonic Plague.

Whilst the dictum of the International Conference convened after the 1910-1911 Manchurian epidemic that killed vaccines confer no protection against respiratory plague infection appears to have remained unchallenged, some attention has been paid recently to the possible value of live avirulent vaccine in the control of pneumonic plague.

GALE (4) administered live avirulent vaccine (single doses of 1,000 million organisms in 1 c.c.) to over 1,000 persons, the great majority of whom had been under no real risk of infection. However, among 104 close contacts included in this group 37 had been inoculated within 7 days of contact and 47 prior to contact so that their escape might have been due to the inoculation. The 6 inoculated persons who contracted plague, included the recovering patient and a few others in whom the vaccine seemed to have increased resistance to the infection.

MEYER and collaborators (9) concluded from a series of intranasal instillation experiments that "active immunization with avirulent strains of *P. pestis* . . . confers on mice a definite and on guinea pigs a marked protection against an intranasal challenge infection".

Valuable though it would be if the efficacy of inoculation with live vaccine for warding off pneumonic plague infection would be confirmed through further field experiences, the importance of the method for the direct control of lung pest would be quite overshadowed by that of chemoprophylaxis.

MEYER (11) established experimentally that guinea pigs failed to contract pneumonic plague when given sulfadiazine or sulfamerazine at the time of infection. Actual results with chemoprophylaxis in the field may thus be summarized:

Locality	Number of Contacts Dosed	Drugs and Dosage Used	Instances of Infection
Yunhwo (China) (12)	2	Sulfathiazole—3 gm. daily for 3 days	None
Oran (North Africa) (13)	85	Sulfathiazole—3 gm. daily, apparently for 7 days	One (pt. recovered)
Nanking (China) (14)	64	Sulfadiazine—6 gm. daily for 1 week to close contacts, 3 gm. daily for 1 week to those under lesser risk	None
Foochow (China) (7)	29	Sulfadiazine—4 gm. on 1st day, then 2 gm. daily for 2 more days	None
Tsinkiang (China) (7)	26	Sulfadiazine—varying doses according to degree of exposure and age	None ³

The results recorded above speak for themselves and clearly indicate that the time-honored but rather distressing method of quarantining the contacts and weeding out those who fall ill has to be supplemented by chemoprophylaxis. In fact, one must wonder if not the latter method might render the shutting up of the contacts in a camp unnecessary. Were it possible to leave those people in their homes, one of the main reasons for the hiding of pneumonic plague patients would be removed.

As will be gathered from the above tabulation, either sulfathiazole or sulfadiazine were used for 3 days or 1 week. POLLITZER (12) had full success when giving after the death of a pneumonic plague patient only 3 gm. of sulfathiazole daily for 3 days to the 2 men who had closely attended the sufferer throughout his illness, one of the 2 even sleeping in the sick-chamber. It seems therefore somewhat dubious whether an increased dosage or more prolonged chemoprophylaxis are necessary—especially if sulfamerazine, recently recommended for this purpose by HAWKINS (15) on account of its slow excretion, is used.

Control of Rat-caused and Flea-borne Plague.

Though MEYER (16) had fully demonstrated the efficacy of sulfaprophylaxis in experimental flea-borne infection, thus far but

³ Excellent results in the control of pneumonic plague through chemoprophylaxis have been recently reported from Madagascar by Favarel and colls. *Bull. Soc. Path. Exot.* 41: 510, 1948.

little advantage seems to have been taken of this method in the control of bubonic plague epidemics.

PLUM (5) who used chemoprophylaxis to a limited extent in a plague outbreak at Nairobi (East Africa) had no full success, 3 persons who had received prophylactic doses of sulfapyridine, falling afterwards ill with plague.

In the 1944 Dakar outbreak the French authorities ascribed the low incidence of plague in a limited group of intimate contacts to sulfadiazine administration (17). Details furnished by GORDON and KNIES (13) are that 20 gm. were given to adults and 6 gm. to children over 3-day periods. Before this was done, there had been 19 instances of infection; afterwards only one of the contacts fell ill with plague.

