REFLECTIONS ON THE IMPORTANCE OF TOXIN SATURATION OF TISSUES, *CONSIDERED IN RELATION TO THE TREATMENT OF PULMONARY TUBERCULOSIS.*

BY

EDWARD E. PREST, M.A., M.D.CANTAB.,
MEDICAL SUPERINTENDENT OF THE AYRSHIRE SANATORIUM.

At the outset it may be stated that this paper has been written with the object of offering a plea for the comparatively simple methods of treatment of this disease, and to draw attention to some of the more important aspects of tuberculin treatment.

There is good reason for believing that a sharp line of distinction should be drawn between tuberculosis attacking fixed organs (a condition which is often referred to as surgical tuberculosis) and tuberculosis attacking mobile organs, the important organs in this connexion being the lungs, though to a far less extent tuberculosis of the pericardium, joints, and alimentary canal might be included. The lungs being constantly in motion and very vascular become when attacked mechanisms for the distribution of toxin.

The course of events which follow when tubercle bacilli invade the lung is very various. In many cases the local tissues will be able at once to destroy the bacilli, otherwise the bacilli will grow and form toxins, which, if of low virulence and the local tissues are resistant, may end in the bacilli, though not necessarily being killed, becoming surrounded by more or less dense fibrous tissue. Unfortunately, in many cases, at some one or more points, destructive processes obtain the upper hand, and although the fibrous tissue tends to limit destruction and at the same time to import a measure of rigidity into the affected lung, the disease continues to spread slowly.

If the bacilli be a little more virulent, they may give off just enough toxin to destroy the immediately surrounding tissues, although not enough to reach healthy tissues beyond, in which case the symptoms of a general character will be slight, but the disease will gradually destroy the surrounding lung tissue; this may be the explanation of those insidious cases in which the lungs are found to be extensively diseased, without any very marked general precedent symptoms.

If the bacilli be even more virulent, and give rise to so much toxin that it cannot all be anchored to the surrounding tissues, and, as there will be less possibility of the production of much fibrous tissue, and there will thus be more mobility of the diseased focus, it will follow that some of the toxin will reach healthy tissues, where antibodies will be formed, which, on again reaching the diseased area, will tend to inhibit the growth of the bacilli there situated. If they completely inhibit growth, a cure will have commenced. If, however, there be so much activity, or the body tissues as a whole yield an insufficient amount of antibody, then the healthy tissues arrive at a condition which I shall call toxin saturation; no antibody can be produced, and the toxin circulating in the system will assist the activity of the bacilli, the disease will rapidly spread, and death speedily follow, unless means are at once taken to counteract this grave condition, and produce once more a condition of hyposaturation. Such a state of affairs does not occur in tuberculosis attacking relatively immobile tissues.

From this it follows that if we are to treat this malady successfully, means for determining the condition of the tissues with reference to saturation by toxin will be of enormous importance. I am of opinion that this is not a difficult matter if all the measures at present at our command be taken. The most important method is an accurate record of the temperature taken in the rectum (by any other method very little information of value can be obtained); the patient should be kept in bed for this purpose. If it is found that the temperature taken in the rectum before rising in the morning is above 36.5° C. (97.7° F.) I am of opinion that the tissues are approaching a condition of toxin saturation; or, if the temperature during the day, when the patient is at rest in bed, rises higher than 37.5° C. (99.4° F.) the same conclusion may be arrived at. The temperature taken before rising is by far

the most significant in cases which are only slightly febrile, and it should be further noticed that the temperature taken at 9 p.m. should be lower than the afternoon temperature. In cases in which the disease is only slightly active, where almost all the toxin is neutralized by the tissues at the seat of the disease, although the temperature may consequently deviate from the normal, yet the remaining tissues of the body may be in a condition considerably removed from saturation by toxin. The symptoms of saturation are the classical symptoms of pulmonary tuberculosis. The mildness of the symptoms in some cases is due probably to toxin saturation being incomplete, at least at all hours of the day and night. A night's rest often sufficiently restores the balance, the patient being thus enabled to struggle on a little longer. It may be concluded that when night sweats occur, saturation is complete at least for part of the twenty-four hours. A temperature such as the above only indicates that the balance has been restored, and gives no indication in itself of the capacity of the tissues to deal with toxin; it follows, therefore, that individuals with the balance only just restored, and those who have a large capacity for dealing with toxin, will exhibit similar temperature charts.

