

ON  
TUBERCULIN IN RELATION TO SURGICAL  
TUBERCULOUS DISEASES.<sup>1</sup>

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To some it may seem an unnecessary expenditure of time and energy to discuss the relation of tuberculin to surgical tuberculous diseases, seeing that this remedy has of late fallen into great disfavour and has been practically given up in practice. I think, however, that most of those who have employed it will agree that, although it has many very objectionable qualities, it also possesses remarkable selective and, within certain limits, remedial properties, and in so far, therefore, is deserving of further study. At the end of April I discussed the whole matter very fully in a paper which I read at the Royal Medical and Chirurgical Society; and with regard to tuberculin itself, I have but little to add to what I said on that occasion, seeing that I have not treated any fresh cases since that time. I can therefore only speak on the subject with three months' further experience of the cases which were then under treatment. My remarks to-day will fall under three headings: (1) The beneficial effects of tuberculin; (2) its hurtful action; and (3) its future.

1. *The beneficial effects of tuberculin.*—The first effect of the injection of a moderate dose of tuberculin—say, from two to eight milligrammes—is, apart from the constitutional disturbance, marked inflammatory action at the seat of the tuberculous disease, indicated clinically by redness, swelling, and exudation, and microscopically by infiltration of the tuberculous tissue with numerous leucocytes. This effect is usually, though to a constantly lessening degree, seen at each of the subsequent injections till from three to ten have been given, when it becomes, as a rule, hardly noticeable. After the lapse of two or three weeks improvement can generally be observed in the local condition; thickening subsides, pain, if previously present, becomes less or may disappear altogether, and in most cases the local condition after from four to six weeks' treatment is better than it was previously, the result depending largely on the dosage and the method of administration. And now, as a rule, where Koch's method of dosage is employed matters come to a standstill; indeed, they not uncommonly begin to go back, and if the treatment is left off at this stage relapse almost always occurs at once and with much greater rapidity than is usually the case where relapse takes place after a corresponding degree of improvement under other methods of treatment.

As regards the ultimate results the following is my experience. I have treated thirty-eight cases of surgical tuberculosis altogether, and three for a time, by Koch's original method of administration—viz., by intermittent dosage, these cases being chiefly lupus, diseases of bones and joints with and without suppuration or sinuses, strumous glands, &c. Of these thirty-eight cases, five have benefited directly and to a marked degree, while three others have also much improved, but how far the improvement in the latter cases was due to the tuberculin, and how far to other treatment, I cannot say. Of the five cases which benefited directly as the result of the treatment, four remain well, and in three of them two months at least have elapsed since the treatment was stopped. Of these, two were cases of well-marked and progressing synovial disease of the knee-joint in children, and at the present time the joints are normal in all respects, and the patients are running about. The third was a case where disease recurred after arthrectomy of the hip, and showed no tendency to improve, and when I was more than once on the point of excising the joint. Here the sinus healed up in a few weeks, and the part is now apparently sound. The fourth case was that of a medical man with tuberculous laryngitis complicated with phthisis. The ulceration of the larynx healed and remains healed, but the patient is still going on with the injections on account of his phthisis, which, how-

ever, is also very much improved; I saw him a fortnight ago on his return from a voyage to New Zealand. The fifth case was also one of tuberculous laryngitis, likewise complicated with phthisis, in which the laryngeal trouble healed and remains healed. As I have said, these cases showed very marked improvement; indeed, apparent disappearance of the disease. Whether this improvement will be permanent—in other words, whether the disease is cured, or whether there will still be a relapse—I cannot of course at present say. Some of the other cases improved for a time, but the disease recurred on stopping the treatment, or various operations were performed as soon as it was found that improvement had ceased. These results are certainly not brilliant, especially when we bear in mind the risks of the treatment, to which I shall presently refer.

