THE PATHOLOGY OF LEPROSY

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There is one aspect of leprosy which is quite simple and straight forward. Leprosy is an infectious disease due to a mycobacterium. Beyond that matters are more complicated. *Mycobacterium leprae* has various biochemical features which help to distinguish it from almost all other mycobacteria. The bacillus was discovered by Hansen over a hundred years ago, being about the third bacterium to be incriminated as a pathogenic agent in man. But it is only in about the last 15 years that it has been transmitted experimentally to animals, first the mouse, which serves as a model for a moderately immune type of infection, later to the Armadillo which is model for a relative low immune form of infection. However, the armadillo has not yet been bred in captivity, and animals caught in the wild have been found to be naturally infected in some cases with a mycobacterial disease indistinguishable from human leprosy. *M. leprae* has still not been cultured *in vitro* despite many claims. The most recent of these is that of Skinsnes. The Skinsnes organism has been identified by competent microbiologists as *M. scrofulaceum*, though Skinsnes claims still that it is related to *M. leprae*. Furthermore *M. scrofulaceum* has recently been isolated by Japanese workers from an armadillo experimentally infected with *M. leprae*. Many workers have thought that this bacillus has a non-acid fast phase but the matter remain in abeyance until proper evidence is available.

Leprosy as we know it was not properly identified as an entity until about 1850, so that ancient reports are a matter for speculation. Nevertheless it is true that in every epoch and culture leprosy has been an object of revulsion. This need not concern us here except to note that the aspects of it that cause horror, its insidious onset and relentless course, punctuated by acute flare ups that produce lasting damage, and the unaccountable way in which a few people only are afflicted, these are some of the aspects also which make the disease of clinical and pathological interest. The special features of leprosy are due partly to properties of the bacillus, partly to responses of the host.

Bacteriology

The generation time of *M. leprae* has been determined from animal experiment as about 13 days. This is the longest generation time of any known pathogenic bacterium in man, and it obviously accounts for the chronicity of the disease.

The optimum growth temperature in animal experiments is about 30°C. It had previously been observed clinically that leprosy is a disease of cool tissues: the skin, respiratory tract, eyes, testes, and the peripheral nerves not so much because they are peripheral but because in some situations they are superficial. Thus the ulnar nerve quite high up would be more likely to be affected than more peripheral nerve twigs that were deeply situated. The one exception to involvement of cool sites is the reticuloendothelial system. This is because the RES organs filter bacilli out of the blood and lymph streams rather than because they are a good habitat for growth. Nevertheless it is known that viable bacilli persist in the bone marrow.

M. leprae is almost non-virulent. This is shown by the fact that 10 million organisms

may be found in a single lesion without causing serious damage. Organism of low virulence also tend to have low immunogenicity. This is the situation in lepromatous leprosy.

Host response

Most people are non-susceptible to leprosy, though there is evidence of an immunological response in people who have been in contact with the disease without acquiring it. The reason why the majority of a population should be highly resistant and a few much less so is not clear. It has not been possible to obtain satisfactory evidence of a genetic factor, though it is difficult to think of any other good explanation.

People with only slight susceptibility may develop self healing lesions. However, early indeterminate (unclassifiable) lesions present a clinical problem because it may not be known whether they are of the self healing type.

People with moderate susceptibility tend to develop delayed hypersensitivity to *M. leprae*, it is fair to say that it is delayed hypersensitivity rather than the bacillus itself that is the cause of tuberculoid leprosy.

It may be noted that it is the combination of low virulence with potential for delayed hypersensitivity that accounts for the broad spectrum of disease that is characteristic of leprosy. Other examples are cutaneous leishmaniasis and some of the mycoses. When an infection is due to a virulent organism, either the patient has immunity or he dies, and the disease spectrum is narrow.

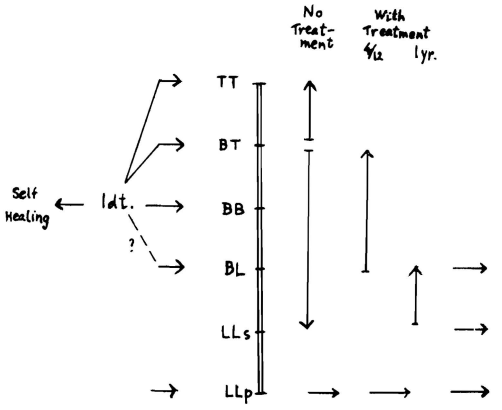
The final characteristic of the host response (or is it of the bacillus?) is that there are protected sites in which the bacillus, in small number, is free from immunological detection by the host. The most important is nerve. Another is the epidermis and the immediate sub-epidermal region. Less important is muscle. These are not the sites that are most favorable for growth when the bacillus is freely established, but they serve for the organism to gain a foothold and multiply. This period of non-detection accounts for the long incubation period. The failure of detection of antigen until it has built up to a certain level, followed by its sudden presentation to an immune mechanism which may be quite sensitive to it, would appear to predispose to hypersensitivity and the reactions that go with it.

