Remarks

ON

TUBERCULIN IN DIAGNOSIS *

BY

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My first attempts, inspired by the then recent publications of Von Pirquet and Wolff-Eisner, to utilize cutaneous tuberculin tests in the diagnosis of tuberculosis were carried out at the Royal Victoria Hospital, Netley, in 1908 and 1909, and the results were reported in the *Journal* of the Royal Army Medical Corps in June, 1909. The method adopted was a modification of the Von Pirquet technique, and the test was applied to known cases of tuberculosis as well as to suspected cases and clinically non-tuberculous persons. The non-tuberculous persons proved to be quite as sensitive to tuberculin as the known cases. The conclusion drawn was as follows:

"The practical point at issue in diagnosis is the presence or absence of active disease. 'Surface vaccination' is quite unreliable as a means of answering this question."

Later, with the introduction of the Mantoux intradermal technique, I decided to try out this method as one perhaps better calculated to differentiate between stages of tuberculous infection, and in 1928 and 1929 I applied the intradermal method both in healthy adults and in known cases of tuberculosis, comparing the results both as to end-point of tuberculin dilution causing reaction and actual size of reaction area. In these tests, reported in the *British Medical Journal* of February 23rd, 1929, the interesting fact came to light that the reactions tended to be, on the whole, more definite and the sensitivity more marked in non-tuberculous adults than in the tuberculous. A further comparison was made, in conjunction with Dr. S. B. H. Walker, during 1929 and 1930, and the intradermal reactions to serial dilutions of tuberculin were studied on standard lines in 100 cases of pulmonary tuberculosis and in 100 non-tuberculous persons under treatment in the Cardiff Mental Hospital, the opportunity to examine the latter being afforded through the kindness of Drs. Goodall and McCowan, the medical directors of the institution during the period. The findings were described in *Tubercle* in July, 1931.

All these investigations tended to the same conclusion, which has been amply confirmed by numerous workers, that, as a test for "active clinical tuberculous disease," the cutaneous and intradermal tuberculin tests are too delicate; and that "positive" reactions elicited by these methods in adults cannot be interpreted to mean "active" tuberculous disease. While this is true, however, the problem of the value of these cutaneous techniques in diagnosis is not quite so simple as it appeared to be when I attempted to exploit tuberculin in the diagnosis of tuberculosis in soldiers in 1909.

POSITIVE REACTION IN EARLY LIFE

It has been proved by many reliable workers that the cutaneous tuberculin sensitivity so constantly observed in healthy adults in "civilized" and "industrialized" communities is, as a rule, absent in infants, and that, while it tends to increase with each year of life, it is still very low in the earlier age groups except in the homes of "open" cases of tuberculosis, where the contacts tend to give a high percentage of positive reactions even in infants and young children. This observation raises the question of the value of a "positive" in early life, and

here the answer is not so simple as in relation to adults. My own view, based, however, on an integration of the observations of others, is that a markedly positive reaction either to the Von Pirquet or the Mantoux tuberculin test has a serious significance during the first year of life. There can, I think, be no doubt that sensitivity to tuberculin proves the existence of tuberculous infection; and, while we have reason to know that infection is, in adults, not merely consistent with health, but usually present, we know also that very early infection, acquired in any considerable concentration before the tissues have had time to accommodate themselves to their bacterial environment, is very likely to lead on to severe and often fatal disease.

A recent paper by Blacklock (1932) indicates the extremely high risk of fatal tuberculosis in the case of infants heavily enough infected to harbour tuberculous lesions visible to the pathologist; and the Registrar-General's statistics show, year after year, that the death rate from this disease is exceedingly high during the earlier life periods. We should, therefore, view with grave anxiety the very early appearance of a "positive" tuberculin response in an infant or in a child in the first year or two of life, since a "positive" implies infection, and infection at this stage usually, though not always, implies the near approach of active disease.

A POSITIVE IN ADULTS

I have expressed the opinion several times already that a "positive" in an adult brought up in an "industrialized" or "civilized" community has little or no diagnostic significance. This view, however, does not extend to "positive" tuberculin responses in adults whose early years have been passed in communities of a "primitive" type and, perhaps we ought to add, "whose more recent ancestors have resided in communities with a primitive type of culture." These adults, comparable perhaps in some respects to the earlier age groups in Europe and America, appear to develop tuberculo-allergy of a much more active variety than is common in adults in communities of an older civilization. Coming from districts which, through the industrial developments of recent years, have lately become endemic centres of tuberculous infection, African natives may possess an allergy potential far higher than what we encounter in this country, yet they are without the relatively high power of tuberculo-resistance common in adult Europeans. In such natives, a well-marked "positive" tuberculin reaction has a much more formidable significance than elsewhere.

