An Address

ON

TUBERCULIN IN THE DIAGNOSIS AND TREATMENT OF TUBERCULOSIS.*

BY

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IN current statement as to the significance of tuberculin in relation to tuberculosis—and still more as to its practical application—one is frequently up against a looseness of conception regarding essential facts. These facts form the basis of any sound practical application of tuberculin in diagnosis or treatment. While the facts are in chief part definitely determined, there has been little attempt to correlate them as the basis of practical procedure.

My aim is to recall fundamental positions and try to show how these afford points of departure for practical observations regarding tuberculosis, with a view to the final goal of detuberculization. This will include considerations bearing on both diagnosis and treatment. In particular I shall take the opportunity of urging once more the therapeutic value of the *percutaneous* exhibition of tuberculin as recommended by me for many years.

While the percutaneous method is serviceable in the treatment of tuberculosis generally, it has a special range of application in the earlier manifestations. It exerts a remarkable inhibitory influence on the first buddings of tuberculosis in childhood. Continued observation as to its effects throughout long periods in many types of tuberculosis has led me to conclude that the method, consistently applied, is capable of effecting the nearest approach to *detuberculization* yet realized.

Experimental Tuberculosis.

The first postulate is a clear conception of tuberculosis, or, stated otherwise, of the process and effects of tuberculization. When an animal, say a guinea-pig, is inoculated with a sufficient dose of tubercle bacilli, whether by injection into the tissues or by inhalation, the animal becomes tuberculized. In illustration, take the effects following the subcutaneous introduction of bacilli—for example, into the groin. Within ten days or thereabout, a local sore is produced at the point of puncture, which tends to continue in indolent fashion throughout the life of the animal. Following the appearance of the sore, more distant effects are speedily registered—first in lymphatic glands nearest to the sore, and then successively in glands and groups of glands at increasing distance from the initial lesion. Ultimately the lymphatic system tends to be involved universally. At varying dates the several viscera—spleen, liver, lungs, kidney—become implicated. The order of events is subject to variation, according as the position of primary inoculation is varied. The histological changes are essentially similar throughout the process. These manifestations in glands and viscera, however variable in degree, constitute collectively the *local effects* of tuberculization.

In addition to these, and dependent on the gradual extension throughout glands and viscera, may be registered more general changes—conveniently termed *systemic effects*. While at first the inoculated animal may present little evidence of disturbance, maintaining and perhaps even increasing in weight, physiological disturbance may be observed sooner or later. The animal tends to assume a shabby aspect, natural firmness is replaced by hypotonus, weight is dropped, the quality of the coat deteriorates, and spontaneous motility slackens. An advancing marasmus leads towards death. Such disturbance forms collectively the *systemic effects* of tuberculization.

Complete Diagnosis.

What occurs in the inoculated animal—guinea-pig, rabbit, or other—may be traced in the tuberculized human subject, with variations, according to the point of primary inoculation, the dose of infection, and the resistance offered, influenced as the last may be by initial qualities in the individual and by varying conditions of environment. In concluding a diagnosis in the human subject it is of the first importance that observation should be directed explicitly and fully to *both* groups of phenomena.

Local (focal) effects in viscera and other structures must be carefully searched for throughout the body. We must get away from undue concentration on one or other focal manifestation, wherever that may happen to be. It goes without saying that a local effect may be such as to call for immediate local treatment, whether in gland, lung, kidney, or elsewhere. But the adoption of such local measures must not be allowed to obscure the presence of tuberculosis in other organs and tissues. The diagnosis of local disorder must be as complete as possible. Beyond the local disturbance, a careful estimate must be made of the degree of general physiological disturbance—in other words, of the *systemic effects* of tuberculization, as these may be registered by evidence of neuro-muscular intoxication (languor, feeling of tiredness, muscular dystrophy, vasomotor phenomena, etc.), by temperature variation, circulatory failure, etc.

The diagnosis, then, of tuberculosis in a given case should be much more complete and definite than it generally is. The determination that the tubercle bacillus is the cause of symptoms occurring in relation to lung, kidney, or other organ—whether that determination be based on actual discovery of the tubercle bacillus in discharge or excretion or on other grounds—is merely the first step to the completer diagnosis which is essential in every instance. The complete diagnosis must be based on the fullest examination possible and be given in terms both of local and of systemic effects.

