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Reactions in Leprosy*

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A system of classification of lepra reactions into four types, namely downgrading reaction, reversal reaction, exacerbation nodules, and erythema nodosum leprosum, is put forward, and each described in regard to origin, histological nature, and immunological and clinical characteristics. Though the four types differ, they cannot in practice always be sharply defined, as two of them may alternate or two types may even occasionally co-exist.

A "reaction" in leprosy is usually defined as an acute episode occurring in the otherwise chronic course of the infection, and which appears to have an allergic basis. To this I would add that the histological disturbance which occurs during reactions is not associated with either the activity or the regression of the leprous granuloma. The object of this paper is to consider lepra reactions as a whole from three points of view: the circumstances of their origin, their histological nature, and their immunological characteristics. But first it is necessary to classify them.

CLASSIFICATION OF REACTIONS

There has so far been no generally acceptable system of classification of lepra reactions. One problem is that the clinical features of some types of reactions (fever and enlargement of lesions) can be confused with simple extension of the disease. The points of distinction have been emphasized in lepromatous leprosy by Wolcott (1947) and in reactional tuberculoid and borderline patients by Campos and de Souza (1954). Nevertheless several authors, including Wolcott, have continued to refer to phases of simple activity as reactions, and with the introduction of many synonyms the nomenclature has become confused. I propose to consider lepra reactions under four headings, namely, downgrading reactions, reversal reactions (both in borderline patients), exacerbation nodules, and erythema nodosum leprosum (ENL) (both in lepromatous patients). The system of classification of leprosy (TT, BT, BB, BL, and LL) is that of Ridley and Jopling (1966).

DOWNGRADING AND REVERSAL REACTIONS

These two reactions make a pair which was first clearly distinguished by Tajiri (1955); they can conveniently be considered together.

A patient with untreated leprosy can deteriorate in two ways: either by the spread of the granuloma without change of classification, or by a change in classification towards the lepromatous end of the spectrum. Similarly, a treated patient can improve either by simple regression of the leprous granuloma or by a movement of the classification towards the tuberculoid end of the spectrum. Simple extension or regression of the granuloma should not be regarded as reactions; but the movement towards lepromatous leprosy is associated with a clinical and histological disturbance that makes up the "downgrading reaction", whereas the movement towards tuberculoid leprosy is associated with the features of "reversal reaction".

Thus *downgrading reactions* are associated with a decline of immunity and a corresponding increase in the number of bacilli and extension of infection in near-tuberculoid and borderline patients. By their nature these reactions are likely to be found only in untreated patients.

Reversal reactions are the opposite. They occur in near-lepromatous and borderline patients when the bacterial load is diminished as a

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result of treatment; and they are associated with a corresponding increase of immunity (Fernandez *et al.*, 1962).

Clinical features

These two reactions have very similar clinical features; there is erythema and swelling of the skin lesions, which may proceed to ulceration; severe cases develop fever and often there is nerve involvement. New lesions can appear; in a reversal reaction they may present a tuberculoid appearance.

Histological features

A reversal reaction is sometimes, perhaps usually, characterized by an influx of lymphocytes in the early stage, but this feature is transient and not always prominent. Oedema in and around the granuloma is the most constant finding, and is most prominent at the height of the reaction. The granuloma often increases in volume and the cytology of the host cells changes progressively towards a more epithelioid form, whilst the number of bacilli in the granuloma progressively diminishes. Foreign-body giant-cells are sometimes seen which give place later on to giant-cells of the Langhans type. In severe cases there is necrosis. In the parts of the dermis not occupied by granuloma there is a "dermal reaction" characterized by the influx between the collagen bundles of undifferentiated cells with large pale nuclei, and an increase of fibrocytes. As the oedema subsides and the granuloma regresses there follows, in the case of severe reactions, a heavy fibrosis and occasionally patches of fibrinoid. These features are not all invariably present, and in mild cases there is little histological sign of the reaction.

Downgrading reactions cannot be followed through so readily as reversal reactions. In sub-polar tuberculoid patients they commence with a loss of the usual compact focalization of the granuloma. The lymphocytes which formerly encompassed many of these foci are dispersed and subsequently their numbers decrease, the granuloma spreads and large giant cells, more foreign-body than Langhans in appearance, often infiltrate through the dermis; they are usually vacuolated (intracellular oedema), and extracellular oedema is a constant finding. Often these changes precede the appearance of bacilli in readily detectable numbers. As bacilli increase the granuloma becomes more and more borderline or lepromatous in its cytology. In severe cases there is a dermal reaction similar to that described in reversal reactions, but it is not followed by heavy fibrosis; instead, there is replacement by granuloma.

