A Lecture

ON

THE ACTION OF TUBERCULIN AND ITS APPLICATION TO THE TREATMENT OF DIFFERENT FORMS OF TUBERCULOSIS.

DELIVERED AT THE MEDICAL GRADUATES' COLLEGE AND POLYCLINIC.

BY

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THE ability to use a drug with success presupposes some knowledge of its action and of how this action is likely to influence the diseased tissues to which it is applied. This would seem a needless remark, and as an abstract proposition it would elicit the agreement of every one; and yet it is a fact that tuberculin is being administered by many at the present time with little or no knowledge of its action, and with still less clear aim in their application of it to the needs of the diseased tissues. Such an empirical use is not justified in the case of tuberculin; for, though our knowledge of its action is still imperfect, it is yet ample to supply us with a rational working basis. It is my object in this lecture to put before you, in outline at least, the main facts of its action, and how this action may be rationally applied in the treatment of different varieties of tuberculous disease.

ACTION OF TUBERCULIN.

One of the first points to grasp in the action of tubercle products is that they are quite innocuous to the non-tuberculous. Hamburger injected 1 c.cm. of Old Tuberculin into a healthy boy without any effects other than those due to the glycerine content, and Schreiber tested 40 newborn infants with doses up to $\frac{1}{10}$ c.cm. without result. Among adults living under modern conditions it is difficult to find individuals who have never been infected with tubercle. The ubiquity of tuberculous infection has only been thoroughly realized of late years, and when Koch suffered a very severe and even dangerous reaction from the injection of 0.25 c.cm. Old Tuberculin into himself, he regarded himself in the light of a healthy control. We now know that such sensitiveness to tuberculin was due to a former infection with the tubercle bacillus, and that nearly all adults show a similar susceptibility to large doses.

TUBERCULOUS SENSITIVENESS.

This brings us to our second point, the corollary of our first—namely, that tuberculous sensitiveness must be present before tuberculin can act, and also that this is only brought about by infection, recent or remote, with the tubercle bacillus. The exact change in the tissues which enables them to "activate" tuberculin we do not yet understand, and it would be unprofitable to discuss the subject here; but reference must be made to the striking likeness of tuberculous sensitiveness to anaphylaxis, which is a closely analogous, though probably not identical, phenomenon, and the fact that lytic action is held by many to afford a plausible explanation of both facts. One of the main points in which they differ is that anaphylaxis is set up by the injection of dead albumen, but tuberculous sensitiveness as we know it has only been produced, hitherto, by the growth of living tubercle bacilli in the body.

Tuberculin Reaction and Negative Phase.

Given tuberculous sensitiveness, tuberculin becomes a powerful drug, and we will consider at once the common results of a full therapeutic dose. Some hours after the injection a train of symptoms appear known as the "tuberculin reaction." These may be "local," at the point of injection; "general," mainly affecting the nervous system; and "focal," at the site of disease. Any one or more of these effects may be present. The local reaction is sometimes useful as a guide to dosage, and there its

utility stops; the general reaction is altogether a disadvantage, save as a warning against overdosage; the focal reaction claims closer attention. Where a disease like phthisis is under treatment, slight focal changes are necessarily hidden, and almost an increase of sputum draws some attention to them. If, however, a visible lesion is under treatment, as in disease of the larynx, eye, or skin, it is found that slight focal reaction—that is, an active hyperaemia of the focus of disease—is the constant result of an effective dose of tuberculin.

Still another phenomenon must be mentioned together with the tuberculin "reaction," and that is the fluctuation of the opsonic power of the blood known as a "negative phase," for these run side by side. The determination of opsonic power is a convenient measure of antibody content in general, for it is probable that other antibodies are also concerned, and that these follow the opsonins in their fluctuation.

Tolerance and Positive Phase.