It may be remembered that at the meeting to which I have alluded I suggested another mode of administering the remedy, which seemed to me to promise better results. It consisted in giving the injections at least twice and better, thrice daily, and so regulating the dose as to avoid febrile and general reaction as far as possible. I do not lay so much stress on the amount to be given at each injection as on the frequency, but I think that where it can be done a fairly full dose should be reached soon, and in my cases I went up slowly or rapidly, according to circumstances, till a decigramme was given at each injection, and in two instances I got as high as three decigrammes three times a day. I have treated by this plan of continuous dosage nine cases from the beginning and three cases after previous unsuccessful treatment by the intermittent method. Of the nine cases, six have improved to such an extent that at present there is no evidence of disease, and that although the treatment has been stopped for some weeks. One was a case of lupus of the face, where the injections were continued for four months, and no local treatment was used. Two months have now elapsed since the treatment was stopped, and there is as yet no recurrence of the lupus, but some enlarged glands in the neck have since suppurated. A second case of very bad lupus is also still without recurrence six weeks after the cessation of the treatment. In this case the nose and both cheeks were affected; one cheek was scraped, one cheek was treated with Unna's salicylic and creasote plasters, but the nose was not treated locally. At the present time the result is equally satisfactory in all parts, but the skin over the nose and lips is much softer than that on the cheeks. The third case was one of spinal disease without abscess, but with marked tenderness &c., in which the treatment was continued for two months; since that time the patient has been free from pain in the back, but she still wears a spinal jacket. There were also two cases with sinuses after operation for tuberculous joint disease where the sinuses have closed and remain so. And the sixth case was one of ulceration of both corneæ which healed. Further, one case of lupus has been under treatment in this way for five months, and is steadily improving. In this case portions were scraped &c., but a considerable part could not be satisfactorily dealt with in this way; and here, curiously enough, as in the first case, although the lupus has been steadily improving, several enlarged glands in the neck have suppurated. Finally, one case of lupus, which had relapsed under Koch's method, steadily improved on adopting this plan. I am far from saying that these cases are really cured, but they have certainly improved very markedly, and the results are much better than those which I obtained with the intermittent method. It is true that the cases submitted to this plan were to a certain extent selected, while the others were not; but nevertheless I think that the results support my contention that the best and indeed, except in rare cases, the only method of administration which promises a favourable issue is the continuous plan. The great objection to it, apart from the trouble, is the expense, which almost debars its use in hospital. I have seen no dangerous phenomena in the cases where it was employed, and the patients have certainly suffered less general disturbance than by Koch's original plan.

One great question with regard to the improvement after the administration of tuberculin is whether it is due to a specific remedial action of the drug on the tuberculous disease, or whether it is merely a secondary result of the inflammation set up in the first instance in and around the affected parts. That a transient acute inflammation involving a part which is the seat of tuber-

<sup>1</sup> A paper read in the Section of Surgery at the annual meeting of the British Medical Association, held at Bournemouth, July, 1891.

culous disease may produce a temporary and sometimes very marked improvement has been long known in connexion with the effect of an attack of erysipelas on lupus—and, indeed, so great has been the benefit in some instances that surgeons have actually inoculated erysipelas in cases of inveterate lupus with the view of curing the disease. That a great part—probably the greater part—of the early improvement after the injection of tuberculin is due to the acute inflammation which is set up in the first instance, I have no doubt; indeed, we see in cases of lupus that the more marked the local reaction at first, the greater and more marked is the subsequent improvement. Nevertheless, I think that tuberculin has a distinctly remedial action apart from this acute inflammation. For example, I have seen that while cases which were being treated by Koch's method have been going back, improvement took place on increasing the frequency of the dose in the way I have described, and that without the occurrence of any marked acute inflammation; and microscopically, we find at the later stages in cases where improvement is still going on, that the changes are no longer those of acute inflammation so much as of atrophy and disappearance of the tubercular elements.

To sum up what I can say as to the good effects of tuberculin, I have nothing to add to what I said in my paper at the Medical and Chirurgical Society—viz., that it is only rarely that we can expect a complete cure by tuberculin alone; that the best—indeed the only promising—mode of administration is by giving frequent doses in the way which I described; and that the treatment must be continued for a long time, and must in most cases be directed rather to keeping the disease in check than to getting a final cure. And as regards the position of tuberculin in surgery, that it is of use in cases of lupus in combination with other methods of treatment, and in cases of bone and joint disease after operation, where healing has not taken place, or where the diseased tissues have been only partially removed.

