Tuberculin sensitivity in tuberculosis

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Summary

It is generally accepted that patients suffering from Mycobacterium tuberculosis infections show positive tuberculin skin tests, with certain rare exceptions. Recognized causes of these exceptions include extreme illness, whether due to extensive tuberculosis or to other severe disease, and certain viral infections, notably measles. It is not so generally recognized that a few patients with pulmonary tuberculosis, generally of rather indolent type, who are not acutely ill, persistently fail to react to tuberculin; and that the range of tuberculin sensitivity observed in patients with the more usual forms of tuberculosis is very wide.

The effect of cortisone in diminishing the size of tuberculin reactions in patients with pulmonary tuberculosis is directly related to the degree of sensitivity; reactions produced by small doses of tuberculin in patients with high sensitivity are greatly diminished or inhibited, while those produced by 100 T.U. in patients with low sensitivity are not significantly altered. Patients with tuberculosis can be desensitized to tuberculin by increasing injections of tuberculin under chemotherapy cover. In patients who have been so desensitized, the addition of cortisone to tuberculin in an intradermal test produces positive reactions in 70%. Among patients with sarcoidosis giving no reaction to 100 T.U., about half react when cortisone is added.

These observations show that in patients with sarcoidosis, a negative tuberculin test cannot be taken to exclude M. tuberculosis infection.

For the purpose of this paper, I shall define 'tuberculin sensitivity' as the cell-mediated Type IV hypersensitivity demonstrated by delayed skin-test reactions elicited by tuberculin in a Mantoux or equivalent test.

The definition of 'tuberculosis' requires some discussion. Originally, it was in morbid-anatomical terms; the ultimate criterion by which it could be decided that a case fell within this category was whether or no the pathologist found tubercles. Koch's demonstration of the association between acid-fast bacilli and this anatomical change led to the possibility of aetiological definition of tuberculosis as the disease caused by Koch's bacillus. All seemed straightforward until it became evident that a number of mycobacteria other than that now identified as M. tuberculosis can cause disease characterized anatomically by tubercles indistinguishable from those of M. tuberculosis infections. As I have pointed out elsewhere (Scadding, 1967a), it is a matter of convenience whether we continue to use the word 'tuberculosis' to denote a disease characterized by the formation of tubercles, adding aetiological terms to it as required, so that when we refer to tuberculosis we should whenever possible specify the causative mycobacterium; or define tuberculosis as the disease caused by one of a limited range of mycobacteria, adopting some other name for disease caused by other mycobacteria. The consistent adoption of the latter usage would require morbid anatomists to deny themselves the descriptive use of the word 'tuberculosis'; they would have to refer to the changes commonly found in mycobacterial infections by some such term as 'epithelioid cell granuloma'.

Whichever of these two usages is adopted, my intention is clearly indicated when I say that I shall be talking only about tuberculosis due to M. tuberculosis, and will not discuss the broader issue of disease caused by other mycobacteria.

It is generally accepted that a negative reaction to a properly performed tuberculin test is strong evidence against a diagnosis of tuberculosis, though certain exceptions to this rule are recognized (Rich, 1951).

These include patients with extensive, long-standing pulmonary tuberculosis who are critically ill and cachectic. Lester & Atwell (1958) found among 1000 patients with pulmonary tuberculosis four who did not react to 250 T.U.; all had 'overwhelming infection', and when their condition improved, the expected positive reactions were obtained. Howard et al. (1970) have recently reported that among nearly 10,000 patients with active pulmonary tuberculosis, intradermal tests with 10 mg O.T. were negative in 0.55%; these were described as critically ill with extensive disease, and it was observed that they tended to have a high leucocyte count with at least 90% of neutrophils.

Patients with tuberculous meningitis with or without miliary tuberculosis may fail to react in the acute stage of the disease. Illingworth (1956) reported the results of tuberculin tests in 184 children with tuberculous meningitis; from his figures, it can be deduced that about 14% were non-reactive to a Mantoux test with 1:100 O.T. It is less widely recognized that patients with acute tuberculous pleural effusion may fail to react to tuberculin during the febrile stage, but show strong reactions later:
I have observed this phenomenon in several patients.

Tuberculin sensitivity may be depressed by several unspecific factors. These include viral infections, particularly measles (Starr & Berkovich, 1964); Hodgkin's disease, even in its early stages (Steiner, 1934; Hoyle, Dawson & Mather, 1954; Lamb et al., 1962); and old age (Johnson, Ritchie & Murray, 1963). Brody, Overfield & Hames (1964) found that up to the twenty-first day after vaccination against measles, poliomyelitis or yellow fever there was slight depression of tuberculin sensitivity, but with a wide scatter of results.