To make large-scale use of chemoprophylaxis when dealing with bubonic epidemics would not be advisable. During these the danger of human infection is much less limited as to space and time than is the case in lung pest where familial explosions are the rule. In rat-caused and flea-borne plague on the contrary, where as a rule merely off-chances for human infection exist, the cases are usually spaced out and in the great majority of instances we find but one victim per house. To administer chemoprophylaxis to the contacts of patients suffering from bubonic plague without lung complications, seems therefore as a rule not indicated. To use the method on a settlement- or precinct-wide scale would be quite expensive and, seeing that the protection thus conferred is of a rather ephemeral nature, the value of the procedure would be questionable.

Certainly, chemoprophylaxis is necessary when dealing with contacts to a bubonic patient with respiratory involvement and advantage of the method should be taken under special conditions, e.g. to replace evacuation when dealing with houses or groups of houses where a particularly heavy rodent infestation or infection rate leads to the repeated appearance of human plague or when trying to eliminate the danger caused by the arrival of a patient in a hitherto plague-free locality. For bubonic plague control in general, however, other methods are of prime importance.

Considerable argument still exists in regard to the program to be adopted—mainly because no agreement has been reached as to the mode or even the value of antiplague inoculation, and because we possess now in DDT a second and most powerful weapon to prevent human infection.

Observers in India (18) have recently cast doubt upon the efficacy of inoculation with single doses of Haffkine vaccine, and have once more expressed the fear that vaccine administration

might be followed by a negative phase during which the inoculated might be particularly susceptible to infection.

The experiences made in China with agar-grown killed vaccine have shown that even administration of single doses was beneficial to some extent. It was unavoidable that people who were injected whilst incubating plague or who contracted infection during the days immediately following inoculation, fell ill. However, we never found any evidence suggesting the existence of a negative phase—on the contrary, when administering for curative purposes during the 1928 South Manchurian outbreak single vaccine doses to recently admitted bubonic plague patients, we saw that the life of these sufferers was often prolonged (19).

It is gratifying to note that these favorable experiences have been fully confirmed through a recent large-scale field enquiry by PATEL and REBELLO (20) in India who also definitely deny the existence of a negative phase.

PATEL and REBELLO state, however, that the reduction of the attack rate through single-dose administration of HAFFKINE vaccine was not sufficiently marked, and we had the same experience in China whenever it was impossible to repeat inoculation one week after the first injection.

For this reason we have watched with great interest the excellent results obtained in Java, Madagascar and South Africa with single doses of live avirulent vaccine. However, the necessity of using the growths within one week after preparation made it inadvisable to change over to this method during the war years. Now communications in China have become greatly improved and moreover a rather stable product may be obtained through lyophilization. Plans have been made therefore to use live avirulent vaccine on a tentative scale in Fukien.

At the same time great attention must be paid to the work of MEYER and his school (21) with a purified crystalline plague antigen. To utilize such a stable standard product for antiplague immunization would be ideal.

The results of flea control obtained in China with DDT were most excellent, and the outstanding value of the method has also been emphasized by antiplague workers in other countries like SIMEONS and CHHATRE (18), GORDON and KNIES (13) and POLLOCK (22). In the opinion of the present reviewer, however, DDT should be utilized in antiplague work to supplement and not to replace inoculation. For adequate use of the latter method not only confers more prolonged protection than routine DDT application but also exerts a most beneficial influence upon results of treatment in persons who fall ill with plague even though they had

been partially immunized. Though we collected several statistics proving this point in China, the figures recently published by PATEL and REBELLO are particularly impressive because being based on a larger sample. The two workers thus summarize their results:

	<i>Treated with Sulfas</i> ⁴			<i>Not Treated with Sulfas</i>		
	Cases	Deaths	Mortality per cent	Cases	Deaths	Mortality per cent
Inoculated	1,586	344	21.7	410	165	40.2
Not inoculated	1,262	575	45.6	723	430	59.5

Thus the mortality of the sulfa-treated who had been immunized was less than half of the fatality rate in the corresponding non-inoculated group, and even amongst the not specifically treated the inoculated showed considerably fewer deaths than the unprotected.