Tuberculin in Diagnosis.

Tuberculin—using that term in wide sense, to include the considerable variety of extracts obtainable by various processes from a culture of the tubercle bacillus—may be said to possess, by reason of its origin and its effect on tuberculized individuals, specific relationship to tuberculosis.

The animal inoculated with tubercle bacilli and the tuberculous patient respond in remarkable fashion to tuberculin. While the individual who remains free of tuberculous infection can tolerate large doses without production of symptoms, the individual who is tuberculized, even in slight degree, yields a response both local (focal) and systemic. The nicety of diagnosis by means of tuberculin depends on the exactness with which the response, focal and systemic, is appraised.

The *focal effects* consequent on a test injection of tuberculin are most directly illustrated by the changes observable in a superficial patch of lupus. These include congestion with increased redness and swelling of the patch itself and the neighbouring tissue, with subsequent exudation and, it may be, crust formation, the effects lasting for several days. The focal effects which are so evident on the surface in the case of lupus are reproduced in similar fashion—it may be in aggravated degree—in relation to tuberculous foci wherever situated in the body. They are to be carefully sought for by all the available methods of physical examination.

In addition to the focal results, *systemic effects* from tuberculin may be traced in the occurrence of malaise and probably disturbance of temperature and circulation. The systemic effects, which may be slight in a case of limited lupus, are correspondingly greater according as the area involved is larger. They become pronounced, and may even be serious, where the foci of tuberculosis are extensive or numerous, more especially in the case of visceral involvement.

Rationale of Tuberculin as a Therapeutic Agent.

In the employment of tuberculin for therapeutic purposes the twofold aspect of tuberculosis must be kept steadily in view. For effective cure both focal and systemic effects of tuberculin are serviceable. If tuberculosis is to be cured locally, wherever the focus be situated, there must be a hastening of the natural tendency towards cicatrization. Such cicatrization is the basis of permanent arrest of the tuberculous process, whatever be the tissue immediately involved. The local stimulation by tuberculin at each tuberculous focus is an important step towards that end. The remarkable effects in this direction are conveniently studied from week to week in connexion with a superficially placed tuberculous lesion under treatment by tuberculin. In the current discussion of tuberculin therapy too little attention seems to have been directed towards this aspect of the subject.

The systemic intoxication occurring in tuberculosis is countered, through the antigenic properties of tuberculin, by the elaboration within the affected system of antibodies or the enrichment of these, if they are to be conceived as already existing.

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Choice of Tuberculin.

The group of fluids collectively termed tuberculins is not very well defined. Remarkable differences of opinion have emerged as to the relative value of different tuberculins. Amidst such diversity it is difficult either to arbitrate or reconcile.

Broadly stated, the conclusion I have formed, after prolonged observation in different directions, is that a tuberculin is likely to be serviceable in proportion to the closeness of its relationship to the tubercle bacillus and the directness of its mode of production. It has seemed to me that the simpler the constitution of the culture medium on which the tubercle bacillus is grown, the more likely will the first of these conditions be fulfilled. On that account the tuberculin of Béraneck has been advocated by me for therapeutic purposes—obtained as it is by a simple process of extraction from a growth of tubercle in a medium free from the addition of artificial peptones.

Whatever be the tuberculin employed, the rationale of its activity in both diagnosis and treatment seems to be that when introduced into the body it acts as an antigen. Tuberculin reactions are based on the interreaction of antigen and antibody in presence of complement.

Since the first introduction of tuberculin in 1890 I have used a considerable variety of products. The net result of those observations has been to reinforce the conclusion based on more theoretic considerations. The tuberculins I use most commonly—both for diagnosis and for treatment (the latter especially in ways to be detailed presently)—are Koch's original tuberculin and Béraneck's tuberculin, in varying excipient and dilution, according to the nature of the case and the purpose in view.

METHOD OF EMPLOYMENT IN DIAGNOSIS.

The familiar division into *subcutaneous*, *cutaneous*, and *percutaneous* methods recalls sufficiently the chief points.

