Editorial

MACROPHAGE STIMULATION AND ACTIVITY IN LEPROMATOUS LEPROSY

The concept of activity, chronicity and regression in the lesions of lepromatous leprosy is relatively unexplored territory. By comparison with most infections, of course, leprosy is always chronic. However, it is generally accepted that in untreated lepromatous infections there is a wide range of variation in the morphological index, which is sometimes unaccountably low. Thus in a large multicentre drug trial based on 17 institutions which represented most of the main endemic areas of the world,[1] 44 out of 138 patients selected for having good active lesions were rejected, mainly on the grounds that their MI was less than 5, or their granulomas occupied less than 15% of the biopsy specimens. At one centre 7 out of 8 biopsies showed lesions with a granuloma of no more than 5%. On the other hand it is commonly found that in relapse, except in the very early stages, the lesions are uncommonly active.[2,3] However, while the level of activity in untreated leprosy is fairly uniform, in relapse it may vary greatly from lesion to lesion. As regards histoid lesions Wade[4] commented that the bacterial load in the particularly 'active' phagocytes was 'simply incredible'. Most subsequent writers have made the same observation, which raises the question of the relationship between the activity of leprosy bacilli and the activity of their host macrophages. In all of this we are considering LL lepromas in which there is no evidence of any difference within the immune spectrum to account for differences in the behaviour of the lesions.

High cell turnover granulomas

In lepromatous leprosy the macrophages are clearly not activated in any specific sense in the way they would be under the stimulus of an agent against which the host was immune, which is thought to be due to the mediation of T lymphocytes. However, there is an alternative sort of stimulation which is associated with high cell turnover as opposed to low turnover granulomas.[5] The turnover rate is due simply to the speed of entry of macrophages from the circulation and their division within the lesion, balanced in part by their

emigration from the lesion. The control of this rate of turnover is not fully understood, but an important factor is the nature of the inducing agent. Thus Freund's adjuvant or paraffin oil induces macrophages with a high cell turnover, measured by the rate of fall in the proportion of labelled macrophages in the lesion, whereas the relatively inert polymer carrageenan induces macrophages with a low cell turnover.[5] High turnover appears to persist as long as the irritation of the inducing agent persists,[6] after which the macrophage life span increase and the turnover rate declines. Such non-specific stimulation is associated with increased phagocytic potential,[7] though the increase is short-lived.[8]

Cytology of activity and regression

There is no way of measuring cell turnover directly in a human granuloma, but proliferative activity, as in histoid lesions,[9] has a similar significance. There is also the cytological approach. The stages in the evolution of mononuclear cells to macrophages and epithelioid cells under the stimulus of BCG have been described morphologically by Adams,[10] both by light and electron microscopy. This study was in guinea-pigs, but the appearances that correlate with degrees of stimulation are essentially similar in human cells of the mononuclear phagocyte series, with slight modifications. The evolution of nucleus and nucleolus is not quite so conspicuous in man, and in leprosy the form of the cytoplasm is greatly modified by the bulk of the bacilli and later, the accumulation of fatty debris (as in an oil granuloma). Viewing the course of a lepromatous infection in this context, at the earliest stage when bacilli are still few and mainly granular one sees granuloma cells some of which are not far removed from mononuclears with round, rather dark nuclei. Others show already some sign of stimulation, the nuclei being paler and the nucleolus more prominent. The cytoplasm is sparse and fairly solid because it has never held any large number of bacilli. The lesion may remain quiescent at this stage for a considerable period, or it may quite rapidly become fully active. The nuclei then are all in the stimulated state just described, though slightly larger than before, and the cytoplasm is bulkier with more bacilli and a little more foamy change, especially in LLp lesions. Regression comes about usually due to chemotherapy, but it may occur also in untreated patients with very long-standing disease (burn-out lepromas). There is much vesiculation of the very bulky cytoplasm due to the increase of fat which is partly of bacterial origin though some is due to cellular degeneration.[11, 12] All surface receptor sites are lost.[13] The surviving nuclei still show signs of moderate stimulation in some cases, but gradually they become pyknotic and disappear, leaving areas of non-nucleated foamy cytoplasmic debris. These changes are illustrated elsewhere.[14]

In BB leprosy the granuloma cells, by light microscopy, have the appearance

of 'immature' epithelioid cells,[10] though by electron microscopy they have the features of activated macrophages.[15] Further up the spectrum one encounters better developed epithelioid cells. But the best example of simple macrophage stimulation in leprosy is the histoid lesion.[3, 14] The nuclei are large and somewhat elongated (whether or not the cytoplasm is elongated). Though loaded with bacilli the cytoplasm is relatively solid because of the high cell turnover. Cellular proliferation accounts also, no doubt, for the expansile type of spread. Ultra-structural evidence of activity has also been obtained.[9, 16] Yet although the histoid lesion appears to be the extreme example of macrophage stimulation in leprosy, it is not a unique or invariable entity. Lesions with histoid features may be found in many cases that are not completely histoid.[2, 3, 17, 18] No evidence has been produced to support the view that they are due to mutant bacilli.[19]