Since DDT application and inoculation merely check the spread of the infection but do not eradicate it, systematic warfare against the rodents must remain the fundamental part of the antiplague program. Whilst all possible attention must be given to rat-proofing, teaching the people simple methods of food protection and abolition of shelterage, and to appropriate sanitary improvements, it is usually necessary to speed up the anti-rodent campaigns through poisoning and/or trapping. The introduction of really potent rodenticides like "1080" (Sodium fluoro-acetate) has greatly improved such work but unfortunately thus far the most efficient poisons are also the most dangerous ones for humans and domestic animals.

Whether rodent destruction should be done in the active plague foci as was successfully practised by MACCHIAVELLO (23) or direct warfare against the animals should be relegated to the plague-free seasons as suggested by writers like GORDON and KNIES (13) and POLLOCK (22) depends upon the local conditions.

Reviewing the present state of plague control, it may be claimed that the problem facing us now is not so much to devise new means to fight the scourge but to apply the available efficient methods on a sufficiently large scale. To do so in urban plague outbreaks is comparatively easy, but to fight rural plague which in China at least becomes increasingly preponderant is a most difficult matter.

We always realized the great value of mobile teams for rural antiplague work, but it was only in the present year that such could be organized by the Plague Prevention Bureau on a fairly

⁴ Mainly with Sulfathiazole.

large scale. The results were most gratifying. In many instances the mobile groups were able to prevent or quickly to suppress outbreaks. When reaching localities where plague had spread already, as a rule quick control of the situation could be established. At the same time good success was obtained when treating the sufferers in their homes. Thus in a rural epidemic near Tsinkiang (South Fukien) there were only 3 deaths amongst 44 bubonic patients given sulfadiazine in their houses (mortality rate 6.82 per cent).

It is of great interest to note that recently some workers in India had the same experience with patients left at home or taken to local Emergency Hospitals. Their results were as follows:

Reference	Drug Used	Number Treated	Number Deaths	Mortality Percentage
Mathur and Goyal (1)	Sulfathiazole	72 ^a	8	11.11
Simeons and Chhatre (1)	Sulfadiazine	303 ^b	18	5.94
Shamanna and Kalappa (1)	Sulfathiazole	17	2	11.76

a) 3 pts. with primary septicemic plague and 6 with lately started or incomplete treatment excluded.

b) 13 moribunds excluded.

It is clear that if the patients are attended at home or taken to local Emergency Hospitals, treatment can be started comparatively earlier and without subjecting the sufferers to a prolonged transport which is apt to promote development of secondary septicemia. This, however, seems only part of the story. In China at least the people often object to the removal of the patients from their homes. If this is not insisted upon, they are far more willing to report incipient plague and they become increasingly inclined to cooperate if they have an opportunity to see for themselves the good results of treatment. A decentralization of rural antiplague work is therefore most essential. As has been stated above, we possess by now efficient methods of plague control enabling us to do good work *for* the people. In order to derive maximal benefit from this program we must do all we can to work *with* the people.

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Summary.

1. The value of the sulfonamides in the treatment of bubonic plague is assessed and the importance of supplementing this therapy in case of serious infections through administration of anti-plague serum or probably better still of streptomycin is discussed.

2. A summary of recent successes in the treatment of pneumonic plague is presented. It is emphasized that anti-plague serum (specially the new rabbit immune serum) or probably better still streptomycin will have to be used to obtain consistently satisfactory results.

3. Whilst possibly inoculation with live avirulent vaccine will prove of some value in the prevention of pneumonic plague, administration of prophylactic sulfa-doses has given most promising results in warding off the appearance of lung pest in persons in intimate contact with patients suffering from this type. The great value of this method of chemoprophylaxis is discussed.