2. *The hurtful action of tuberculin.*—In considering the remedial properties of tuberculin, we must not omit to consider also its hurtful action, which in many cases outweighs its good effects to such an extent as to lead to its abandonment or preclude its employment. The most striking of the bad effects of tuberculin are the fever and the illness which accompany the early injections unless very minute doses are administered. The fever, which is sometimes very high, is accompanied by sickness, headache, pains in the limbs, cough, and marked general depression; and, although these effects do not usually last longer than one or two days, yet recurring frequently even in a lessening degree, they pull down the patient very much, so that after the first fortnight of treatment it is usually found that the patient has lost weight, is thinner, weaker, anæmic, and altogether in a worse condition than before. No doubt, once this stage is past, the patient rapidly picks up; but its occurrence is a serious matter, and the symptoms have in some cases been so severe as to necessitate the suspension of the treatment.

The local inflammation which occurs at the early period of the treatment may also lead to serious complications, more especially where the disease is located in internal organs. Where the tuberculous disease is extensive or scattered throughout an organ—such as the lung—the inflammation occurring around the deposits may of itself lead to very serious consequences—for example, pneumonia. And not only is the inflammation dangerous *per se*, it is also dangerous as tending in various ways to aid the spread of the disease. It is, however, possible that this spread might not occur to any serious degree as the result of the inflammation alone were it not that, as I shall presently point out, tuberculin, apparently in some cases, predisposes the tissues to fresh infection, and thus, while the inflammation may open the way for fresh infection, it is not improbable that that accident might not occur at all, or only to a very limited extent, but for this predisposing action on the part of the remedy.

Among the ways in which it is conceivable that the local reaction may aid the extension of the disease, the following seem to me to be not unlikely:—In the case of the lung, for example, the increased amount of fluid sometimes poured out into the bronchi after the early injections, carrying with it, as it must, cheesy material and tubercle bacilli, may be imperfectly expelled, and consequently reinhaled into healthy parts of the lung, where it starts fresh foci of disease. Again,

where the tuberculous deposit involves the pleura, the inflammatory action may lead to its communication with the pleural cavity, and consequently to infection of the whole serous surface. Similarly, where the tuberculous disease involves the wall of a blood or a large lymphatic vessel, a communication may be established with the circulation, with the consequent occurrence of secondary deposits elsewhere, or of an acute general tuberculosis; and further, the exuded fluid distending the tuberculous foci and the tissues around them, may carry tubercle bacilli away with it and deposit them in the neighbouring parts, and thus lead to the occurrence of fresh disease in previously healthy parts. These views probably apply also to tuberculous joint disease and other surgical affections, as well as to disease of internal organs, although not to the same degree on account of the different structure of the parts. So far as my own experience goes these dangers are almost entirely theoretical. Except in one instance—a case of tuberculous laryngitis—I have not seen any evidence of infection of previously healthy parts during the treatment, and none of my patients have developed acute tuberculosis. Nevertheless it is clear from the experience of others that such accidents can occur, and it seems to me most probable that they take place in one or other of the ways which I have just mentioned.

Another objection to the general employment of tuberculin is its danger in cases where sepsis is present. Where a tuberculous sinus or cavity contains also pyogenic organisms, the increased amount of fluid exuded as the result of the early injections supplies pabulum for these organisms, while the weakening and possible necrosis of the wall of the sinus or cavity enables them to penetrate into the tissues, and, it may be, set up very grave septic troubles. No doubt, by providing free exit for discharge these dangers may be avoided to a considerable extent, but by no means altogether; and in several of my cases where septic sinuses were present I have been compelled to give up the treatment on account of the increased septic trouble. Indeed, I regard the presence of sepsis as a very grave complication, and one contraindicating in most cases the use of tuberculin. At one time I thought that this substance actually predisposed the body generally to septic processes, but I have not been able to obtain any support to this view from experiments on animals. Thus I have treated rabbits with tuberculin before and after injection of pyogenic organisms, and have at the same time in a corresponding number of animals injected the pyogenic organisms without employing tuberculin, and on the above view I expected that the septic processes would be more marked in the former than in the latter animals. This, however, did not prove to be the case; in fact, on the contrary, the suppuration was less and more limited in the animals treated at the same time with tuberculin than in the others.

