Clinical observation and experimentation show that the noxious agent in typhoid is both bacterial and toxic in nature; consequently, if an antityphoid serum is to be efficacious, it is essential that it should possess both antibacterial and antitoxic properties. A serum possessing merely antibacterial properties may be harmful instead of useful. For instance, by destruction of the microbic bodies and the liberation of the endotoxin, a violent intoxication of the system may follow, if the toxin is not at the same time neutralised by the specific antitoxic properties of the serum. This is partly the explanation why certain anti-typhoid sera, proposed from time to time, although possessing high antibacterial properties, did not give, in practice, the satisfactory results expected, owing to the nature of the reaction accompanying their use limiting their scope of application.

The same phenomenon is observed in the toxic cases of typhoid where bacteriophage is employed.

It is on these principles that in 1926 investigations were started on the preparation of an anti-typhoid serum with a view to the specific treatment of typhoid fever.

After inoculation of the detoxicated endotoxin of the typhoid bacillus, according to an original process, animals acquire a high antibacterial and antitoxic immunity, which allows them to resist massive doses not only of virulent typhoid culture but also typhoid toxin.

The serum of the horse hyperimmunised according to this method, reinoculated into new animals, confers on them a passive protection, both antibacterial and antitoxic.

By concentration and purification of the serum, according to the same method which is used for Anti-Diphtheria and Anti-Tetanus serum, one obtains finally a therapeutic product consisting of pseudo-globulin. The sensitising protein portion of the serum, the euglobulin which is responsible for the majority of the serum reactions, is eliminated through the process of purification.

This serum, after experimental titration and adjustment of its protein and salt content to isotonic conditions, constitutes the concentrated and refined serum which has now been used in the treatment of more than 2,000 cases in general practice, hospitals and mines both in and outside the Union.

Clinically, if one studies the effects of serum treatment in Typhoid Fever, one will notice that the first change which can be observed in most of the cases is an antitoxic action which in some cases appears a few hours after the injection, but usually within 24 hours and is characterised by the sedation of the nervous and ataxo-dynamic symptoms: Where delirium or coma exists, the patient becomes more restful, ceases to complain and often regains consciousness within 24 hours.

This antitoxic action is usually accompanied by a fall of temperature of 1 to 3 degrees with a tendency to rise again after 36 to 48 hours, this being an indication for another injection of serum. A second injection of 20 c.c. will result in a further amelioration of the condition—the headache disappears, the earthy complexion improves, the tongue becomes moist, the pulse and tension improve, the temperature drops and the patient emerges from his typhoid state.

A third injection given 48 hours after the second injection is usually sufficient to complete the improvement, and to ensure a permanent return to normal.

The temperature in some cases goes down gradually to normal; in other cases, although the curative action of the serum is evident, the temperature remains high for a few days, to drop suddenly in crisis to normal, as in the case of Pneumonia.

At this period, i.e., seven to eight days after the commencement of the disease, a
critical polyuria is observed in most instances, accompanied by profuse perspiration, which is a favourable indication of the condition of the patient.

With regard to the route of inoculation of the serum, the best results are obtained by the intramuscular route. There is no advantage in using the intravenous route, which although being the quickest in response, possesses, however, some disadvantages. In addition to the possibility of an individual susceptibility to protein and danger of shock, the rapid introduction of a foreign protein may also result in a sudden drop of the blood pressure. This is particularly to be avoided in Typhoid, especially where a deficiency of the suprarenals is observed as a result of the specific typhoid intoxication, as is the case in a certain proportion of cases. For these reasons, in Typhoid, as in any other serum treatment, it is advisable in cases showing a tendency to low pressure to give the serum by the subcutaneous route, accompanied by adrenalin treatment.

Serum Treatment at Different Stages of the Disease.

In the early stages of Typhoid Fever, corresponding to the septicaemic stage of the disease, serum treatment results usually in a rapid regression or arrest of the symptoms, somewhat similar to the condition which is observed in experimental animals. This rapid improvement is usually accompanied by a big drop in the temperature to normal or often below normal and convalescence within a few days after the beginning of the serum treatment.