Following the tuberculin reaction and negative phase, after these have run their course, a very distinct rebound to conditions of increased health is generally observable. The patient experiences a feeling of heightened well-being, appetite increases, and weight is gained. In the foci of disease secretion diminishes and healing often proceeds apace; in lung disease the sputum may diminish. Corresponding to this improved clinical picture, two points present themselves to special methods of investigation. First, the patient becomes for a week or two "refractive" or tolerant to tuberculin—that is, it will need an increased dose to cause as large an effect as the first dose produced; secondly, there is an increase in the opsonic power of the blood, and probably in the content of other antibodies also, so that we have at this stage what is spoken of as the "positive phase" of immunization.

Now I think we have collected shortly enough material to supply us with some discussion on the action of tuberculin, and we will turn for a moment to the disease which we desire to influence.

LOCALIZED TUBERCULOSIS.

If we consider, first of all, a case of localized tuberculosis we find that we know, among others, the following facts: First, the opsonic content of the blood is below normal; secondly, the opsonic content, and therewith probably the presence of other antibodies, is especially low in the focus of disease; thirdly, the striking point about this focus is its very deficient blood supply. Localized tuberculous areas are but poorly vascularized, and on this account both disease and repair when left to themselves are extremely slow. The tubercle bacillus is walled in from the protective substances in the blood; bacillary substances filter through but slowly to stimulate the production of antibodies; food for nutrition of the cells in the neighbourhood is kept constantly scarce. Now, we may consider how an efficient dose of tuberculin will influence the course of localized tuberculosis.

Effect of Tuberculin.

First, the immediate effect of a dose of tuberculin possesses an element, the focal reaction, which is of infinite value in the treatment of localized disease. The main difficulty is at once overcome; blood, carrying antibodies and nutriment, is brought to the area of disease. This becomes obviously more vascular, and the plasma passing through it is increased.

Secondly, in the period following the reaction there is a general increase of antibodies in the blood shown in the "positive phase" of opsonic power, so that at the next injection more highly protective blood will flood the focus of disease. The result of the focal hyperaemia and the increase of antibodies shows itself in a marked healing tendency observable in visible tuberculous areas in the second week after an injection.

Practical Application.

We may now consider the administration of tuberculin in cases of localized tuberculosis from the point of view of practice. It is obvious from what has gone before that the following aims must be put before us:

1. To irrigate the diseased area by the production of a mild but prolonged focal reaction.
2. To keep the opsonic power of the blood at a high level for as long a period as possible.

The Dose.—These aims are generally served by the administration of an insoluble preparation of tuberculin in as large a dose as the "general symptoms" of the tuberculin reaction permit. The preparations of tuberculin most slowly absorbed are the endoplasm preparations, T.R. and B.E. and their congeners, and T.R. is probably the best for this purpose. The "general symptoms" must be kept within strict limits of time and scope, or weight is lost and general well-being declines. Generally a few days of slight malaise are all that are wisely permitted, but need for limitation of dosage may come from the side of local considerations, for if caseous material is present a marked focal reaction will cause this to soften, and the desirability or otherwise of this has to be decided in each particular case.

The Interval.—The other main practical point for consideration in the tuberculin treatment of localized tuberculosis is the interval between the doses, and this is governed by two factors. First, we desire to give the positive phase of antibody formation full scope, and experience teaches us that two or three weeks covers this period. Secondly, we have got to wait for the passing off of the "refractive period" to tuberculin which, as we have already mentioned, follows each effective dose. The means of measuring this I shall not enter into here, but it is found that it corresponds very closely in duration with that of the opsonic immunizing response. In all cases the interval must vary with the dosage. If a highly efficient dosage is employed the interval may be about three weeks; if a subefficient dose is for some reason used the interval may be shorter, perhaps ten days. A too short interval can always be shown by inequality in the effect of the dosage—a dose falling within the refractive period will be inefficient, and will consequently be followed by a shortened refractive period, so that the next dose will fall outside this, and will have a greater effect. Thus large and small effects will alternate.

Having found the suitable dose and gauged the suitable interval, in a straightforward case of localized tuberculosis little more is needed for success than to keep the ball rolling till healing occurs. It will be found when progress is made that sensitiveness becomes less as the area of disease diminishes, and so the dose may need to be raised from time to time to keep it effective.

AUTOTOXIC TUBERCULOSIS.