Regulation of activity

It can be concluded, therefore, that some leprosy lesions exhibit cytological and proliferative evidence of a form of non-specific stimulation that is commonly associated either with adjuvants or with organisms which excite a strong immunological response. What is it that stimulates such a response in some cases of lepromatous leprosy, though without any apparent immunological enhancement? The question deserves to be formulated though it is difficult to answer.

The duration of the cellular response is related to the load on the macrophages.[6] It seems clear also that bacterial multiplication stimulates an influx of macrophages, which in lepromatous leprosy are probably the ideal host cells for bacterial multiplication. Thus one can envisage a self-perpetuating cycle in which bacterial multiplication stimulated an influx of more host cells which would favour a further increase of multiplication. But this would not explain why the hyperactive response is more common in relapse than in primary infections, or why the latter are often so chronic. Furthermore, one often gains a strong impression, though it has never been documented, that in relapse, at least, cellular activity is sometimes at variance with bacterial activity. There must be some other factor or factors in operation.

Immune complexes and antibody

Some of these points could possibly be explained by the involvement of immune complexes or antibody.[20] Immune complexes at antigen–antibody equivalence can induce granuloma formation, and an antibody excess enhances the process possibly due to its effect in delaying the degradation of the

complexes by the macrophages.[21] Thus high antibody levels might in theory help to explain both the cellular and bacteriological activity, and in part the immunological failure of lepromatous leprosy.[22] It would not be surprising if in relapse, which represents in effect a second infection, there might be a sharp rise in antibody levels, which on this hypothesis would stimulate bacteriological activity in those lesions where renewed activity was originating. But although there are a number of reports of raised antibody levels in lepromatous infections, especially before treatment and during reactions, the only study to deal with relapse was one on BT leprosy.[23] Nor, apparently, has there been any correlation of antibody levels, which vary widely, with degrees of activity in untreated patients. At present, therefore, there is no direct evidence to substantiate a governing role for bacterial antibody on the kinetics of the granuloma. However, Preston[24] found that mice susceptible to *M. lepraemurium* possessed a serum factor which suppressed the bactericidal performance of the macrophages. The hypothesis is plausible.

A self-perpetuating cycle

The role of antigenic load on macrophage performance is not likely to be less important than that of antibody, and it is a factor which is readily investigated. Clinico-pathological observations give strong grounds for thinking that the total antigenic load is directly correlated with immuno-depression, and that it must be one of the most important determinants of macrophage performance. Recent work provides immunological[25] and experimental[26] evidence that it is an important secondary cause for deficient T cell function. More antigen would of course produce more antibody.

The mechanics of macrophage control by lymphokines are outside the scope of this review, but there is one other immunological mechanism that cannot be overlooked. Schorlemmer *et al* (27) find that a common factor among agents that stimulate macrophages is an ability to activate complement by the alternative pathway. The enzymes which are released from the stimulated macrophages themselves cleave C_3, which is itself synthesized by the macrophages. A similar cycle involves factor B and cathepsin. Hence the agents which recruit macrophages are produced by the macrophages themselves, independently of serum factors.

Thus there appear to be multiple factors tending to produce a self-perpetuating cycle of enhancing activity, which is precipitated most frequently by the stimulus of relapse. If such a high level cycle of antigen–antibody–macrophage influx is the explanation for hyperactivity in lepromatous leprosy, then the slow development and low morphological index of some primary infections might be due, presumably, to the low level of the components which would be needed to start the cycle. The cases under consideration are those in

which the bacilli are already established at their site of optimal multiplication in the sub-papillary plexus of the dermis.[28] Thus neural protection, which is thought to favour bacilli in the early dormant phase of lepromatous infections (as well as in tuberculoid leprosy), would not be relevant to the situation in question. But it might mean that bacilli which had thrived up to a certain point in a protected environment lacked the capacity for rapid advance outside the environment.

From the foregoing discussion it would appear that the prime factors that stimulate or allow activity in lepromatous leprosy, cellular and bacterial, are vagaries of certain factors that are amongst those responsible for inducing immuno-depression. For this reason alone the question of activity deserves further study. More would be learnt about it if it were customary to record the approximate level of bacteriological and histological activity of immunological studies on leprosy patients.

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