The study of serum treatment is particularly interesting in cases treated at the period of fastigium of the infection or of continued fever, as the characteristic symptoms of intoxication are more definite at this stage and the antitoxic action of the serum more evident.

In cases where after three injections of 20 c.c. of serum, although the condition of the patient has improved the symptoms have not quite subsided, the serum treatment should be prolonged by intramuscular, or subcutaneous injections of 10 to 20 c.c. in order to avoid any possible exacerbation of the disease.

In particularly severe cases where, after the initial dose of 20 c.c. has been given, no improvement seems to occur, subsequent injec-

ions should be increased to 30 or 40 c.c. given at two day intervals, half intramuscularly and half subcutaneously.

There is no benefit in giving massive doses of serum. The repetition of the serum injec-
tions is more important in order to insure a gradual and full bacterial sterilisation of the multiple organic foci. Such foci, in insufficiently treated cases, tend to cause relapse or chronic infection such as cholecystitis, the frequency of which is well known.

Although a large proportion of cases treated during the third or fourth week of the illness still benefit by serum treatment, the therapeutic action of the serum is limited at this stage by individual factors such as visceral complications or mixed infections which contribute to make each case an individual syndrome. Considering, however, the excellent results obtained in some desperate cases even with delayed treatment the use of serum even in such cases seems advisable.

In Typhoid, as in other infectious diseases, there are a certain proportion of cases whose feebleness or lack of immunological response is responsible for the severity of the syndrome observed. In these cases the introduction of the serum treatment bringing possibly the specific antibodies which the organism is unable to form actively itself, gives sufficient stimulus to control the infection and converts a dark prognosis to a rapid convalescence. The same results are obtained in cases where the temperature persists for many weeks, presenting an undulant curve, appearing to reach to normal, only to start a new curve of exacerbation.

One or two injections of the serum are usually sufficient to control the temperature within a few days.

The same remarks apply to the relapse of typhoid, where the serum provides the auxiliary passive aid in reinforcing the natural immunity, insufficient to control a new exacerbation of the infection.

If an interval of more than ten days has elapsed since the previous course of serum treatment, care should be taken to desensi-
tise the patient by repeated subcutaneous injec-
tions of 0.1, 0.2, 0.3 c.c. of serum at inter-
vals of 2 hours.

Besides the antibacterial and antitoxic action of the serum, it has antihaemorrhagic properties also. Apart from the normal haemostatic action which is possessed within limits by normal horse serum, typhoid serum
possesses specific antihaemorrhagic properties which will compensate for the deficiency of coagulation of the blood. This has been observed to a more or less marked degree in a certain proportion of typhoid patients, and has been reproduced experimentally in animals, on the same lines as venom and antivenom.

**Cases of Typhoid Complicated by Mixed or Secondary Infection.**

Although these clinical forms, the frequency and gravity of which are well known, limit to a great extent the therapeutic effects of typhoid serum therapy and often run a fatal course, a certain proportion of them in spite of their clinical gravity are susceptible to control by mixed serum therapy, if taken in time. By using typhoid serum combined with B. Coli serum and polyvalent gangrene serum excellent results have been obtained in a number of severe cases of secondary infection of intestinal origin which were complicated by perforation. Similar results were reported by Professor Weinberg in Paris using Dr. Grasset's typhoid serum incorporated with his antigangrenous serum, as well as by Professor Hawes in Singapore.

Daily injections of 20 c.c. of concentrated anti-Coli serum or 20 c.c. of antigangrene serum are repeated during the acute period of the infection. The serum is given on alternate days until all general and peritoneal symptoms have disappeared. The same procedure can be adopted in complicated cases of dysentery as well as in complicated abdominal cases such as suppurated appendix, intestinal rupture and peritonitis.

Unfortunately, typhoid serum treatment is sometimes nullified in pure or mixed infections which are exceptionally toxic from the commencement, or in cases of delayed treatment, on account of the deep intoxication of the system, followed by organic deficiency.