These two reactions result from the recovery or loss of the patient's capacity to produce a cell-mediated immune response towards *Myco. leprae*. The change in classification that follows may be striking, especially histologically, and it varies with the severity of the reaction: a shift from BL to BT would probably be associated with a heavier reaction than would a slight shift. The most severe reactions tend to be those that involve patients in the middle of the spectrum (Cochrane, 1964): towards the poles stability increases. Patients close to the LL pole may have fairly mild reversal reactions which take them to BL, but seldom further, and they occur only after fairly prolonged treatment when there has been a considerable fall in the bacterial load. Reactions of this type in LL patients are very mild and abortive, and it may be difficult to decide whether the reaction is an attempt at reversal or a mild exacerbation.

It has recently been shown that reactions that closely simulate reversal reactions can be induced in experimental leprosy infections in thymectomized-irradiated mice by the intraperitoneal injection of lymphocytes (Rees and Weddell, 1968). Immunity in leprosy is mediated by lymphocytes produced in the paracortical areas of the lymph nodes (Turk and Waters, 1968). The same is true of other mycobacterial infections; but in most of them the numbers of bacilli are smaller than in leprosy and a shift in the immunological balance might not be expected to produce such a severe reaction.

EXACERBATION NODULES

If during an active phase of lepromatous leprosy, usually a relapse, one lesion becomes exception-

ally large and loaded with many times more bacilli than most other lesions, a quite pronounced reaction occurs; but it is confined to the one exceptional lesion. This is another example of a disturbed immunological balance, only in this case the imbalance disturbance depends on one lesion being notably different from the others. Histologically an exacerbation nodule shows heavy polymorphonuclear infiltration and considerable cellular disintegration identical to that of ENL. But there is no systemic upset. It is more a matter of academic interest than of practical importance.

Closely related to it, I believe, is the histoid lesion. The histology of the histoid lesion seems to me to be that of any hyperactive lepromatous nodule as seen in relapsing leprosy (Pettit *et al.*, 1966), and although the activity gradually subsides, histoid lesions are probably all initially hyperactive. Wade (1963) referred to "local reactional changes" in his more active cases, which consisted in oedema and necrosis and in some cases polymorph infiltration, but ENL, according to Wade, never occurs in them. The point to be emphasized is that occasionally relapsing nodules and histoid lesions may both be characterized by the presence of foci of epithelioid cells, suggesting that these types of lesion are often sub-polar though they are in general lepromatous.

ERYTHEMA NODOSUM LEPROSUM

Clinical features

The features of ENL are well known, but it should be emphasized that the typical crops of small painful red nodules are not the only manifestation of the condition. Severe ENL can give rise to very large painful red plaques, with necrosis and ulceration. Nor is the skin the only organ affected; lymph nodes, liver, and spleen are often enlarged, and iridocyclitis, orchitis, and painful enlargement of the nerves commonly occur. Less common manifestations of ENL are swollen joints and nephritis. The temperature is raised and polymorphonuclear leucocytosis is present even in mild reactions.

The majority of these manifestations are at sites where bacilli are commonly found. The centre of a reaction coincides with a bacillary focus; and generally speaking the more severe the reaction the larger the bacterial mass involved. Exceptions to this, however, are the joints, renal lesions, and possibly the uveal tract. These are probably secondary effects of the reaction, and they suggest an allergic condition; but it may be noted that in two cases of ENL with rheumatoid-like arthritis the histology of the joints was marked by polymorph infiltration (Karat *et al.*, 1967), in contrast to true rheumatoid arthritis and in line with the tissue reaction in ENL.

Histological features

In the majority of relatively mild cases of ENL the reaction site differs from that of all other reactions because it occurs not in the major skin lesions but in small, clinically inapparent lesions, where there are few bacilli; frequently it is on the edge of the subcutaneous fat. However, the centre of the reaction always appears to coincide with a bacterial focus, however small, and is never seen in normal skin. The presence of polymorphs is the essential and predominant feature of the early stage of the reaction lesions, and there is much cellular distintegration. Most cells are increased in the early stage; later there may be significant numbers of lymphocytes (Mabalay *et al.*, 1965). Vasculitis or vascular necrosis is prominent in some, though not all, lesions.