It is, however, comparatively easy to distinguish between these cases by the following methods. If it is found that a very little exercise causes the temperature as described above to deviate from the normal—that is, if on the following day, the temperature taken in the rectum before rising in the morning is higher than 36.5° C. (97.7° F.) the tissues are nearly saturated with toxin. On the other hand, if a large amount of exercise causes no increase of this temperature, it follows that either there is no approximation to toxin saturation, or else the bacilli are so shut away from contact with the tissues generally that only an inappreciable amount of toxin can reach them, even after violent exertion, or that the tissues of the body have become tolerant to toxin. It follows, therefore, that, besides being useful as a method of treatment in chronic cases, the capacity to do a large amount of work without unfavourable symptoms is a circumstance indicating a favourable prognosis. The method of treating cases by severe physical exertion with the intention of distributing toxin to the healthy tissues and the consequent production of immunity is disadvantageous in so far as it produces activity in the diseased focus, and advantageous in so far that any toxin so distributed can act on a very large number of different tissues.

Another method of gauging the amount of toxin saturation is to administer tuberculin. The action of tuberculin on an organ previously infected with tuberculosis may be threefold: (1) Action at the site of inoculation; (2) general reaction, indicated by temperature and symptoms of malaise; and (3) action upon the diseased focus. Neither (1) nor (2) denotes the presence of active tuberculosis, but only indicates that the tissues of the body have been so changed that they are able to activate the injected tuberculin. The general reaction will therefore be absent in the case of persons who have never been infected and in those in which tolerance to the activated tuberculin has been achieved, though a cure may not have taken place. If a sufficiently large dose be injected, it follows that there may be a severe general reaction, even in cases of surgical tuberculosis, but as the disease is local, there will be no great danger of the reaction persisting; the reaction will occur rapidly and will be soon over; when lasting for a prolonged period, it indicates renewed activity in some vascular tuberculous focus.

If a small dose such as 0.00003 c.cm. of P.T.O. be administered to a patient with high fever, there will be no reaction at the site of inoculation, because the tissues at this spot will be toxin saturated, the symptoms, however, will become markedly more severe, and the signs of activity in the affected portions of lung will be considerably increased. If a larger dose be administered the symptoms will be more pronounced. In such a case tuberculin has been administered unwisely to a patient whose tissues are saturated with toxin, the toxin injected presumably reaches the tissues involved in the disease, and assists its spread.

On the other hand, if a similar dose of tuberculin be administered to a patient having a temperature ranging permanently above 37° C. (98.6° F.), but not reaching

higher than 37.6° C. during the twenty-four hours, when the patient is in bed, one of three events may occur: (1) There may be no local reaction, the temperature will probably be raised slightly and headache or sickness may be complained of; in this case also it may be assumed that the tissues are saturated with toxin, and that the tuberculin has been harmful. Or (2) there may be a local reaction at the site of injection, and within a few hours the temperature may conform to the normal, and be as low as 36.5° C. (97.7° F.) the next morning. In this case it is probable that the bacilli in the diseased tissue are only slightly active, and the toxin produced is not sufficient in amount to have saturated the tissues completely. Or (3) there may be no local reaction, but an increase of temperature during the next twenty-four hours, together with other symptoms of intoxication; after this preliminary rise, the temperature may fall to normal. In this case it is assumed that the tissues at the site of inoculation were unable to deal with the whole of the tuberculin injected, and therefore some of this reached the actual focus of disease and stirred it up to greater activity, producing as a result more autogenous tuberculin, which, on reaching tissues in other parts of the body not saturated with toxin, caused the production of antibodies, which, on reaching the diseased tissues, inhibited the action of the bacilli. This latter method is not a very satisfactory means of bringing about a cure, for if the focus of disease, owing just to the right amount of antituberculin not being formed, is not inhibited, it will probably cause extension of the disease and a persistently abnormal temperature.