In typhoid, as in diphtheria or Tetanus, there are cases where massive doses of serum do not seem to exert any therapeutic action on the course of the disease. One cannot expect, therefore, that typhoid serum will exert a regenerative action in anatomic lesions or necrotic foci, such as deep intestinal ulceration or have a rapid curative action in deeply intoxicated organisms. Nevertheless, if one cannot expect serum treatment where applied "in extremis" to alter the situation favourably, there have been some cases considered as desperate, where serum treatment applied as the last resource, completely altered the prognosis.

Delay in the use of serum cannot be too strongly deprecated. In Typhoid, as in other infectious diseases, the earlier in the stage of infection at which serum treatment is commenced, the better are, as a whole, the therapeutic effects. Moreover, the results are obtained with the minimum volume of serum, the smallest number of injections, the duration of the disease is so much the shorter and the chances of complications are reduced to a minimum.

It is for these reasons that, particularly in country districts where on account of the distances the results of laboratory investigations such as blood culture and Widal are likely to be delayed for a few days, it is advisable whenever the clinical evidence suggests typhoid, to administer an initial dose of the serum, pending laboratory confirmation of the diagnosis.

Moreover, since the serum is so prepared as to be polyvalent, not only against the typhus bacillus, but also against the Paratyphoid bacillus A and B, it is unnecessary to delay treatment whilst the typing of the microbe is being carried out. A delay of a few days, is, indeed, sometimes sufficient to alter decisively the clinical course and the prognosis of the disease.

Some cases which are apparently mild at the commencement, suddenly present a severe toxic aspect. It is consequently of the utmost importance to start the serum treatment without delay, whether the case is apparently mild or obviously severe. This precaution obviates the resorting to serum treatment when the gravity of the condition minimises the chances of success.

To return to the question of the polyvalency of the typhoid serum, investigations which have been carried out during the last few years in connection with the Health Bureau of the League of Nations, have shown that the protective properties of typhoid serum are not only effective against the African strains but are also effective against typhoid strains of widely different origin.

Protective tests performed on experimental animals with nearly a hundred typhoid strains of European, Asiatic, American and Australian origin received from various scientific Institutions specialising in immunological studies on typhoid, have demonstrated as a whole the wide polyvalency of the serum.
The immunological results have found confirmation in the various clinical documents received from different countries outside the Union where anti-typhoid serum has been used. Apart from the satisfactory results and documents relating to Rhodesia, Portuguese East Africa and the Belgian Congo, a particularly interesting clinical investigation has been carried out at Singapore in connection with the Far East Bureau of the Department of Health of the League of Nations at the Central Hospital for Infectious Diseases, where the serum was tried in 1931 by Professor Hawes in very severe conditions, and has been used since systematically for the treatment of typhoid fever with very satisfactory results.

Professor Hawes has stated that this serum was by far the most curative agent for typhoid he had used. In order to emphasise the severity of the tests, he said that in no case had he given the serum before the fifth day of the disease and in some cases after the thirteenth day. In all cases except those almost moribund a remarkable change took place in the appearance of the patients who in a day or so became less toxic, coming out of the typhoid state, appearing much brighter and taking an interest in their surroundings. No deaths took place where the serum was given before the 14th day, the duration of the disease was shortened, and no relapse or complications occurred. Excellent results have also been reported from the Roan Antelope Mine, Rhodesia.

POSSIBLE REACTIONS WHICH MAY FOLLOW SERUM TREATMENT.

Although in consequence of the concentration and purification of the serum, the chances of reactions are reduced to a minimum, there are always, as in any serum treatment, a certain proportion of cases in which serum therapy is accompanied by reactions of varying intensity. These are of two kinds, primary and secondary.

The latter are the more common and usually of a benign nature; the former are in most cases the result of a previous sensitisation and are of a more serious character.

Before starting any serum treatment, it is important to enquire about the past history of the patient, in order to ascertain if at any period of his life he had been submitted to any serum treatment or prophylactic serum inoculations such as antitetanus. Particular attention must be given to men who were injured during the last War, a great proportion of them having received prophylactic inoculations. As a result of these previous serum inoculations, these persons have been sensitised to a later inoculation of serum and are susceptible of developing rapid reactions or shock, unless they are desensitised.