In Report No. XXX (vol. v) of the South African Institute for Medical Research (1932) will be found an account of tuberculin tests on South African native mine recruits on arrival for work at Johannesburg, together with the results of a "follow up" of the tested groups through their subsequent periods of work in the gold mines. On page 97 of the Report the results of this inquiry are set forth, and show that the incidence of tuberculosis was about five times as high among those who had given a "positive plus" reaction than in those found negative to the dilutions used, 1 in 5,000 and over; while the mildly positive reactors were intermediate. The actual figures of incidence, based on 93,000 natives tested with tuberculin by the intradermal method, were as follows: in those recorded as "positive plus," 1,547 per 100,000; in those recorded as merely "positive," 683 per 100,000; and in the "negative," 347 per 100,000. These figures can only mean that the "positive plus" reactions were associated with active, though clinically unrecognizable, tuberculous lesions which tended to become generalized during the stress of a new and exacting occupation. This does not mean that a "positive plus" reaction was diagnostic, even in these highly susceptible

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persons, of clinically active tuberculosis. It merely means that, out of 3,879 persons giving these marked reactions, sixty developed clinically active tuberculosis during the following year or so of work on the mines. The remaining 3,819 got safely through their mine contracts without being recognized as tuberculous, in spite of the repeated weighings and examinations which are in operation to detect and remove recognizable cases.

Has a strongly positive reaction any similar significance in this country? I have already expressed the opinion that in infants and young children it has this same kind of significance; that it must be taken to mean the presence of an active focus which, in early childhood, is always accompanied by danger of generalization. In European adults, however, my own observations, as far as they go, do not suggest any such relation. Out of 100 mental cases tested with graded dilutions of tuberculin in 1929 and 1930, eight have since developed tuberculosis. Of these, one had reacted up to a dilution of 1 in 100,000, two to 1 in 10,000, four to 1 in 1,000, and one had been negative even to 1 in 500, the strongest concentration used.

Here the incidence was definitely greater among those who had been proved to possess low or negative tuberculin sensitivity; but the figures are too small to be of much importance. A far larger number have since been tested elsewhere by one of my co-workers, and it is hoped that a follow-up of their tuberculosis incidence will throw further light on the point at issue.

VALUE OF A "NEGATIVE" IN EXCLUDING TUBERCULOSIS

So much for the diagnostic value of a "positive" reaction to a cutaneous tuberculin test. But there arises also the question of the diagnostic value of a "negative" in excluding tuberculosis. Recent work by Dr. D'Arcy Hart has, in my opinion, gone far to prove that the diagnostic value of a "negative" may be very great, especially in childhood. I propose, however, to leave this question, so far as it concerns childhood, to Dr. D'Arcy Hart himself, who is taking part in this discussion. All I wish to say is that, in attaching any weight to the value of a "negative" in excluding the presence of tuberculous infection, the negative must be made as conclusive as possible; it is quite insufficient to stop short at a Von Pirquet test, even with full-strength tuberculin, or at a Mantoux test with 1 in 1,000 tuberculin. Many persons negative to these concentrations are, in reality, positive if tested intradermally with 1 in 100 or 1 in 10.

There is another aspect of "negative" findings, however, which deserves notice, especially in regard to adults—namely, the loss of tuberculin sensitivity which goes with advanced tuberculosis. This is hardly likely to introduce practical difficulties in diagnosis, as the nature of the disease is usually beyond doubt at the advanced stages in which the test may become negative. But if the word "diagnosis" be extended to include prognosis, then cutaneous and intracutaneous tuberculin tests may be said to have some significance, though only in the terminal stages. It does not appear that tuberculin sensitivity is ever absolutely lost until the very end, but there is a gradual fading of sensitivity, affecting both the intensity of the reaction to strong concentrations and the end-point of reaction to graded dilutions, as the resistance of the patient wears out under the stress of progressive disease. This fading of tuberculin sensitivity should, I think, be definitely distinguished from the desensitization which may arise in the course of a successfully resisted infection or through tuberculin therapy; a desensitization which is, in my opinion, to be associated rather with the acquisition of immunity than with loss of resistance.