(a) Subcutaneous.

As was natural, Koch's early proposals were on the line of subcutaneous injection, and attention was drawn to effects following such introduction into the tuberculized subject. These results were suitably grouped as (1) *general*—for example, temperature and pulse disturbance; (2) *focal*—that is, changes occurring in the tuberculized area such as I have already described in relation to lupus; and (3) *local*—that is, changes occurring more or less definitely about the point of puncture.

(b) Cutaneous and Percutaneous.

The last-named results—that is, local results—are conspicuous in proportion as the tuberculin in course of introduction comes into contact with the skin structures. Such evident local phenomena naturally became the object of closer observation on the part of numerous workers. Thus emerged the surface reaction associated with the name of von Pirquet, and that associated with the name of Moro.

It is needless to go into details of procedure in respect of these surface tests or the interpretation of results thereby obtained. It is sufficient to recall the fact that the wide application of such methods, which speedily followed von Pirquet's pronouncement, resulted in a fresh orientation of the tuberculous problem—in respect more especially of the frequency of infection and its incidence in childhood.

The observations based on the von Pirquet and allied procedure have proved of epidemiological rather than immediate clinical value. They have revealed that tuberculosis is almost universally distributed throughout civilized communities and that the occurrence of infection takes place for the most part during childhood. A positive reaction to the von Pirquet or to the Moro test indicates that the patient is tuberculized. So long as the reaction remains positive the patient cannot be said to be *detuberculized* in the strict sense, whatever course of treatment may have been followed.

This negative fact has its reassuring aspect in light of the "phenomenon of Koch." The tuberculized animal is not infected afresh by the introduction of living tubercle bacilli. The results following attempts to reinoculate an already tuberculized animal differ widely from those following the primary inoculation and are comparable with the results following a considerable dose of tuberculin when administered to the tuberculous subject.

The further life history of the tuberculized individual is dependent on the degree of his resistance. This varies from time to time by reason of varying physiological conditions

of the individual himself and variations in the conditions of his environment.

Interpretation of Response.

While the local manifestations following the diagnostic test may reveal little beyond the fact that the subject of the test is tuberculized, the systemic, and, in still greater degree, the focal effects are much more definite and detailed. When carefully scrutinized and analysed they are capable of affording exact information—both qualitative and quantitative—as to the presence and distribution of the disease.

A correct interpretation of the evidence thus attainable is dependent on the experience of the observer and the delicacy of the methods employed. When properly carried out, the procedure affords a demonstration regarding the extent and character of the existing tuberculous involvement which is remarkably precise. Few diagnostic procedures in clinical medicine possess greater nicety in respect of the information thereby obtained. Of attendant risks frequently cited by critics of tuberculin I have seen none, when the tests have been competently carried out. The postulate of competence in this case is no less necessary than in the case of many other exact clinical methods.

*METHODS OF EMPLOYMENT IN TREATMENT.**(a) Subcutaneous.*

The therapeutic application of tuberculin has for the most part been carried out by means of subcutaneous injection. The value of the procedure has been assessed variously by different writers. From the statements made in current literature one fact seems to emerge clearly—namely, that the judgements expressed are frequently second-hand, not based on serious observations of the writer himself. Sometimes, even if based on the writer's experience, negative statements are less convincing than they might be by reason of apparent haste and insufficiency in the procedure that has been followed.

The competing claims of different schools of thought as to the rationale of the action of tuberculin have led to confusion and embarrassment. Exaggerated claims for one or other scheme of dosage have been the fruitful cause of not unnatural scepticism on the part of the practical man who, in rule of thumb fashion, may have tried one or other system and found it wanting.

The continuous use—since its introduction—of tuberculin in suitable cases has convinced me that the procedure has specific curative value. The case must be properly selected—in other words, the remedy must be exhibited at the appropriate stage—and the dose must be suitably graduated according to the result obtained from time to time in the given case. These are details which demand judgement based on experience. The interval between successive doses must be similarly gauged, as also the duration of treatment and the desirability, after appropriate resting period, of a further series of injections. Some cases lend themselves to less intense, others to more intense, lines of treatment. A satisfactory result cannot be looked for unless efficient treatment be maintained for a sufficient length of time. Throughout the whole period of treatment watchful care will be taken to detect the slightest expression of super- (hyper-) susceptibility. If this supervene, dosage should commonly be reduced or the exhibition of tuberculin suspended for the time being.