If a suitable dose of tuberculin be administered, we can gauge from the result whether toxin saturation is almost complete or otherwise, for if a small dose causes a rise of temperature in a case where the temperature was previously normal, we may assume that toxin saturation is almost complete. It should be remembered that when it is thought necessary to use tuberculin for diagnostic purposes, the tissues will, as a rule, be considerably removed from toxin saturation.

A transient rise of temperature does not necessarily imply any increase of focal disease, but is due to the activation of the injected tuberculin in a patient who is obviously intolerant of any considerable amount; the symptoms being slight, it will therefore follow that if this activated tuberculin result in the formation of large amounts of antibody, as may well happen where the tissues have been comparatively uninjured by autogenous tuberculin, after a transient feeling of malaise, enormous improvement may follow. On the other hand, supposing the patient be nearly toxin saturated, the activated tuberculin, even if the dose be small, may stir up tuberculous foci, and the primary reaction may be continued into the fever, caused by increase of the disease.

It seems sufficiently obvious that if a patient be able to utilize without injury large doses of tuberculin, the prognosis is relatively good. The disadvantage of using large doses for diagnostic purposes would seem to be that they establish a tolerance to the poison, which destroys sensitiveness and necessitates large doses of tuberculin being used in the after-treatment.

When tuberculosis attacks non-mobile organs such as the skin, bones, cornea, brain, choroid, etc., toxin saturation is unlikely to be present; at the same time tolerance to any considerable amount of tuberculin is unlikely to have been achieved; in such cases relatively small doses of tuberculin, administered at considerable intervals in order to avoid destruction of sensitiveness, may bring about a cure without producing a focal reaction. If we are quite sure that the products of ulcerative destruction can be got rid of without danger, we may give larger doses if we are sure the larger doses will not stir up disease elsewhere which is quiescent. The avoidance of focal reactions when we are treating tuberculous tumours of the brain would seem essential. In glandular tubercle the minimum dose should be administered which is active, and no effort need be made to destroy sensitiveness, whereas the production of focal reactions may cause enlargement instead of diminution, and where the glands are deep-seated serious consequences may follow.

In administering tuberculin to cases of pulmonary tuberculosis we have to consider first the presence or absence of toxin saturation. This is discovered by putting the patient to bed and taking the rectal temperature as

advised above. If the temperature be normal we then try the effect of exercise; if this does not cause a rise of temperature we may begin with a small dose of tuberculin.

In order to obtain a correct notion as to the administration of tuberculin to cases of pulmonary tuberculosis, they may be divided into classes:

1. Very early cases, without fever, which may have been diagnosed by injections of tuberculin, a safe procedure in so far as the tissues are far removed from toxin saturation. In these cases the unsaturated tissues are able to make use of a comparatively large dose of tuberculin, and, although the general reaction may be severe, it will only be transient. If the same dose be repeated it will be found that a certain amount of tolerance has been established to the poison.

2. Cases commencing with hæmoptysis without previous symptoms; such cases are, for obvious reasons, not toxin saturated, and may be treated on the same lines as surgical tuberculosis, or, perhaps better, by means of gradually increasing doses of tuberculin given every five days, just keeping the tissues sensitive. In any event, big doses in such cases are unlikely to produce serious symptoms, though for greater security a relatively small dose should be commenced with.

3. The ordinary so-called early case, which is slightly febrile, where, as a rule, toxin saturation is, or is almost, complete. These cases must be treated by rest in bed and ordinary sanatorium treatment until their temperatures are normal, when very small doses of tuberculin may be commenced, advantage being taken of their recovery to allow of the destruction of a certain number of bacilli by means of the tuberculin, which will in itself aid the restoration to hyposaturation.

4. Cases which have existed for a considerable period, and where, owing to fibrosis and highly resistant tissues, toxin saturation is not complete, but where the disease slowly spreads locally. These cases are also best treated by the method above described.