I recently tested by the Mantoux technique six patients who had been under treatment for considerable periods

by my friend Dr. Gilchrist, all of whom had arrived at a toleration of large doses of bacillary emulsion given subcutaneously. In one, the Mantoux test was completely negative in every dilution down to 1 in 500, the strongest concentration used. Four were negative to 1 in 10,000 but weakly positive to 1 in 1,000, that is to say, less sensitive than is commonly the case in tuberculous persons of their type. One, however, although he had received a subcutaneous dose of 0.7 c.mm. of bacillary emulsion a week earlier without reaction, experienced a sharp constitutional as well as a marked local reaction to about 1.1 c.mm. of old tuberculin intracutaneously. Apart from this anomalous case which was apparently tested just at a moment of raised tuberculin sensitivity, treatment with tuberculin had definitely lowered the allergic potential of these patients, yet all of them were doing well and in no sense "terminal" cases.

F. Allen, testing native mine workers at the Witbank Coal Mines in the Transvaal, has observed that "old mine workers," tested for a second time after some years of work, tend to be definitely less tuberculin-sensitive than at their first tuberculin test on arrival. Here it would seem that the repeated exposure to reinfection incident to life in the mines and in the compounds has had the effect, not of raising, but of lowering the allergic state, though such men appear to be, on the whole, more resistant than new arrivals. One lesson appears to stand out clearly from all this South African work, with which I have had the privilege of being closely associated—namely, that while a marked positive Mantoux reaction is by no means diagnostic of clinically recognizable tuberculosis, it is to be regarded as the sign of an active, though "larval," lesion from which infection may, under unfavourable circumstances, generalize throughout the organism. Another lesson, of greater importance from the point of view of the pathogenesis of tuberculosis, is that marked tuberculo-allergy may exist without any corresponding acquisition of tuberculo-immunity. Immunity and allergy may be due to the same cause, infection, but they are not in any sense identical or even, necessarily, coexistent.

Cutaneous tuberculin tests, then, whether of the Von Pirquet or the Mantoux type, or of the type of Stichreaktion of Epstein, are reliable tests for allergy, and, by implication, for infection; but they are not of much value as tests for clinically active tuberculosis in adults nor as tests for the existence of acquired immunity.

KOCH'S SUBCUTANEOUS TEST

There remains, however, the subcutaneous tuberculin test as originally devised by Robert Koch. This test is definitely inapplicable to persons with pyrexia, a fact which greatly limits its utility in differential diagnosis; nor is it safe as a test in persons likely to be harbouring lesions of the easily activated type. In such persons, focal and general reactions are things to avoid, and there is no justification for exposing them to the risks incidental to activation of their lesions for the sake of an added point in the search for a diagnosis. There is one type of case, however, in which the risks are minimal and the advantages to the patient sometimes sufficiently important to justify the subcutaneous test. I refer to the chronic, productive, inert, sputum-negative cases which often come to our notice as ex-soldiers seeking to establish a claim to continuance of pension. These chronic and resistant cases stand the subcutaneous test well as a rule, and the risk is not serious. Koch's opinion was that a positive reaction to a dose of 10 milligrams might be regarded as diagnostic while there was no chance of a positive reaction of the general or pyrexial kind in a healthy person until the limit of 25 milligrams was reached. These quantities are, perhaps, expressed too

exactly, and, in the light of modern experience, most of us will hesitate to draw the line sharply between tuberculous infection of a degree consistent with health and tuberculous infection just severe enough to constitute disease. But, of all the tuberculin tests, the subcutaneous method of Koch remains the most valuable in diagnosis. It depends upon general and focal reactions which are, in themselves, evidence of active disease, and, when elicited by tuberculin, may be accepted as diagnostic of clinically active tuberculosis. The only thing against it is its risk, and, in my opinion, there is no excuse for taking any avoidable risk in the attempt to establish a diagnosis.

I have indicated one kind of case in which Koch's original test may be applied with safety, and there are doubtless fairly numerous cases in which the subcutaneous test may be used without ill results by experienced physicians. Apart from these, it appears to me that the Mantoux test, applied with due skill and interpreted with discretion, is calculated to give valuable information, whether positive or negative, in the earlier years of life, and that, apart from the diagnosis of clinically active tuberculosis, this test is invaluable as a means for determining the distribution of infection in communities in which epidemiological investigations are contemplated. On the whole, for purposes of diagnosis in man, the tuberculin test, in all its varieties, is definitely inferior to the combined radiological, physical, and laboratory examinations which have come to be the routine methods.