Technique.—The selected tuberculin is suitably diluted with normal saline, with the addition of 1/2 per cent. phenol in the case of weaker solutions for purposes of conservation. With simple aseptic precautions, the injection is conveniently made into the areolar tissue beneath the skin of the back. Care should be taken that the point of the needle pierces the skin completely. In this way the occurrence of local irritation and swelling (phlegmon) about the point of puncture is avoided.

(b) Cutaneous and Percutaneous.

Observation of the effects produced locally in relation to the skin have led to the exhibition of tuberculin cutaneously and percutaneously.

Cutaneous (Sahli's Method).—Thus Sahli was led to substitute for subcutaneous injections a process of multiple cutaneous vaccinations by means of a special needle. More recently he has introduced the practice of intradermic injection, the tuberculin being deliberately introduced into the skin tissue. He has shown that a considerable part of the tuberculin thus injected is absorbed and produces general effects. He believes that the intensity of the intradermic

reaction affords a gauge of the degree of immunity of the patient—that is to say, of his susceptibility to tuberculin—and is at the same time a guide to the determination of the appropriate dose, and so to the avoidance of troublesome reactions, systemic or focal. Treatment is thus directed from time to time by effects open to the eye of the physician. The evidence submitted by that distinguished observer in favour of the therapeutic value of tuberculin and of the efficacy of this method of introduction is convincing.

Percutaneous (Author's Method).—For some twelve years I have been making extensive observations on the effects of the exhibition of tuberculin by *percutaneous* as opposed to subcutaneous method. These observations have led to very interesting results in a number of directions. For the present I limit myself to a brief statement regarding a therapeutic method which the experience of these years has remarkably justified.

One of the first points to emerge in the course of these studies was that, when tuberculin in varying combinations was rubbed firmly into the skin of a tuberculous patient, it was freely absorbed. Moro observed that a local skin eruption followed the inunction of tuberculin mixed with lanolin, and recommended the procedure for diagnostic purposes. Petruschky has testified to the absorption through the unbroken skin of tuberculin exhibited in the form of a liniment which he used in treatment.

Observations on a great variety of subjects satisfied me that the obvious local eruption was in many cases associated with signs of focal reaction, and in much slighter degree with evidence of general reaction. The focal changes may be readily followed in cases of lupus and other superficial manifestations of tuberculosis, as also in glandular tuberculosis. It is likewise traceable in pulmonary and other visceral tuberculosis.

Results and Advantages of Percutaneous Method.

My therapeutic procedure is based on these facts. Tuberculin administered percutaneously by inunction is absorbed and exerts a specific influence on tuberculous processes wherever situated, analogous to those resulting from subcutaneous injection. The curative influence becomes speedily obvious. I have records of its successful use in a great variety of tuberculous manifestations.

Assuming its therapeutic value, the method has numerous advantages over the other methods of exhibition. Something may be said for the absence of pain or discomfort. The procedure is not an operation in the mind of the patient. This has significance in all cases, but especially in children—the dread of the recurring puncture is excluded. The local (skin) reaction, while generally definite enough, causes little if any discomfort. The cutaneous response seems to afford in some degree a gauge of the susceptibility of the patient. In this way dosage may be regulated in respect of amount and frequency.

In simpler cases, with a few definite instructions from the physician, the method may be carried out to some extent by an intelligent nurse or parent, or, it may be, by the patient himself. In pulmonary and other visceral tuberculosis, greater caution is, of course, necessary, and procedure, dosage, etc., will be guided by observation of focal and systemic effects, in addition to those occurring on the skin surface. This necessitates careful surveillance on the part of the medical attendant.