The last objection to the use of tuberculin to which I need allude is one which had not impressed me to the same extent in April that it has since, because I was at that time continuing the treatment. It is that tuberculin not only does not produce immunity, but actually in some cases apparently predisposes the body to the tuberculous infection. Hence, unless the treatment is continued till the bacilli have died out (and even in some cases while the treatment is being continued), recurrence may take place with startling rapidity and the disease may extend locally more quickly than before the treatment, and may also break out in other parts of the body. In cases of lupus more especially, I have been much struck with the rapidity of the relapse after the cessation of the treatment, and not only with the relapse in parts where the disease formerly existed, but also with the rapid extension of the disease into previously healthy skin. Lupus is, as we all know, a slowly progressing disease, and yet in one case I saw the disease make such rapid progress after the cessation of the injections that distinct extension could be made out in two days. In the spring I made some experiments to see whether immunity could be produced in guinea-pigs by means of tuberculin. For example, three guinea-pigs were treated with tuberculin, and twenty-one days after treatment was commenced were inoculated with tuberculous material. During that time one had thirteen doses of 2 centigrammes every day; a second had eighteen doses also of 2 centigrammes every day; and a third had six doses of about 2 decigrammes every third day. From three to eight days after the last dose these three animals were inoculated with tuberculous tissue, and, at the same time, three other guinea-pigs which had not been treated

were inoculated with the same material. In those animals which had been treated with tuberculin the disease appeared earlier and progressed more rapidly than in the others. In other words, not only was immunity not produced, but the animals were actually rendered more liable to the disease. The clinical observations on man are for the most part in accord with this experiment on guinea-pigs, especially where the doses given have been very large.

We have therefore in tuberculin a substance which, on the one hand, possesses certain remedial properties, but which, on the other hand, exposes the patient to a series of risks which are of grave importance; and though these risks may be minimised to a certain extent by modifications in the mode of administration and in other ways, yet they must be carefully considered before the treatment is commenced in any given case.

(To be concluded.)

## OBSERVATIONS ON THE TEMPERATURE OF PHTHISICAL PATIENTS IN RELATION TO THE TEMPERATURE OF THE ATMOSPHERE.

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OF the many varied forms of treatment that have from time to time been in vogue for phthisical patients none has received wider attention or has gained credit with greater justice than the climatic. And yet the exact form that this treatment should take has been itself a subject of much difference of opinion. At first a voyage was advocated, later Madeira, New Zealand, and South Africa were extolled for the good effects of their air. But within the last few years an entire revolution has taken place, and instead of a warm, relaxing climate, clear and bracing air is chosen to which the patient is to be sent. At the same time high elevation above the sea-level is held to be a great advantage, and it is to these combined qualities that the valleys of Davos and the Engadine owe their present reputation in the treatment of consumption. It is, I believe, a generally accepted truth among physicians especially qualified to give an opinion on the subject that consumptive patients enjoy better health in all respects during the winter than during the summer months, and this, too, allowing for the facts that hæmoptysis is more common in hot weather and that the very heat is likely to increase the night sweating. Certainly in late spring and early summer there apply for admission to hospitals a number of patients who having been under observation and treatment as out-patients for a considerable time nevertheless have such a rapid increase in their symptoms that they are no longer fit to be out-patients, and are easily recognised as suffering under very active or acute phthisis. Now, have these two last facts anything in common? Is there any cause which operating for the benefit of patients at Davos operates for the benefit of patients in England during the winter months, and ceases to operate or is replaced by a damaging cause during the summer months? In a word, is there any relationship between the temperature of phthisical patients and that of the external air? To determine that question is the object of the present paper. The cases that have been used in this investigation may be included under the head of "acute phthisis," and it will be well to indicate briefly the form of consumption that is meant by that name. At the outset it must be plainly understood that by "acute phthisis" is not meant "acute tuberculosis," with its tubercles widely disseminated throughout the body. The latter disease is so unlike in its course that of ordinary phthisis, that little good would come of considering it in this connexion. But acute phthisis is often characterised post mortem by the circumscribed area in which tubercles are found. Perhaps it is only one upper lobe, while the rest of the lungs is almost free. In the affected part tubercles are very thickly studded, and caseate rapidly. Excavation proceeds by strides, and in a very short time the lobe, or possibly the whole lung, may be shelled out. During life the rapidity of the process may be evidenced by the detection with the microscope of many scarcely altered yellow elastic fibres in the sputa. In fact, this form of phthisis is very closely allied to, if not identical with, the disease formerly called "caseating pneumonia." Night sweats are profuse and anorexia is common; diarrhoea

