

## **Hypothesis: Do phases of immunosuppression during a *Mycobacterium leprae* infection determine the leprosy spectrum?**

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*Summary* The failure of the cell-mediated immune response to *Mycobacterium leprae* in leprosy is amply documented, but the immunoregulatory mechanisms involved are unknown. It is suggested that suppressor mechanisms could explain the spectrum of immunity observed in leprosy, and a primary specific immunodeficiency need not be invoked. Three major phases of suppression can be identified. The primary suppression phase may be a consequence of the neural predilection of *M. leprae* which insures preferential exposure of bacillary antigens to suppressor cells in the spleen, rather than to effector cells in the draining lymph node. This view of the leprosy spectrum can accommodate recent findings of an HLA association of tuberculoid leprosy. It also has implications for the interpretation of leprosy vaccine trial data.

Despite many years of intensive research since the pioneering studies of Mitsuda in 1919, the reasons for the failure of the immune system in leprosy remain obscure and controversial. Successful chemotherapy of leprosy and clinical management of its complications are possible with our present state of knowledge, but the development of effective methods for immunotherapy and immunoprophylaxis of leprosy will be greatly facilitated by a clearer understanding of the immunoregulatory derangements which underlie the leprosy spectrum.

### **Deficiencies of the host**

The spectrum of leprosy is the result of an infinitely varied interaction of the intracellular bacterial parasite, *Mycobacterium leprae*, and its human host.

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Efforts to understand this complex host–parasite relationship may focus either on the deficiencies in the defences of the host or on the escape mechanisms employed by the parasite. In the decade just ended, a major effort has been directed toward elucidating the immunologic deficiencies of the human host. A variety of specific and non-specific immunodeficiencies have been documented, both *in vivo* and *in vitro*.<sup>1</sup> However, the question of which of these alterations are causes of the infection and which are its effects remains unresolved.

Particular attention has been given to the possible immunogenetic basis of a specific immunodeficiency in leprosy. In numerous studies, the first of which was reported from AHRI,<sup>2</sup> the frequency of HLA types in groups of leprosy patients and in controls has been analysed. These studies, and more recent ones which have examined the influence of HLA-D identity with a lepromatous patient on the lymphocyte transformation response to *M. leprae* of normal siblings of the patient,<sup>3</sup> have generally failed to support the concept of an HLA-linked specific immunodeficiency in leprosy. However, studies of shared HLA haplotypes in families of leprosy patients in Surinam<sup>4</sup> and India<sup>5,6</sup> have shown evidence of an HLA association of susceptibility to tuberculoid leprosy, but not to lepromatous leprosy. A study of HLA-DR antigens in Mexican leprosy patients<sup>7</sup> is in accordance with the family data. Of course, a gene controlling a specific immunodeficiency (immune response gene), or one controlling susceptibility to lepromatous leprosy by another mechanism, could be linked to a locus other than HLA. Additional family studies in several populations are needed to clarify the influence of HLA-linked or other genetic factors in susceptibility to lepromatous leprosy.

### **Strategies of the parasite**

It is likely that the decade ahead will also see additional research efforts to delineate the escape mechanisms employed by the parasite in its fight for survival. Escape mechanisms of *M. leprae* which have already been identified include its ability to penetrate and grow in non-defensive cells (e.g. Schwann cells,<sup>8</sup> smooth muscle fibres<sup>9</sup> and endothelial cells<sup>10</sup> which cannot be activated by immunological mechanisms to destroy the invader. Even within mononuclear phagocytes which do have the capability to be activated by sensitized T cells to destroy intracellular parasites, *M. leprae* may possess an activity which blocks phagosome–lysosome fusion and thereby forestalls its own destruction.<sup>11</sup>

