ART. XX.—*The Prophylactic Treatment of Enteric Fever by Inoculation.* By WALTER C. STEVENSON, M.D., B.Ch., B.A.O., D.P.H., B.A. Univ. Dubl.; Lieutenant, Royal Army Medical Corps, Royal Infirmary, Phoenix Park, Dublin.

THE subject of the prophylactic treatment of enteric fever by the inoculation of a vaccine consisting of dead typhoid bacilli and their toxins was first treated in the *British Medical Journal*, January 30th, 1897, in an article by Prof. Wright, of Netley, and Surgeon-Major Semple, A.M.S.

From time to time articles from the pen of Prof. Wright and others have since appeared on the method and its development. A short *résumé* of the *rationale* of the method will be of interest to those who have not been able to follow the steps by which Prof. Wright gradually advanced our knowledge of the mode of treatment proposed by him.

It is observed that when the human subject has been prostrated about a week with enteric fever certain conditions exist:—1. His spleen is enlarged. 2. The characteristic typhoid spots are present on the patient's abdomen. 3. When his blood is tested for Widal's reaction it is found to clump typhoid bacteria.

The bacteriological course of events seems to be somewhat as follows:—

The typhoid bacillus is swallowed in milk or in water, or in some manner finds its way into the intestines. By attacking Peyer's patches, and setting up inflammation there, and finally by the lymph stream, the bacilli enter the blood in considerable numbers. Now they find themselves in a very unsuitable medium in which to thrive, as the blood normally possesses a strong bactericidal and agglutinating power for this particular organism. In the blood stream the toxins are washed off the bacteria, and their feeble condition is testified by the loss in their staining power.

Human blood serum is capable of agglutinating and killing a certain number of typhoid bacilli, which fact can easily be shown experimentally. If the serum, having destroyed its full complement of bacilli, is strained away from them, it will be found incapable of harming any further quantity of

enteric germs. It is, in fact, as if a definite chemical compound is formed by the protoplasm of the bacterium and the bactericidal and agglutinating substances in the blood.

There is a distinction between the agglutinating and bactericidal properties of the blood, as was demonstrated by the "Berne Serum," which had been put on the market for the treatment of enteric. It was found that when this was added experimentally to the blood, although it increased agglutination, yet it destroyed the bactericidal power of the blood—not a very desirable result.

Using Ehrlich's conception of protoplasm, and, by way of simile, mentally representing it as a benzene ($C_6 H_6$) group, or molecule, we perceive that the bactericidal substance of the blood attacks the vital ring of the protoplasm of a bacterium (C_6 in $C_6 H_6$), tearing it asunder and destroying its existence as a definite compound and radicle, while the agglutinating substance combines with the less vital side-chains of the group (H_6 in $C_6 H_6$). The side-chains in protoplasm function by uniting with food stuffs.

Bactericidal substances kill the bacteria, while the agglutinins act principally on their capsules, causing agglutination, immobilisation, spherulation, and sedimentation of the bacilli.

Finally, agglutination is measured by the Widal reaction, or Prof. Wright's sedimentation test^a; while Prof. Wright estimates the bactericidal power^b by finding what relative volume of blood will render sterile a volume of 24-hours' old broth culture of typhoid bacilli. The result is given as the number of typhoid bacilli one cubic millimetre of blood will kill.

In the *Lancet*, July 5th, 1902, a particularly quick and easy method of counting bacteria is described by Prof. Wright. It consists of making a film cover-glass preparation of a mixture of, for instance, one volume of a 24-hours' typhoid broth culture, and an equal volume of a five-fold dilution of blood. The number of red blood corpuscles and of bacteria are counted separately in one or more fields. If the number of red corpuscles present represent red blood corpuscles at

^a British Medical Journal, Jan. 16th, 1897.

^b Lancet. Dec 1st, 1900; March 2nd, June 1st, 1901.

the rate of one-fifth of 5,000,000 per cubic millimetre (5,000,000 being the number normally in one cubic millimetre of blood), the number of bacteria per cubic millimetre can easily be estimated.

For convenience, agglutination and the bactericidal power of the blood may be classed as its "bacteriotropic" properties.

Typhoid bacilli having therefore gained entrance into the blood by some means, they are carried round in the circulation till a number of them are finally caught alive in the mesh-work of the spleen. But, as already stated, the bacilli cannot live in the unchanged fluids which bathe this organ; and it must be that only those bacteria which happen to be situated in limited areas in the spleen where bacteriotropic substances are diminished, or not present, that can thrive and form colonies.

Two factors probably combine in forming these localities. Firstly, the blood and lymph stream is slowed down, and then partially or completely shut off from the area of the colony, which area must of necessity be very small. Secondly, the bacteriotropic substances combining chemically with the outlying bacteria, the injurious properties of the blood or lymph are diminished for those lying in the distal part of the colony, where growth is most vigorous. The spleen is consequently enlarged and congested, due to the irritation of the microscopic miliary colonies scattered through it.

The fact that the bactericidal power of the blood permeating these colonies is diminished is capable of demonstration. If a piece of spleen is taken which must contain several colonies, or, better, the blood from a typhoid spot which is a single colony, and this is compared with the blood from the finger, it is found that the latter blood still kills typhoid germs, while in the former typhoid bacilli are comparatively uninjured.