and hæmoptysis are rare (the latter especially so), while the temperature is markedly hectic in character. The prognosis of such cases is bad; of the 160 patients which constitute my series, twenty-seven died in the hospital, and thirty-two were registered as being "worse" when they left. The patients are as a rule young, the average of my cases being twenty-six years and ten months.

The grounds upon which this class of case has been chosen for the investigation are three:—1. The hectic nature of the temperatures, often showing a difference of from 4° to 5° between morning and evening temperatures, will allow a better comparison to be made than where differences are smaller, and also small individual variations do not make so much difference in the general result. 2. There can be no question about the activity of the disease. 3. There is much greater presumption in favour of careful taking of temperatures when the pyrexia is known to be great than when the temperature is normal or nearly so. Whatever be the individual view as to the advantage or disadvantage of a high temperature *per se*, everyone agrees that it is an index of the activity of the disease. The higher the temperature of the patient, the more active is the disease, and *vice versa*. Now what is true of the individual is also true of the class to which he belongs, and it may be taken therefore for granted that (cases of acute disease only being under consideration) if of two classes of patients the temperature of one class is lower than that of the other, that class whose temperature is lower is more favourably situated with regard to the disease than that whose temperature is higher. Hence the welfare of the cases under discussion varies inversely as the height of the temperature above normal. To make differences come out in greater contrast, I thought best to confine my inquiry to the two extremes of temperature in the year, and hence chose the following periods of twenty-five days each:—(a) 1887: July 14th—Aug. 7th; (b) 1887–8: Dec. 20th—Jan. 13th; (c) 1888: July 20th—Aug. 13th; (d) 1888–9: Dec. 20th—Jan. 13th. During the hot periods the average temperatures for the last fifty years as given in Whitaker's Almanack is 62°, while during the cold periods it is 37°. During the above-mentioned periods there were in the hospital 33 cases, 17 cases, 28 cases, and 22 cases respectively, quite fortuitously 100 cases in all. First, then, with regard to the external temperatures. An average temperature for each period was obtained by simply adding the means of the maxima and minima of each day, and dividing by the number of days (twenty-five) in the period. This method showed that in the periods above *a* was 3·3° above the average for the last fifty years; *b* 8° below; *c* 0·8° below; *d* 5° above. Secondly, with regard to the patients. The male and female cases for each period were set into groups, and the sums of their temperatures on each morning and evening of the period were found. Dividing these sums by the number of cases in a group gave an average temperature, which was charted, corrected to two places of decimals. Next, the same was done for these temperatures as for the external, and hence a single average temperature was also found for all the patients during each of the four periods. They are as below:—

| Period.                         | Average temperature<br>of patients. |
|---------------------------------|-------------------------------------|
| 1887, July—August ... ..        | 99·680                              |
| 1887–8, December—January ... .. | 99·090                              |
| 1888, July—August ... ..        | 99·516                              |
| 1888–9, December—January ... .. | 99·734                              |

Comparing the two sets of results, and omitting the winter period of 1888–9 for the moment, we see that the relationship is perfect, and that the order in both classes—patients and atmosphere—is the same:—1. July—August, 1887. 2. July—August, 1888. 3. December, 1888—January, 1889. But the difficulty is the greatest with the temperature of the patients in December—January, 1888–9. These, so far from being lower, actually come out at the top of the series, and, moreover, as there is only 0·009° between the average of the female and of the male cases during that period, it cannot but be something intrinsic in the temperatures, and not dependent upon error. Now, this difficulty is not insurmountable. Owing to the fact that the whole of the hospital, corridors included, is artificially warmed during winter, it is hardly fair to compare winter and summer

<sup>1</sup> Jubilee year, well remembered for the extremely hot and dry summer.

<sup>2</sup> A cold and wet summer. One is struck by the little difference there is between *a* and *c*, when one considers the vast difference there seemed to be between the years.