In case of doubt, the safest way is to proceed as if the patient was sensitised and to proceed before treatment to a sensitivity skin test, eventually followed by desensitisation. This test is very easily done. It consists of inoculating a small quantity of serum such as 0.1 to 0.2 c.c. into the skin of the forearm, as in the case of a Schick test. If within one hour after inoculation no appreciable local reaction is observed, which shows that the patient is not sensitised, serum treatment can be started immediately without danger.

If on the contrary, the patient is sensitised, within five minutes to one hour after this small injection a local reaction will appear around the point of inoculation. It is characterised at first by a red crown, developing from the site of the injection, which spreads rapidly to reach one or two inches in diameter and is accompanied usually by a swelling of the skin and an itchy sensation, as in the case of Urticaria. This reaction remains for perhaps an hour and then gradually fades away. It indicates an individual sensitivity of the patient to the serum and the necessity of desensitisation before a larger therapeutic dose may safely be injected.

Serum desensitisation can be achieved according to the method of Besredka by injection of an increasing volume of small quantities of serum. The desensitisation can be obtained by a different route. The quickest is the intravenous route but it requires particular technical conditions such as dilution of the serum, whilst the subcutaneous route, although requiring more time, is the easiest and most commonly used. Particularly, subcutaneous injections of 0.1, 0.2, 0.5, 1 c.c. of serum are carried out at roughly two hourly intervals.

These injections, particularly the first one, are usually followed by some local reaction, redness and oedema. But, as a result of the gradual desensitisation, the reaction following the last injection of 1 c.c. should not be of a more intense character than the one observed after the first injection of 0.1 c.c.

In practice, in order to proceed quite safely, it is advisable to proceed the first day to
desensitisation and the next morning to repeat
the last dose of 1 c.c. If the last injection
is not followed within 30 minutes by any ab-
normal local or general reactions, one can
safely give the first therapeutic dose.

Unless the condition is urgent, it is always
wise to give the first therapeutic dose by the
subcutaneous route. The subsequent doses
can be given intramuscularly unless certain
signs of sensitivity are still observed, such as
an increase of the temperature or of the pulse,
after the first injection. In these conditions
it is better to continue the full treatment by
the subcutaneous route.

With regard to the secondary reactions,
they usually appear from 6 to 12 days after
the beginning of the serum treatment and are
variable in their intensity and manifestations.
As in any serum treatment, they are the re-
sult of the reaction of the system to the intro-
duction of a foreign protein.

Whilst in some cases a rise of temperature
of 1 to 4 degrees is observed during two to
four days, in other cases the rise of tempera-
ture is accompanied by various manifestations
such as skin eruptions, urticaria, joint pains
and enlargement of glands.

Although sometimes troublesome by their
intensity, these reactions are very rarely of a
serious character. The frequency and inten-
sity of these serum reactions can be to a cer-
tain extent minimised by the use of different
products such as Adrenalin, Ephedrin and
various calcium salts. Injections of 0.3 to
1 c.c. of a solution of adrenalin 1 in 1,000
repeated twice a day during these manifesta-
tions, usually reduce their intensity. With-
out waiting for the possible appearance of
these serum reactions, one can to a certain
extent prevent them by the use of the same
products more or less prophylactically from
the beginning of the serum treatment.

A routine procedure should be adopted in
any kind of serum treatment, giving as a pre-
ventative measure a combined adrenalin and
calcium treatment: adrenalin either orally or
in injections and a solution of calcium salts
such as Calcium Lactate or gluconate in doses
of 1 to 3 gm. a day. This procedure is com-
menced at the beginning of the serum treat-
ment and should be continued for 12 to 15
days.

In typhoid perhaps more than in any other
infectious disease, each case must be con-
sidered as a separate entity warranting indi-
vidual consideration both as far as general
and serum treatment are concerned.

Every science is born from a correspond-
ing art and the desire to perfect it.—Comte.