5. Cases with extensive disease, where, owing to prolonged auto-intoxication, a considerable degree of toxin tolerance has been established. These are cases which have lost their sensitiveness, and may show a subnormal temperature. In these cases tuberculin may be administered, commencing with a small dose and rapidly increased until such a point be reached that they again become sensitive, and benefit may then be expected.

6. Cases exhibiting a large amount of caseous disease it may be well to treat as cases of surgical tuberculosis with small doses repeated at intervals of at least a week, in order to avoid ulceration of large masses of diseased tissue—a process not without danger.

In gauging the amount of sensitiveness upon which a cure depends, advantage may be taken of the reaction at the site of inoculation, and for this purpose the back of the forearm is most suitable. The absence of redness or swelling at the site of injection may be due either to toxin saturation being complete or to tolerance on the part of the tissues to the dose injected. Absence due to the first cause will be accompanied by fever and other symptoms. Absence due to the second cause will be unaccompanied by any symptoms. In the first case the tuberculin should be stopped for a time and the patient confined to bed; in the second the dose can be increased without injury. Carl Spengler has pointed out the relationship between the reaction at the site of injection and the focal reaction; in order that use may be made of this phenomenon it is essential that the injections be made on the back of the forearm.

There is some reason for thinking that it may not be wise to give the injections too often, or to increase them too rapidly, as by that means sensitiveness is too quickly destroyed, before the bacilli still capable of being reached by the antibodies have been destroyed.

In those cases in which any degree of toxin toleration has been acquired, when giving tuberculin great care must be taken to watch symptoms and physical signs, as there is reason to suppose the giving of tuberculin to such cases may hasten the fatal event, without any marked deviation of temperature.

Finally, I should like to draw the attention of those who are called upon to treat this disease, even if tuberculin be not used, to the paramount importance of preventing toxin saturation occurring in early cases, for it should be remembered that in such cases if the sensitiveness be preserved it may be possible, by comparatively simple measures, such as absolute rest followed by graduated exercise, to bring the disease to a standstill. Unfortunately, the neglect of rigid treatment in such cases allows of so much increase in the diseased process that all kinds of complicated measures may be required before a successful issue is obtained. The object of treatment should be to

cure the disease where possible without using up healthy lung tissue in the process. Whether it is so important to avoid using up sensitiveness with a liberal hand is not quite so clear, but at any rate we should avoid confounding toxin toleration with immunity.

EIGHTIETH ANNUAL MEETING

OF THE

British Medical Association.

*Held in Liverpool on July 19th, 20th, 22nd, 23rd, 24th,
25th, and 26th.*

PROCEEDINGS OF SECTIONS.

SECTION OF DISEASES OF CHILDREN.

Mr. ROBERT JONES, President.

PRESIDENT'S INTRODUCTORY REMARKS.

AFTER welcoming the members of the Association and the visitors to Liverpool and to the meetings of the Section over which he presided, the Chairman called on Mr. H. J. Stiles to open the discussion on the after-results of the major operations for tuberculous disease of the joints.

DISCUSSION ON THE AFTER-RESULTS OF MAJOR OPERATIONS FOR TUBERCULOUS DISEASE OF THE JOINTS.

OPENING PAPER.

By HAROLD J. STILES, M.B., F.R.C.S.Ed.,

Surgeon to the Chalmers Hospital, Edinburgh, and Surgeon to the Royal Edinburgh Hospital for Sick Children.

WHILE I fully appreciate the honour of being invited to open this discussion, I am equally alive to the difficulty of the task which has been set me. The opinions which have been expressed with regard to the radical treatment of tuberculous joints have changed so much within recent years that the time has now come when it is hoped that a more definite decision may be arrived at regarding the indications for and the place to be assigned to radical procedures. Such a decision can only be come to after a careful analysis of the results which have been obtained by such procedures.

During the fourteen years that I have been surgeon to the Royal Edinburgh Hospital for Sick Children I have advocated and practised conservative treatment in the earlier stages of tuberculous joint disease. In cases, however, in which the disease has progressed in spite of conservative treatment, and in those in which the disease was already far advanced when the children were brought for advice, I have always deemed it expedient to resort to operative procedures. By operative procedures I wish it to be understood that I mean procedures sufficiently radical to remove, as far as possible, the whole of the disease. In this paper I shall not, therefore, refer to those half-hearted measures which I believe to be the reverse of beneficial.