4. Since for reasons stated in the text sulfa-drugs are only of a rather limited usefulness in the prevention of bubonic plague, it is necessary to utilise anti-plague inoculation, DDT application and rat-control methods when dealing with rodent-caused and flea-borne infection. The relative merits of these three methods are discussed.

5. According to observations recently made during rural plague outbreaks in China and India, remarkably good results may be obtained when treating bubonic plague patients in their homes or in village emergency hospitals. The great value of such a decentralisation of rural anti-plague work is appreciated.

Zusammenfassung.

1. Der große Wert der Sulfapräparate für die Behandlung der Beulenpest wird erörtert, und die Notwendigkeit wird betont, in Fällen schwerer Infektion diese Behandlungsweise durch Injektion von Pestserum oder vielleicht zweckmäßiger durch Darreichung von Streptomycin zu ergänzen.

2. Die neuerdings erhaltenen günstigen Resultate in der Behandlung der Lungenpest werden zusammengefaßt. Um stets gute Erfolge zu erhalten, ist es notwendig, für die Behandlung dieser Pestform Pestserum (besonders das neu eingeführte Kaninchenserum) oder vielleicht besser Streptomycin heranzuziehen.

3. Möglicherweise wird das lebende avirulente Pestvakzin wertvoll für die Bekämpfung der Lungenpest sein. Es muß aber betont werden, daß die prophylaktische Darreichung von Sulfapräparaten sich als sehr aussichtsreich erwiesen hat, um die Erkrankung von Personen, die in nahem Kontakt mit Lungenpestkranken waren, zu verhüten.

4. Da aus den im Texte besprochenen Gründen die prophylaktische Darreichung von Sulfapräparaten von nur beschränktem Wert für die Verhütung der Beulenpest ist, ist es notwendig, im Falle

dieser Pestform Schutzimpfung mit Vakzin, DDT und Maßnahmen gegen die Ratten vorzunehmen. Das Verhältnis der Wichtigkeit dieser drei Methoden wird einer Erörterung unterzogen.

5. Neuerdings wurden in China und Indien ausgezeichnete Erfolge in der Pestbekämpfung außerhalb der Städte erzielt, wenn die Kranken zu Hause oder in lokalen Notspitälern behandelt wurden. Eine solche Dezentralisation der Pestbekämpfung auf dem Lande ist daher von großem Werte.

Résumé.

1° Les auteurs fixent la valeur des sulfonamides dans le traitement de la peste bubonique et soulignent l'importance de l'administration de serum anti-peste, ou même mieux, de streptomycine comme thérapie supplémentaire dans les cas sérieux.

2° Ils présentent un sommaire des résultats obtenus récemment dans le traitement de la peste bubonique. Ils indiquent qu'il faut employer le serum anti-peste (particulièrement le nouveau serum immunisant de lapin), ou mieux encore, la streptomycine, pour obtenir des résultats satisfaisants et continus.

3° Il est possible que l'inoculation avec un vaccin avirulent vif ait une certaine valeur comme mesure préventive dans la peste pneumonique. Cependant l'administration de sulfa-doses prophylactiques a donné des résultats très encourageants dans la prévention de la peste pneumonique chez des individus en contact intime avec des malades souffrant de ce type de peste. La valeur considérable de cette méthode de chémoprophylaxie est discutée.

4° En vue des raisons indiquées dans le texte, les sulfas ne sont que d'une valeur limitée dans la prévention de la peste bubonique. Il est donc nécessaire d'employer l'inoculation anti-peste, le DDT et les méthodes de contrôle des rats quand il s'agit d'infections causées par les mouches et les rongeurs. Les auteurs discutent les mérites relatifs de ces trois méthodes.

5° Selon les observations faites récemment en Chine et dans l'Inde pendant des épidémies rurales de peste, on peut obtenir des résultats fort encourageants en soignant les malades de peste bubonique à domicile ou dans des hôpitaux de secours dans les villages. Les auteurs soulignent l'importance qu'il y a à décentraliser l'organisation des mesures préventives contre la peste dans les régions rurales.