When the treatment of such a disease as phthisis comes to be considered, it is obvious that we have a very different state of things to those present in localized tuberculosis. Our aims are similar—namely, the production of a good supply of antibodies and the improved blood supply of diseased areas brought about by mild focal reactions. If, however, we try to fulfil these aims in a manner similar to that which is successful in localized tuberculosis, we soon meet with failure. In the first place, the small dose which is efficient in a case of localized disease is obviously futile in a patient whose tissues are already flooded with autotuberculin. In the second place, the presence of this autotuberculin may and does greatly change the response of the patient's tissues to tuberculin, so that the size of an effective dose differs enormously in various patients and in the same patient at different times. On the one hand there may be increased sensitiveness to tuberculin; on the other hand, a considerable amount of tolerance may have been naturally produced. Thirdly, we are met at once by the pertinent question, Are we going to do any good by giving more tuberculin to a patient who is already getting too much?

The Foundation of Tolerance.

Let us turn once again to the action of tuberculin before we go further into autotoxic disease. We have seen how a dose of tuberculin is followed by a "refractive" interval. In cattle this is so marked as to be utilized by dealers in passing off tuberculous beasts as healthy. A dose of tuberculin is given before the deal, and the animals no longer react to the test injection of tuberculin given by the buyer. In the human we have seen that an interval of two or three weeks has to be waited if the same dose of tuberculin is to be repeated with equal effect. Suppose, however, we elect to give our second injection during the refractive period, if we desire it to be effective we must raise the dose. The effect of this second dose is to raise tolerance still further, so that the third dose must be bigger still;

and so with injections at short intervals, we must constantly raise the dose if we are to obtain each time the action of tuberculin—namely, mild focal reaction and stimulation of antibody formation. By this means we obtain, in addition to the effect of each dose, a *tolerance* to tuberculin established, so that at the end enormous doses are given with the same effect as minute doses at the beginning. This should be our aim in autotoxic disease. When large doses have been reached treatment is no longer hindered by the occurrence of some amount of autoinoculation; at the same time the patient is rendered tolerant of the poisons issuing from his focus of disease.

In cattle, as we saw, a single dose will produce considerable tolerance; in man a regular sequence is needed to achieve this result. If, instead, large and irregularly-spaced doses are given, tuberculin poisoning and increased sensitiveness generally result, and this is what has commonly happened in autotoxic disease. To interrupt the vicious circle absolute rest is needed, so that autoinoculation is reduced to its lowest point. When this is done we find that phthisis patients divide themselves roughly into the following three categories:

A Classification of Phthisis.

1. Those who have symptoms of autoinoculation even at rest.
2. Those who only get such symptoms on exertion.
3. Those in whom no symptoms are produced by full work.

To consider the last two categories first, we may say that Group 2 is amenable to tuberculin treatment, whether applied subcutaneously or by the exploitation of autoinoculation on similar lines, as by graduated labour. It is obvious that subcutaneous tuberculin is more easily controlled than autotuberculin, and it has besides many other points in its favour. During its administration autoinoculation must be kept at a minimum till large doses are reached.

The patients in Group 3 are mostly on the road to cure, and their danger lies in the fact that, just as in localized tuberculosis, their lesion may not suffice to keep them supplied with tuberculin. On this account a course of tuberculin from outside is valuable, and can be followed up by large doses at longer intervals over a considerable period.

When we turn to Group 1 we find a much more difficult subject for consideration. A large number in this group will be beyond the reach of any but symptomatic treatment; many will be cases with marked secondary infection where tuberculin if it is used must be employed in extremely minute dosage and with great caution; some will be acute cases in which tuberculin is worse than useless. The first endeavour in cases of this group must be to bring them as near as possible to Group 2 by all the means we have of checking autoinoculation in phthisis. "Typhoid" rest must be enforced, talking and excitement must be avoided, and visitors kept at a distance; cough must be reduced to a minimum. By these means many cases may be coaxed into Group 2, but if fever does not give way to these methods, tuberculin, preferably T.R. or B.E., may be tried in doses one-tenth or one-hundredth of those with which a course is usually commenced. This measure is closely reminiscent of the minute dose recommended by Wright to put an end to a prolonged negative phase, and it is not infrequently successful. If this fails, a larger dose may be given experimentally, since sometimes a smart reaction is the turning point in these feverish cases. This is not done altogether without risk, but this must be put against the chance of doing much good, and the responsibility is often worth taking.