As the time at my disposal is all too short to enable me to do anything like adequate justice to so wide a subject, I feel that I shall be pardoned if I base my remarks entirely on my own personal experience. I shall confine myself, therefore, to the results of the major operations performed for tuberculous disease of the large joints at the Royal Edinburgh Hospital for Sick Children during the decennium from 1901-1911. I shall leave out altogether the consideration of the shoulder and wrist joints; tuberculous disease in these joints is relatively infrequent,

and the material at my disposal has not been sufficient to enable me to bring forward statistics which would add to the value of this discussion. With regard to the other large joints, my material comprises 205 resections, of which 63 were of the knee-joint, 59 of the hip-joint, 54 of the elbow-joint, and 29 of the ankle-joint.

The hospital records of each of these cases have been carefully epitomized and arranged in tabular form in order that the more important facts might be brought out and statistics compiled. Moreover, every endeavour has been made during the last three months to trace the individual patients, and to get as many as possible to return to hospital in order that they might be personally examined, and a record of their present condition obtained.

In this work I have been fortunate in obtaining the co-operation and assistance of Dr. John Fraser, who was formerly my house-surgeon and private assistant, and who has recently been appointed assistant surgeon to the hospital. Were it not for his help I could not have presented my results with anything like the same statistical accuracy. Let me here also take the opportunity of thanking those of my professional brethren who have taken so much trouble in the examination of those patients who lived remote from Edinburgh, for the purpose of filling up the special forms embodying the various questions asked in order that an exact estimate of the patient's present condition might be arrived at. In spite of all our endeavours unfortunately 66 patients (32 per cent.) could not be traced.

Knee-joint.

My statistics show that in tuberculous affections of the knee the disease has originated much more frequently in the synovial membrane than in the bone.

In primary synovial cases all surgeons are agreed as to the successful results to be obtained by conservative means provided the patient is presented for treatment at a sufficiently early stage of the disease. Unfortunately, however, by the time patients of the hospital class are brought for treatment the disease has frequently already reached the stage of destruction of cartilage, articular caries, and periarticular abscess.

Some surgeons prefer to open the abscess and continue conservative treatment in the hope of obtaining Nature's cure by ankylosis. Under the term "conservative treatment" is included iodoform injections, Bier's congestion, x rays, and tuberculin. My own opinion is that this line of treatment has proved so uncertain in its results that it is better, when the disease has reached the stage I have referred to, not to proceed with or continue conservative treatment, but to perform a radical operation which has for its object the removal of all the disease and the production as quickly as possible of a firmly ankylosed joint in good position.

As far as the prospect of curing the disease goes, excision gives better results in the knee than in any other joint, but at the expense, of course, of loss of mobility. The preservation of the other functions—namely, stability and weight-bearing capacity—can almost be guaranteed. In diffuse tuberculous disease of the knee-joint I have practically given up all operative procedures which do not aim at producing osseous ankylosis. Simple synovectomy, either alone or combined with division of the crucial and lateral ligaments, rarely gives satisfactory results. Unless the crucial ligaments are divided there is great risk of recurrence, due to incomplete removal of the disease at the posterior aspect of the joint, especially in the pouches behind the condyles.

With regard to the technique of the operation, it is a matter of no great importance which of the various incisions are employed, provided free enough access be obtained to enable the whole of the diseased synovial membrane to be removed. Having removed all the diseased soft parts, only sufficient bone need be taken away to ensure osseous ankylosis. The simplest, as well as the most certain, means of ensuring firm and accurate apposition of the bones is to nail them together. If properly introduced, the nails do no harm, and the patient is quite unconscious of their presence. Not only do they ensure osseous union, but they also render the after-treatment much easier. The firm fixation afforded by the nails does away with any necessity for complicated splints, and plaster-of-Paris need not be employed until after the wound is soundly healed. While introducing the nails