Depression of delayed hypersensitivity reactions is observed in sarcoidosis; but it should not be assumed that the factors concerned in its causation are the same as those depressing tuberculin sensitivity in other diseases (Scadding, 1967b). Certainly, there are important differences between the depression of tuberculin sensitivity in sarcoidosis and in Hodgkin's disease.

Although these exceptions to the rule that patients with M. tuberculosis infections react to tuberculin are well known, it seems to be not so generally recognized that the range of tuberculin sensitivity in patients with the more usual forms of tuberculosis is wide; and that at one end of this range there are a few patients, not acutely ill and without intercurrent disease, who in spite of proved tuberculosis have persistently negative skin reactions to tuberculin (Mascher, 1951; Scadding, 1956; Kent & Schwarz, 1967).

Such patients present variable clinical features. In my experience they can be ranged between a group who have localized lung lesions with no unusual feature except the negative tuberculin test and a group who have widespread pulmonary infiltration with an indolent course, approximating in clinical and radiological features to sarcoidosis.

Most of the cases reported by Mascher (1951) and by Kent & Schwarz (1967) fell into the first category. I will quote one of my own cases to illustrate this group (Scadding, 1956; case 2):

**Case 1.** A woman aged 34 complained of tiredness and loss of weight for 4 months. The chest radiograph showed patchy shadowing in the middle zone of the right lung. Intradermal tests with tuberculin up to 1:10 O.T. proved negative. Nevertheless, of eight sputum specimens, one showed acid-fast bacilli on microscopy, and one on culture produced tubercle bacilli of normal virulence for the guinea-pig. Treatment with antituberculosis drugs produced considerable clearing of the infiltration. Repeated tuberculin tests remained negative. Eleven years later, there was evidence of some fibrosis and calcification at the site of the infiltration, and the skin still failed to react to 1:100 O.T.

I will now describe briefly two cases in which a widespread infiltration in the lungs was associated with a negative tuberculin test, so that the clinical and radiological picture suggested sarcoidosis; but nevertheless, tubercle bacilli were eventually found, and chemotherapy was followed by the expected response.

**Case 2.** (case 1 of Scadding, 1956). A man aged 26 developed an acute right-sided pleural effusion and chronic diarrhoea. Tubercle bacilli were found in both sputum and stools. He was treated for 3 years in a sanatorium. Five years later, the diarrhoea recurred, he lost weight, and generalized mottled shadowing appeared in the lungs, the left being very much more affected than the right. Mantoux tests with 1:100 O.T. (100 T.U.) were persistently negative. No tubercle bacilli were found either in stools or in sputum. Treatment with streptomycin and PAS was followed by great improvement both symptomatically and radiologically. Two years later, the skin reacted to 1 T.U. with 10 mm of induration and some vesicles. Followed for a further 10 years, he remained well, with only slight residual fibrotic changes in the left lung.

**Case 3.** A routine chest radiograph of a woman aged 36 showed widespread patchy mottling. A Mantoux test with 100 T.U. was negative. Eight months later, she was feeling tired and had developed a slightly productive cough; and the radiographic shadows had become denser. At this stage, the sputum for the first time was found to contain tubercle bacilli, sensitive to streptomycin, PAS and isoniazid; and the skin reacted to 10 T.U. Anti-tuberculosis chemotherapy resulted in considerable resolution, and 6 years later she remained well, with evidence of only slight residual scarring in the chest radiograph.

In these two cases, the clinical and radiological features at first resembled those of sarcoidosis, and the skin failed to react to tuberculin; eventually tubercle bacilli were found, and there was a response to antituberculosis drugs. Unlike Case 1, in which the skin remained insensitive to tuberculin, both later developed tuberculin sensitivity.

I have drawn attention several times (Scadding, 1960, 1967b, 1971) to the tenuous character of the demarcations between cases of this sort, cases which conform to the clinical picture of sarcoidosis although tubercle bacilli are isolated from them once or on a few occasions, cases in which the illness seems to have both 'sarcoid' and 'caseating' phases, and cases which conform throughout to a 'sarcoid' picture. The investigations of Kent et al. (1970) are relevant to this point. They carried out what they rightly called an 'aggressive' search for evidence of mycobacterial infection in thirty cases with clinical and radiological features of sarcoidosis, supported by the finding of non-caseating granulomas in
biopsies. Tubercle bacilli were isolated in sixteen; four of these had positive Kveim tests. Three others showed acid-fast bacilli microscopically in biopsy material. Of these nineteen patients, only six reacted to 5 T.U.; some of the non-reactors failed to react to 250 T.U. in intradermal tuberculin tests.