At the other extreme are the large necrotizing lesions. Cellular infiltration similar in kind to that of the small pink node is usually intense and often affects the whole dermis, but not the subcutaneous fat. Oedema also is intense in some cases, especially in the superficial dermis. Again, there may be necrosis of small blood vessels; or a large blood vessel may be found whose wall is heavily infiltrated with bacilli. In three relatively small necrotizing lesions which I biopsied it was evident that the part affected by the reaction is wedge-shaped, as in an infarct, and also like the infarct, there was a large arteriole at the base of the wedge. In each case the arteriole was histologically normal. Lepromatous granu-

loma and AFB were equally distributed inside and outside the wedge; but polymorph infiltration involved only the granuloma within the wedge. Thus it seems possible that ENL may depend partly on foci of bacterial antigen and partly on vascular supply.

"Dermal reaction", as described in reversal reactions, can cause much disruption of elastic fibres and collagen in ENL. Although this happens in necrotizing lesions it is most marked in the clinically "normal" lepromatous lesions of patients with very mild ENL (Ridley and Wise, 1964). In these cases the reaction is presumably due to antigen that has diffused out of the granuloma into the surrounding dermis.

When lymph nodes and nerves are involved in the ENL process the reaction is again characterized by the presence of polymorphs (Karat *et al.*, 1968; Job and Bhaktaviziam, 1967).

Immunological features

ENL occurs characteristically in patients with lepromatous leprosy, but there is evidence that it tends to be most severe in those in whom the disease is very close to the lepromatous pole. Though ENL may supervene before treatment has been started, it seldom does so except in patients with long-standing infections, in whom the bacilli are already granular (Ridley, 1960). Much more typically, ENL occurs in patients who have been receiving chemotherapy for a year or so. During this time there is usually a significant fall in the bacterial load; the bacilli become granular and undergo considerable degeneration with the release, no doubt, of antigenic material both in skin lesions and, by absorption, in the reticulo-endothelial system. There is also evidence that the number of bacilli in the circulating blood of patients with ENL is greater than in any other patients (Lowe, 1933). In other words, there are rather complex alterations in the balance of forces between host and bacillus; but the development of ENL is not associated with any shift in immunological status or classification. It is probably associated chiefly with the humoral immune mechanisms.

Generally speaking, the more severe the reaction, the larger the bacterial mass involved; in the case of one exceptionally severe and fatal necrotizing reaction, the bacilli at the biopsy site were not only numerous but solid staining (Waters and Ridley, 1963). One gains an impression therefore that different patients have different "reaction potentials". In those with a low potential, only small masses of bacilli are involved; in those with a high potential, large masses are involved. We do not know what this reaction potential is, but we can say that in general it is greatest in those patients who initially harbour a heavy bacterial load, yet retain a small residue of resistance to it.

CONCLUSIONS

Despite the differences between them, the various types of reaction sometimes cannot in practice be sharply defined. Downgrading and reversal reactions may alternate with one another (Campos and de Souza, 1954; Fernandez *et al.*, 1962). I have seen ENL and an exacerbation nodule co-existing in different parts of the same lesion. Forms of reaction intermediate between ENL and reversal reaction have been reported (Waters and Ridley, 1963). Mild reactions occur that are atypical and abortive. Histologically, it has been found that there is about as much variation within each type of reaction as there is between the types; it is sometimes impossible to give a definite classfication of a reaction from a single biopsy specimen.

It is to some extent possible to predict reactions and their severity. The patient with advanced lepromatous leprosy and a heavy bacillary load is more likely to develop severe ENL than the patient with early disease and fewer bacilli: and the middle of the spectrum patient is the most likely to suffer from a violent reversal reaction. But reactions cannot be accurately predicted in individual cases, partly because it is impossible to predict the way in which alterations of the patient's bacillary load will affect his immune status. We know that the increased immunity that

precipitates a reversal reaction leads to rapid destruction of leprosy bacilli: but we cannot yet forecast whether the level of immunity of a patient will be affected by changes in his bacillary load due to treatment or failure of treatment. It is clear, however, that a reactional tendency is fundamental to leprosy.

SUMMARY

Four types of leprosy reaction can be identified which are distinct from the simple activity or regression of the infection: downgrading and reversal reactions (in borderline or sub-polar leprosy) and exacerbation nodules and ENL (in polar or sub-polar lepromatous leprosy). Downgrading reactions and exacerbation nodules occur in patients with active infections. Reversal reactions and ENL are more likely to be encountered when the infection has been arrested.

The four types of reaction are distinct and each one has a different significance for the patient. But they may be hard to define, both clinically and histologically.

All reactions are associated with bacterial antigen and with an alteration in the immunological balance between host and bacillus. Downgrading and reversal reactions are associated with changes in cell-mediated immunity; ENL with the humoral immune mechanisms.

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