It will thus be seen that the power of treating patients in Group 1 with tuberculin depends upon our power of bringing them into or near to Group 2, but there will always remain certain cases of advanced but chronic disease where tuberculin tolerance can be set up with advantage although cure is no longer possible. By this means comfort may be promoted and the patient to some extent protected against the symptoms of his disease, even though this must in the end overcome him.

Practical Application.

Consideration having been given to the theoretical side of tuberculin administration in autotoxic disease, we may turn shortly to the practical side.

Since the reactivity of patients varies enormously according to their sensitiveness and how far this is covered by tolerance, it is well to begin with a dose so low that it is certain to be ineffective. Actual dosage I shall not mention here, since I have long discarded the standards usually adopted and measure my tuberculin in cubic millimetres of original solution; and though this is the best and simplest of all methods, the doses in a new standard would be difficult to grasp in a lecture. Having begun with this small dose, it may be very rapidly raised till some effect is noted. This must be looked for in a local reaction, or, failing this in some slight general effect, such as a flattening of the temperature, or a slight rise, or slight symptoms in the patient. Having reached this point, the doses must be raised more gradually, and for the graduation of dosage nothing is more suitable than a geometrical progression such as that supplied by Lawrason Brown in Klebs's *Textbook of Tuberculosis*. By this means risk of large reactions is reduced to a minimum, and yet, with skilful adjustment, the dose may be kept sufficiently near the reacting point to efficiently call forth an immunizing response, the main points of which we have already laid down as the slight focal hyperaemia and the stimulation of antibody formation. It is unlikely that fever reactions will be altogether avoided, and this brings us to a parting of the ways among various exponents of the art of tuberculin administration. There are, as you know, certain people who ignore reactions, and, in their struggle to establish tolerance to large doses, will allow the patient to react violently again and again. Those who have treated localized tuberculosis, where the foci of disease are under the eye, cannot look on this method with favour. They know how caseous material will soften and discharge itself under large focal reactions, and though such a process in the lung may in certain cases be inevitable and lead to no harm, in other cases this is far from being the case.

By avoiding such large reactions we are putting possible danger on one side. By allowing mild reactions occasionally, and keeping the dose near the reacting point we are fulfilling those conditions which experience has taught us to rely on in the treatment of visible lesions. In this way the whole course of treatment is directed towards the healing of the tuberculous areas, and tolerance is but a valuable by-product of the tuberculin administration. This may be called the method of utilizing reactions. A third method in the administration of tuberculin aims at the avoidance of all reactions, and has not much to recommend it unless its safety.

The consideration of the method of pushing the dosage through reactions, with the aim of rapidly reaching tolerance to large doses, tempts me to the question of the value of such tolerance. Is there sufficient evidence of its value to justify us in making it an aim? If we turn to animal experiment for a moment we find that tuberculous disease protects against further infection with the tubercle bacillus. Experiments have been done on cattle, guinea-pigs, and, more recently, apes, which show that if virulent bacilli are injected into a healthy animal, no symptoms follow immediately, but after an interval symptoms of tuberculosis appear, and the animal dies. If similar injections are given to a tuberculous animal, on the other hand, a violent "reaction" immediately follows, but the animal shows no fresh tuberculous disease. Here we find that sensitiveness to tubercle products (not tolerance) is associated with protection against fresh infection. We might, therefore, fear that by producing tolerance we were removing a valuable safeguard against the further spread of disease.

We are, it is true, removing from the patient, for a time, the power of autoinoculating himself, and this might be a danger where tuberculin was withheld. It is, however, highly unlikely that tolerance removes in any way the power of the tissues of the tuberculous to deal with the tubercle bacillus. More probably the injected tuberculin is "activated" as before, and tolerance only protects the tissues, the nervous system, and focus of disease, from the toxic effect which follows. This may be by the production of some such body as the "antituberculin" of Wassermann, which is shown to increase under tuberculin administration on the intensive system. If this is the case the condition underlying tuberculous sensitiveness is not removed, but its effects are mitigated.