The effect of cortisone on tuberculin sensitivity

In 1952, it was demonstrated that about 50% of patients with sarcoidosis who failed to react to an intradermal test with 100 T.U. showed reactions to the same dose of tuberculin, either when they were given cortisone systemically, or when 1.25 mg of cortisone acetate was mixed with the tuberculin (Pyke & Scadding, 1952). This led to a study of the effect of cortisone mixed with tuberculin on skin reactions to tuberculin not only in sarcoidosis but also in patients with bacteriologically proved pulmonary tuberculosis (Citron & Scadding, 1957).

The first step in investigating these patients was to determine by graded tests the dose of tuberculin that would cause an area of induration in the range 5–20 mm in diameter. Among sixty-six patients with active pulmonary tuberculosis, representing the general run of such cases, twenty reacted in this way to 1 T.U., nine to 2 T.U., nine to 5 T.U., fifty to 10 T.U. and eight to 100 T.U. Thus there was a very wide range of tuberculin sensitivity in these patients with active pulmonary tuberculosis; 15% of them reacted only to 100 T.U., and among these there were three with reactions of only 4–5 mm in diameter.

The effect of cortisone on these reactions varied inversely to the size of tuberculin dose required to produce a reaction of the required size; that is to say, it varied directly with the degree of tuberculin sensitivity of the patient. Reactions produced by small doses of tuberculin in patients of high sensitivity were inhibited or greatly reduced; those produced by 100 T.U. in patients of low sensitivity were, on the average, unchanged; and those produced by intermediate dosages were reduced, the magnitude of the reductions being ranged smoothly between these two extremes.

At the time when these observations were made, the possibility of reducing the tuberculin sensitivity of patients with pulmonary tuberculosis was being studied. It is of interest, in the present context, that it proved possible, under cover of anti-tuberculosis drugs, to desensitize a high proportion of these patients, all initially highly sensitive to tuberculin, by intramuscular injections of increasing doses of tuberculin, until their skin failed to react to 100 T.U. Eleven of sixteen patients who had been desensitized in this way gave reactions ranging from 4 to 14 mm in diameter, when tested with tuberculin plus cortisone.

Among forty-nine patients with sarcoidosis, twenty-eight failed to react to 100 T.U.; fourteen gave reactions ranging from 4 to 12 mm in diameter to tuberculin plus cortisone. Those sarcoidosis patients who reacted to tuberculin reacted to tests with tuberculin plus cortisone in a similar manner to patients with pulmonary tuberculosis of similar tuberculin sensitivity.

These observations are relevant to the problem of the relationship between mycobacterial infection and sarcoidosis:

(i) The very wide range of tuberculin sensitivity in pulmonary tuberculosis indicates that in sarcoidosis the negative tuberculin test which is seen in many cases does not rule out an active role for mycobacteria.

(ii) In tests with tuberculin plus cortisone, tuberculin-negative sarcoidosis patients behave more like pulmonary tuberculosis patients who have been desensitized to tuberculin than any other group. In particular, it should be noted that Fairley & Matthias (1960) found that in sixty-two tuberculin-negative Hodgkin’s disease patients only 8% showed a reaction to tuberculin plus cortisone.

(iii) Citron & Scadding (1957) surveyed their tuberculin-negative sarcoidosis patients who were tested with tuberculin plus cortisone for the presence of calciﬁed residues which in inhabitants of Great Britain can reasonably be attributed to primary tuberculosis, and for a history of the isolation of M. tuberculosis in the past. These evidences of old M. tuberculosis infection were found in ﬁve of fourteen who reacted to tuberculin plus cortisone, and in seven of fourteen who did not react. If the effect of cortisone in these cases was to make manifest a very low residual tuberculin sensitivity, as seemed to be the case in the desensitized pulmonary tuberculosis cases, and if sarcoidosis was due to some unidentified agent, infection with which depressed tuberculin sensitivity, it would be expected that the addition of cortisone to tuberculin in a skin test would demonstrate residual tuberculin sensitivity in a much higher proportion of those who had evidence of old mycobacterial infection than of those who had not. The fact that such evidence was found in as many of the non-reactors to tuberculin plus cortisone as in the reactors is thus evidence against the hypothesis that a specific infective agent causes sarcoidosis and depresses tuberculin sensitivity.

References


Fairley, G.H. & Matthias, J.Q. (1960) Cortisone and skin


