THE SIGNIFICANCE OF PROTEIN AND NON-PROTEIN TUBERCULIN SENSITIVITY AND INSENSITIVITY IN SARCOIDOSIS

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ONE of the more perplexing features of sarcoidosis is the abnormally high rate of insensitivity to tuberculin injected intradermally. In any large urban community in England very few adults between ages 30 and 65 will be found not reacting to a dose of 100 units (0.002 mg.) of tuberculin; fewer still will be found in a comparable age-group of ambulant cases of tuberculosis, yet half or more of a group of cases of active sarcoidosis may be found to be insensitive to 100 units of Purified Protein Derivative (PPD) tuberculin.

The significance of this 'anergic' state in patients showing lesions with sarcoid histology, is fundamental to understanding the immunological abnormality in this condition.

Implications of Cutaneous Tuberculin Reactivity

It is usually assumed that the protein element in the tubercle bacillus is the agent responsible for stimulating cutaneous tuberculin reactions. Hartston and Muggleton (1962) have shown that other and non-protein fractions are more closely and specifically associated with tuberculin sensitivity. They demonstrated reactivity in 'normal' and tuberculous subjects, to a lipopolysaccharide fraction of human-type tubercle bacillus and that following BCG vaccination, there developed a spontaneous local skin reaction at the site of the previous prevaccinal non-reacting injections. Similar studies have been made in cases of sarcoidosis. The findings are reported here and their significance is discussed.

Tuberculin allergy depends for its pathogenesis on an immunological reaction taking place in the affected tissues between the provocative antigen and antibody. When mycobacteria such as tubercle bacilli or BCG invade the body, their chemical constituents are incorporated into the protoplasm of capillary perithelial cells, connective tissue cells, epithelial cells, reticulo-endothelial cells and lymphocytes which thereby become sensitized to the incorporated chemical

substances, provoke antibodies to them and manifest hypersensitivity reactions when they recognize this alien bacterial antigen reintroduced. Once the chemical union has taken place and been 'registered' in the cells, it is no longer essential for living bacilli to subsist in the body to maintain tuberculin hypersensitivity. By this mechanism the affected tissue cells accentuate their capacity to hydrolyze bacterial walls, meet their cytoplasm and generate the factors which create and transfer tuberculin allergy. This response is developed to its highest degree under the influence of mycobacterial lipopolysaccharides.

When the bacterial wall is readily breached hypersensitivity reactions rapidly follow, these may be as damaging to the host as to the bacterium, as in caseating tuberculosis. When the invading bacterial wall for any reason is unaffected or only very slowly disintegrated, then a cellular granulomatous reaction is more likely to ensue as happens in sarcoidosis and leprosy.

Tuberculin Insensitivity

These responses may be inhibited by desensitizing with repeated subcutaneous doses of tuberculin or by some other functional modification of the antibody-forming mechanism such as interference with the normal activity of lymphocytes. Although tuberculin desensitization abolishes the local (skin) responses to tuberculin it does not impair immunity already acquired.

Failure to react to tuberculin occurs in those who have never met adequate amounts of mycobacteria to stimulate the response, or in infected people in whom the immunity mechanism has failed.

The vascular constituent of the tuberculin reaction but not the cellular infiltrate can be inhibited by direct suggestion under hypnosis (Black, Humphrey and Niven, 1963). Advanced active tuberculosis and other conditions in which suprarenal deficiency occurs may be accompanied by suppression of tuberculin sensitivity.

In sarcoidosis, absence of cutaneous response to tuberculin is more likely to occur when the condition is active, that is, when non-caseating epithelioid-cell follicles can be demonstrated in biopsies of tissue and sarcoid deposits are manifest. This anergic state may persist (Scadding, 1960) even when cases of sarcoidosis develop pulmonary tuberculosis with bacilli in the sputum.

Patients whose tuberculin-negative sarcoidosis follows an episode of typical tuberculosis may also have been anergic during their tuberculous activity.

The frequency of the non-reactor state in sarcoidosis is clearly an important pathological condition which poses certain questions. Is it better for the body in sarcoidosis to be able to respond to tuberculin or better that it should maintain an immunological tolerance to chemical fractions of mycobacteria? Which part of the mechanism of adult tuberculin sensitivity is at fault? Is it a failure of the tissue cells at the test site to recognize or to respond to the tuberculin antigen? Is there no antibody circulating or has the antibody produced been diverted from the skin and got fixed elsewhere? Are the lymphocyte cells abnormal?

Sarcoidosis patients not reacting to tuberculin can in most cases be 'converted' by adequate BCG vaccine given by multipuncture or by intradermal injection. In the author's series of 62 cases (34 'active' and 28 'quiescent' or old) 21 were non-reactors to tuberculin both protein and non-protein. Seventeen of these were given BCG vaccine and among these, 14 thereafter reacted to PPD but not to non-protein lipopolysaccharide. The 41 tuberculin-sensitive sarcoidosis cases reacted to both PPD and lipopolysaccharide. The significance of the sarcoid cases' failure to react to lipopolysaccharide fraction of human type *M. tuberculosis* after BCG vaccination is surprising and difficult to explain. It is possible that in these circumstances the sarcoid patient can make antibody to the protein fraction of mycobacteria but not to the lipid and polysaccharide.

Discussion

A group of five patients (not sarcoid) with active pulmonary tuberculosis, whose protein tuberculin sensitivity had been abolished by desensitizing with a prolonged course of subcutaneous tubercle bacillus extracts continued to react to lipopolysaccharide. Sarcoidosis patients who do not

react to protein or non-protein tuberculins will become reactors to both after a subcutaneous 'donation' of leukocytes from a known normal tuberculin reactor.

It seems therefore that the antibody-forming mechanism can be stirred to activity, but the readiness of 'indigenous' lymphocytes to change to epithelioid cells and be diverted from normal activity makes them suspect as the weak link in the sarcoid's chain of immunological rectitude.

Converting the non-reacting sarcoid patient to tuberculin hypersensitivity appeared to have no beneficial effect on the sarcoidosis lesions except in one patient who developed bouts of erythema nodosum on both legs soon after BCG vaccination. During the healing of one crop of these red nodes a long-standing sarcoid skin lesion on one calf quickly disappeared and has not returned, although long-standing lung lesions have persisted.

One patient with widespread sarcoid nodules on the skin of his face and in both axillæ and who reacted to protein and non-protein tuberculin, was desensitized with subcutaneous injections of PPD and lipopolysaccharide. After seven weeks of this he failed to react to 750 units of intradermal PPD and to 50 micrograms of lipopolysaccharide and the facial and axillary lesions rapidly faded and shrank away. In this case at all events, there is no doubt of the benefits of not reacting to tuberculin.

There is another hint of advantage to the sarcoid patient in a reduced tuberculin sensitivity. Women with sarcoidosis who become pregnant, tend to improve during the late months and early puerperium and to relapse afterwards. It is a common finding too, that tuberculin-reacting normal women develop much weaker tuberculin sensitivity during pregnancy.

Summary

The factors influencing tuberculin sensitivity and insensitivity are described. Their condition in sarcoidosis is discussed. It is suggested that the sarcoid patient who reacts to tuberculin might benefit from desensitizing and conversion to a non-reactor state.

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