On the other hand, there is no reason to suppose that

tolerance adds anything to immunity against further disease, and for this reason the common use of the word "immunity" where tolerance is meant is greatly to be deprecated. All that tolerance does—and this is no small advantage, is to free the patient from those symptoms of autotuberculin poisoning which were undermining his health, and from dangerous focal reactions, which were spreading the disease. At the same time it enables us, as we have seen, to treat autotoxic disease with doses of tuberculin so large as not to be unduly interfered with by autoinoculation. The value of tolerance depends, then, on the need of it in any particular case, and not in all cases of phthisis is tolerance to large doses required or even advisable. The need, on the other hand, of obtaining repeated response to tuberculin, in the form of mild focal reaction and antibody stimulation, is common to all varieties of tuberculosis. This appears to be Nature's method of cure, and if it is followed on rational lines, and the needs of each individual case carefully studied, it will be found that we have in tuberculin, and the control of autotuberculin, all or nearly all that we need for the cure of tuberculosis.

At the end I must apologize that I have tried to cover an impossibly wide field in this lecture. Its title was hurriedly supplied many months ago, and I did not realize at the moment to how big a business I was committing myself.

A THIRD SERIES OF TWENTY CASES OF PULMONARY TUBERCULOSIS TREATED BY CONTINUOUS ANTISEPTIC INHALATION.

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In a paper read before the Therapeutical Section of the Royal Society of Medicine on November 2nd, 1909, and published in the *Proceedings* of that Society, and also in the *BRITISH MEDICAL JOURNAL* of December 11th, 1909, I advocated the treatment of incipient and early pulmonary tuberculosis by means of continuous antiseptic inhalation, and narrated 30 cases in which it had been employed with success. In a second paper, printed in the *Lancet* of November 19th, 1910, I related 20 additional cases similarly treated; some of these were advanced or complicated cases. I desire now to record a third series of 20 cases, making a total of 70 cases treated by the method of which full details were given in my first paper.

Case 51.

A patient, aged 26, a draper's assistant, was sent to me by Case 3, July 29th, 1910. His sister died seven years ago from phthisis at the age of 23 years after eight months' illness. He had suffered for eighteen months from repeated "colds" and frequent cough, with occasional slight hæmoptysis. In March, 1909, he entered a sanatorium and remained in it twelve weeks (weight on admission 10 st. 1 lb.—it rose to 10 st. 12 lb., but fell again to 10 st. 8½ lb.). Since June 20th, 1909, he had been at work, and had again "caught cold." His cough and sputum were as troublesome as before he entered the sanatorium, and his weight was only 9 st. 12 lb. Cough was frequent, short, and loose—he expectorated into a flask. He looked wasted, worn, and ill. All the characteristic dull areas of pulmonary tuberculosis (as described in my first paper) were present, and those at the left upper and lower apices were specially large. Over the whole left upper lobe in front and at both lower apices there was marked crepitus on inspiration, and very defective air entry at the right upper apex.

He was advised to remain in bed for two weeks and practise continuous antiseptic inhalation in the method and with all the details mentioned in my first paper. I saw him a second time on August 15th, 1910; he had then lost another pound, the weight having fallen to 9 st. 11 lb. But his cough was less troublesome, his sputum less profuse, his dull areas distinctly smaller, and the pulmonary crepitant sounds were much diminished.

He persevered with the treatment, and on September 26th, 1910, was much better, felt "quite a different man." Cough was "very much better," and sputum "very much less." His evening temperature was still about 99.4° F. (morning 97.8° F.). His weight was still 9 st. 11 lb., but he felt very much stronger, and no longer fatigued by walking. "Felt as if he would not recover at the last visit, but now feels that he is getting well." The physical signs showed an increased improvement. Had not been able to wear his inhaler at night. He spent the next four months at Southbourne, wearing his inhaler about eight