The bacilli having once started to grow in the spleen they commence to send their toxins into the blood current. The first effect is that the toxins combine with the bacteriotropic substances normally in the blood, and before the tissues have time to react sufficiently the bactericidal power of the blood is lowered—that is, a "negative phase" of immunity is induced in the body. It is now probable that some bacilli find an

opportunity of disseminating through the system with comparative impunity, and subsequently they grow to colonies, as the miliary colonies found in the small intestine and the typhoid rash. Possibly, the reason why the colonies are seen on the abdomen particularly is on account of the thinness of the skin there, and the good superficial blood supply of this region owing to its protected position.

Soon, however, the stimulation of the toxins in the blood acting on the tissues causes an outpouring of antitoxins, or antibacterial substances, and thus the bactericidal and agglutinating properties of the blood increase considerably above normal—that is, a “positive phase” of bacteriotropic power is reached. This explains the Widal reaction in the blood serum of an enteric patient when the disease is well established, causing the clumping and death of typhoid bacilli, even with high dilutions of the serum.

A struggle ensues now between the toxins and bacteria on the one hand, and the bacteriotropic substances formed by the body on the other. If the agglutinating and bactericidal power continue high in the blood, prognosis is favourable; while if they fall and remain very low, prognosis is grave. If there are no complications convalescence results when the body cells have produced sufficient bacteriotropic substances to neutralise the toxins produced and to kill the bacteria. In most favourable cases the system responds well to the toxic stimulation, and the patient commences life again with his bactericidal and agglutinating powers increased—that is, his body presents a highly unfavourable medium for enteric germs to develop in. If, on the other hand, as sometimes happens, the response of the body has only just been sufficient to kill the typhoid bacilli, there may be little or no bacteriotropic elements left in the system, and the patient will be less able to resist enteric than previous to his illness. Several patients who had been invalided home from S. Africa after enteric have gone out again and succumbed to that disease.

Now, if with safety and facility an individual can be placed in the condition of one who has convalesced from an attack of typhoid fever with his powers of resisting it greatly increased, the object of introducing a prophylactic treatment of enteric will have been achieved. This immunity is brought

about during the course of the disease, as we have seen by the stimulation of the toxins of the typhoid bacilli, causing the production of a condition antagonistic to the germs of that disease. It is easy to obtain for the purpose of this treatment typhoid toxins, seeing that a broth culture must abound in them. All that is necessary, therefore, is a broth culture which has been sterilised by heating up to 60° C., which kills the typhoid bacilli, but does not affect its toxins. A certain quantity of carbolic acid is then added to the broth, and its sterility is tested by the absence of growth when nutrient media are inoculated with it. The culture is standardised and sent out in capsules for single administrations, or bottles with several doses. Usually the dose is 1 cc. for the first injection, and 1½ to 2 cc. for the second. The method of administration is by a sterile hypodermic needle, the fluid being injected into any part of the body, preferably where the tissues are lax, as in front of the axilla or in the skin of the abdomen.

At first, in this treatment, one large dose of typhoid vaccine was used. It was then found that the bactericidal power was decreased for a considerable time, as long as a fortnight or three weeks—that is, the “negative phase” of immunity was prolonged. This was gradually followed by the “positive phase” with increased bactericidal power. This prolonged negative phase is not a desirable circumstance, as during that period the individual is somewhat in the condition of the patient who recovers from enteric fever with his power of resisting a subsequent attack impaired. This result was obviated by giving an initial small dose when there is a very short or no “negative phase;” for if the blood be tested the day following inoculation the bactericidal power will have been already raised. When after ten days a larger dose is administered, a still greater bactericidal power will be gained, usually a short “negative phase” intervening.

The symptoms produced by this treatment are trivial. Of 70 cases of inoculation carried out by the present writer on board ship only one patient took to bed, for one day and a half. His evening temperature was 101° F., and was 99° the following morning. In another case it caused vomiting about three hours after inoculation. The symptoms were

mostly local. Two hours after the injection the muscles in the region of the wound were stiff, and painful on movement. This sensation was at its worst the following morning, and subsided slightly during the day. On the fourth morning most of the stiffness had disappeared. On the second inoculation local symptoms were little marked, but a feeling of malaise was experienced for a couple of days.

The immunity brought about by typhoid vaccine seems to be similar but more certain than that produced by long residence in a locality where enteric fever is endemic. Fresh arrivals in such a place are more likely to contract the disease than those who have been exposed for some time. Some of Prof. Wright's assistants, though they have never been inoculated by him, have an abnormally high degree of immunity against enteric, due to their constant work in the laboratory.

Inoculation does not absolutely prevent the disease, but statistics show that the percentage of cases among those who have been so treated is very considerably less than among those who have not, though all were equally exposed.

In conclusion, it is reasonable to expect, and ascertained facts as far as they go prove, that this system of treatment is a satisfactory one for the prophylaxis of enteric fever. But, as pointed out above, discretion is necessary in practising it in the presence of an epidemic where an overdose of vaccine would for a short period lower the power of resisting this disease.

ART. XXI.—*Errors in Diagnosis, Avoidable and Unavoidable.*^a By ALFRED PENNY, L.R.C.P.I., L.R.C.S.I.

I HAVE no new treatments or remarkable or interesting cases to bring before your notice. On the contrary, I fear you will find this paper dull and uninteresting. It is a record of failures; of things done which ought not to have been done, and of things undone which ought to have been done. About twenty-two years ago the late Mr. Ernest Hart, the then editor of the *British Medical Journal*, made an entirely new departure in his management of that

^a An Address read before the Chelsea Clinical Society, 1902.