The curative influence on superficial tuberculous foci (cutaneous, glandular, etc.) is commonly apparent within a few weeks and is as a rule continuous. Thus, for example, a crude agglomeration of enlarged glands becomes progressively reduced in size, the indefinite mass is resolved into individual discrete glands, each of which tends to get smaller and smaller until finally reduced to a mere fibrous remnant. These shotty remains may be felt for a long time. The process of recovery by cicatrization may similarly be followed in scrofuloderma and lupus. In the latter the advance of the curative process is, as might be expected, relatively slow. A similar retrogressive influence may commonly be traced in visceral tuberculosis.

Anticipative Detuberculization.

I have alluded to the advantage which the percutaneous method has in the case of children in respect of ease of administration. Its continued use in children leads to much more significant results. When the treatment (instituted, it may be, for an enlarged gland) is maintained for months—that is, long after the gland for which it was begun seems to

have recovered—there may be frequently traced evidence of a more general influence on enlarged lymphatic glands throughout the body, associated with a general improvement of health and condition, which is justly interpreted as an expression of progressive *detuberculization*. Our records include many children in whom such *detuberculization* has been effectually achieved. The remarkable progress from week to week compels attention.

I strongly advise the adoption of this line of treatment on the earliest indication of chronic glandular enlargement in children. In this way the process of tuberculization—so frequent in children—may be successfully countered at a time when the advancing infection is limited to the lymphatic system. By an arrest at that stage the graver incidents due to involvement of viscera are anticipated and prevented. Such a curative and preventive course of treatment may be suitably maintained for months without any disturbance of the child's ordinary life. The exhibition of tuberculin by inunction has the advantage that in most cases it interferes little with the life and occupation of the patient.

Formulae for Percutaneous Administration.

In developing the percutaneous method I have made very prolonged observations with various tuberculins in varying excipients. On the whole I am inclined to recommend the use of either Koch's original tuberculin or Béraneck's tuberculin. Both commonly effect a satisfactory surface response. Either tuberculin is used in varying strength from 10 per cent. up to 50 per cent. As excipient I prefer "eucerin"—that is, a mixture of 5 parts of oxycholesterine from wool fat and 95 parts of paraffin ointment. Eucalyptol in small quantities may be added for conservation of the ointment as in the following formula:

R, Tuberculin (Orig. K.) ...	...	...	10-50 per cent.
Eucalyptol ...	...	...	5 per cent.
Eucerin ...	...	...	ad 100.

Misce bene.

Sig.: Tuberculin ointment, with caution.

For simple cases treatment may conveniently be begun with 25 per cent. tuberculin. In young subjects, or where there is doubt as to the number and extent of foci involved, it is well to commence with 10 per cent. When the response to the lower dosage is slight, the proportion of the tuberculin is increased. In all cases attention must be paid not only to the local response but also to the focal and systemic effects.

The actual amount of tuberculin applied to the skin in a straightforward case (using, say, 25 per cent. dilution) may be estimated as approximately 0.1 c.cm. The ointment containing this is rubbed (worked) into the cleansed skin over an area of 1 to 2 square inches by means of a small sterilized glass rod. As already indicated, the inunction may be suitably repeated—in the absence of contraindication—once weekly. Where the response is slight the applications may be made at shorter intervals.

CONCLUSION.

It is an essential postulate for effective approach to the treatment of tuberculosis that we have in view the significance and potential of tuberculous infection in the life history of the infected individual. The possible resultants from infection are extremely various both in kind and in degree. Granted that a child has become infected, the variety of expression of such tuberculization is illimitable; from slighter manifestations hardly registrable, to one or other of the graver forms which may lead to crippling or death—and this at any point throughout life, short or long as that may be.

In order to meet the width and gravity of the issue, the aim of therapeutic procedure must be radical—that is, directed, not, as unfortunately much of the interference presently countenanced is, towards a mere incident of the disease, but towards the ultimate, essential cause of the spreading infection.

If the validity of any method of *detuberculization* be established it is clear that the earlier in the life history of the infected individual it is adopted, the speedier and completer will be the effect achieved. It is because extensive observations on a great variety of clinical conditions and at different ages have convinced me that the method proposed has effective value, not only in limitation of local effects but in the direction of general *detuberculization*, that I solicit for it your consideration and a *patient trial*. "Lightning" results are precluded by the nature of the process. It behoves us to remember that if it takes long to come, tuberculosis, at the best, takes long to go.