Evolution of the infection: early diagnosis

The early stage of the disease, when the bacillus is not yet fully established, is characterized either by one or a few organism lying undetected, with no reaction, in a nerve bundle or immediately under the epidermis. Or it is characterized by a very small granuloma of a few cells at the same sites when a few bacilli have been detected and destroyed. Either of these findings in a biopsy would be diagnostic of leprosy, but to find the one or the other may need cutting serial sections through the whole block. This is a great deal of work and is often not practicable. Even when this is accomplished the evidence may be inconclusive. There may be only Schwann cell proliferation, which is fairly good evidence when it is sufficiently severe to cause disorganization of the nerve structure, or there may be only a non-specific cellular infiltrate.

Classification

Classification by histology is more successful than diagnosis, or at least it is less work. The object is to place the patient in the spectrum of immunity, which is what determines the clinical and pathological features, and also the prognosis (Fig. 1). The most accurate way of doing this at present is histology. The features which have been found to correlate with the position in the spectrum are:



- The type of granuloma cell, epithelioid or macrophage.
- The bacterial load of the granuloma cells.
- The degree of involvement of the protected sites, nerve and epidermis.
- The number and distribution of the lymphocytes in the lesion.

All these features have subsequently been found to correlate with the results of the lymphocyte transformation test except surprisingly, the presence of lymphocytes in the lesions (lymphocyte transformation is not a good index of classification because results with it are affected very heavily by reactions). A brief reference to these histological features is all that is possible here.

Granuloma: Epithelioid cells are always epithelioid cells. But macrophages vary greatly in form. The typical foamy cell of Virchow, particularly if it is vacuolated, is typical not so much of lepromatous leprosy as lepromatous leprosy in regression. In active disease, in which there is a rapid cell turnover, the macrophages have a much more solid cytoplasm. The most active cases of all are often those seen in leprosy in relapse, which unfortunately is one of the commonest reasons today for the taking of biopsies. However, inrelapse this histological activity does not always correlate well with the solidity of the bacilli, which is the usually accepted evidence of the activity of an infection. There are various possible explanation for this. The ability of macrophages *in vitro* to digest *M. leprae* depends not on the origin of the macrophages (tuberculoid or lepromatous) but on the presence of sensitized lymphocytes.

Bacterial load: While the finding of epithelioid cells or macrophages places the patient in the top or the bottom half of the spectrum, the bacterial load of these cells is a useful indication of the position in the middle range of the spectrum.

Protected sites: These have already been considered. The severest forms of involvement of nerve or epidermis are indicative of TT.

Lymphocytes: Trapping of lymphocytes in lesions in appreciable numbers occurs both in the TT-BT region and in BL leprosy. We have recently obtained evidence that the lymphocytes in TT are T cells and those in BL are B cells (M.J. Ridley). The significance of large numbers of B lymphocytes in a lesion is not clear, but it correlates with resistance to downgrading in an untreated patient or predisposition to upgrading towards tuberculoid after treatment.

Reactions

The occurrence of reactions of the delayed hypersensitivity type has been referred to earlier and explained, at least in part. The other sort of reaction is erythema nodosum leprosum (ENL) which often occurs in lepromatous leprosy. Neutrophil polymorphs are found around granulomas in which there are usually quite small numbers of bacilli. Immune complexes can sometimes be demonstrated in the region of the polymorphs. This suggests an Arthus type of reaction which comes about when there is not too big an excess of antigen, though the site probably depends on the level of antibody as well as the level of antigen.

Lepromin Reaction

The early (48 hours) reaction is assumed to be due to soluble antigens, and the late (3 weeks) reaction to insoluble antigens, probably those liberated by destruction of cell walls. Usually the two reactions go together. However,by careful adjustment of dilutions the early reaction becomes positive in most of those who have been in contact with leprosy but not at all in non-contacts. By contrast the late reaction is positive in most normal people but is the better index of their potential resistance to *M. leprae*.

It is worth recalling the work of Kooij and Pepler who found that even normal skin extracts, free of *M. leprae* antigen, gave skin test reactions weaker than, but parallel to, those of lepromin prepared from lepromatous lesions. One wonders whether this might be a clue to some antigenic relationship between the leprosy bacillus and skin,and nerve which is of ectodermal origin.

Future developments

The biggest problem in leprosy at the present time is that of relapse, due partly to drug resistance and partly to the failure of patients to take the drugs given to them. The relapse of an infection which follows can be attributed partly to "resisters" (resistant bacilli) and partly to "persisters", bacilli which do not get killed for some reason by drugs to which they are sensitive.

The problems of the therapy of leprosy are being tackled by the Thelep programme of WHO; those of immunology by the Immlep programme, the ultimate aim of which would be the preparation of an effective vaccine. Among other problems there is the one of transmission: the biggest source of output of bacilli is clearly the nose of active lepromatous patients. But the route, or routes, of intake are undetermined. Most of all, perhaps, one would like to know the specific factors that led to the spontaneous eradication of leprosy from the countries of northern Europe, for leprosy is not essentially a tropical disease; when today, for all our chemotherapy and knowledge we can scarcely begin to eradicate the disease from countries in which it is still endemic.