THE POSITION TO-DAY OF TUBERCULIN IN TREATMENT*

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The introduction of tuberculin was one of the great tragedies of medical research. Premature in its birth, damaged by the excessive zeal of its earliest exponents, or foster-parents—for Koch himself was cautious in his original claims—it has received the fate of the cripple, at times excessive care, at others neglect. Forty-two years have elapsed since its first introduction, and it remains a baffling and elusive enigma, in spite of an almost incredible amount of investigation, scientific and otherwise. To-day some authorities claim that it is not specific in its effects, and that it should be entirely discarded in treatment. On the other hand, there are enthusiasts who claim a specific and curative action for it and recommend its use widely, while there are others who have used it continuously for many years and are convinced that it has a definite though limited value. The time would therefore seem ripe for a critical and practical review of its effects in treatment. If this discussion could serve to clarify the position, especially to determine which of the three attitudes I have just mentioned is the correct one, then a notable success will have been achieved.

I should like to put forward the following points for discussion:

1. Is tuberculin useful in treatment?
2. If so, what are the indications and contraindications for its use?
3. What forms is it best to employ?
4. Dosage—spacing and limit of doses.
5. How should it be given?
6. How does it act?

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TUBERCULIN IN TREATMENT

It may be worth while to consider briefly certain opinions concerning tuberculin.

(a) It is generally accepted that it is completely innocuous to a healthy non-tuberculous person, even in large doses, while in those who have been infected it produces the well-known tuberculin reaction with its three effects—local, focal, and systemic—in greater or less degree, depending on the form employed and the method of administration. It has been supposed until recently that this reaction is specific, and that it is an allergic phenomenon. Both of these contentions have now been called in question, since other protein substances are said to produce a positive reaction in tuberculous patients, and the skin effects have been stated to be due to a general non-specific hypersensitiveness to toxic substances in this disease.

(b) It is significant that its routine use has been greatly restricted in many sanatoriums, and entirely discarded in others; it receives scant mention in most textbooks of medicine and in special manuals on diseases of the chest. Fishberg, in the latest edition of his well-known textbook, joins the ranks of those who advise against its use; he does so on the grounds that it is not certain that its action is specific, that it is difficult to estimate accurate dosage, especially of different preparations, and that it is altogether wanting in therapeutic effects when given in infinitesimally small doses, and may be decidedly harmful in large amounts.

(c) I have always been much impressed by the fact that, in the so-called surgical localizations of the disease—that is, in glands, bones, joints, and the ocular and genito-urinary systems—tuberculin has a considerable vogue, and that, in these conditions, it is the three well-known preparations of Koch which are chiefly employed, whereas in pulmonary tuberculosis the varieties and modifications of tuberculin which have been advocated are remarkably numerous, extending to more than a hundred. This has always suggested to me that there must be some fundamental difference between medical and surgical tuberculosis, and it is evident that the effects of tuberculin have been disappointing in the strictly medical cases, notably in pulmonary tuberculosis. The fact that so many attempts have been made to modify tuberculin for medical as opposed to surgical use in treatment suggests that it has been found wanting in some respects. On the other hand, I cannot but feel that if it were entirely useless it would have been discarded long ago, and would not be the subject of a serious discussion forty-two years after its introduction. My own experience would lead me to believe that tuberculin has definite therapeutic uses, and that these are considerable in the localized or surgical manifestations, and strictly limited in the pulmonary forms of the disease.

INDICATIONS AND CONTRAINDICATIONS FOR ITS USE

In cases of pulmonary tuberculosis I have only found tuberculin useful in those patients in whom the disease has progressed satisfactorily towards arrest, but who are left with a small amount of expectoration containing tubercle bacilli. A short course of tuberculin may serve to get rid of the bacilli, to dry up the sputum, or to do both. Such effects alone, if established, would justify its use, since the patients are often enabled to return to their families and to their work without fear and without risk. Many employers will not take back a patient of whom it cannot be certified that the sputum is tubercle-free. Tuberculin has been recommended in chronic cases slow to settle down, of the type described by Inman as "resting afebrile, ambulant febrile." I am less sure of its value in such cases, and I think its effects