Another important escape mechanism is likely to be the ability of the parasite to generate suppressor cells in its host.<sup>12–16</sup> Why these suppressor cells subvert the immune response in one individual and not in another becomes a central question. One possibility is that the induction of suppression in leprosy and the concomitant dissemination of the infection may require the

establishment of a focus of infection in a peripheral nerve.<sup>17</sup> The peripheral nerve endoneurium, which is where the bacilli are localized, has long been known to lack lymphatic vessels.<sup>8</sup> Consequently, bacilli in the nerve have access to the circulation from bacillated endothelial cells,<sup>18</sup> but they do not have access to lymphatic drainage. Evidence from experimental animal models suggests that immunological suppression develops following preferential stimulation of the central lymphon compartment (spleen) via the circulation.<sup>19</sup> It is thus possible that leakage of bacilli into the circulation at an early stage of the infection promotes the development of suppressor cells in the spleen. At the same time, peripheral lymphon stimulation, i.e. activation of effector cells in the draining lymph node, which is essential for the establishment of cell-mediated immunity (CMI), is by-passed. In other words, the leprosy bacillus, by its fastidious choice of cellular habitat, may accomplish an 'inversion' of the immune response, i.e. excessive central lymphon stimulation prior to effective peripheral lymphon stimulation. The result could be a specific suppression of the immune response to *M. leprae* antigens which is mediated by suppressor cells formed in the spleen.

The postulated importance of the lack of lymphatics in the site of predilection for the development of suppression in leprosy is analogous to that shown for privileged sites for allografts. Sites such as the hamster cheek pouch and the anterior chamber of the rat eye lack lymphatics, thus giving alloantigens preferential access to the spleen via the circulation which causes suppression of allograft rejection.<sup>20</sup>

Already there is experimental evidence that lack of access to lymphatic vessels may also be crucial in allowing an intracellular parasite to evade the host's defence mechanisms. In experimental cutaneous leishmaniasis, the blocking of the access of the inoculum to lymphatic vessels transforms a self-healing local infection into a disseminated and progressive disease.<sup>21</sup>

The generation of suppressor cells in the mouse is controlled by genes within the I region of H-2, i.e. within the major histocompatibility complex (MHC).<sup>22</sup> Since the human analogue of the murine I region is thought to be the HLA-D locus, it follows that some of the HLA-D-associated factors<sup>5</sup> which govern susceptibility to *M. leprae* infection could operate by controlling suppressor cell generation. If so, we have in the process of suppressor cell induction the convergence of the parasite's escape mechanisms and the host's genetically controlled immunoregulatory mechanisms which influence the outcome of a leprosy infection.

### **The leprosy spectrum: a spectrum of suppression?**

The spectrum of leprosy could arise from the varied interaction of the slowly enlarging bacillary population with the host's immune system. The nature of

this interaction may determine the relative amounts of suppression and immunity which are generated. The leprosy spectrum as described by Ridley, Jopling, and Waters<sup>23,24</sup> can be derived from this interplay of suppression and immunity as follows:

#### POLAR TUBERCULOID LEPROSY (TT)

TT leprosy, in its purest form, may represent a localization of the infection to the primary intraneural focus. Neither bacillary dissemination, nor the suppression which accompanies it, has occurred, and the immune response to *M. leprae* in polar tuberculoid leprosy is, therefore, unimpaired.

#### BORDERLINE LEPROSY (BT, BB, BL)

If, on the other hand, a suppression phase accompanies the dissemination of the infection from its primary focus, the borderline types of leprosy may result. It is the interruption of this state of suppression with the subsequent appearance of delayed type hypersensitivity (DTH) to *M. leprae* antigens which precipitates active clinical leprosy. Either decreased suppressor function or a stronger antigenic stimulus for production of effector cells, or a combination of the two, could tip the balance in favour of immunity and cause the eruption of the multiple infiltrated skin lesions characteristic of borderline leprosy. Borderline leprosy ranges from the paucibacillary borderline tuberculoid (BT) to multibacillary borderline lepromatous (BL) depending on the length of the preceding suppression phase and the extent of bacterial multiplication and dissemination.

A second phase of suppression may follow the active phase of borderline leprosy if continued bacterial multiplication occurs despite the established DTH. This is the suppression phase which accompanies downgrading into subpolar lepromatous leprosy. Alternatively, the second phase of suppression may be interrupted by a 'reversal' reaction. Reversal reactions frequently, but not invariably, occur following the initiation of chemotherapy.<sup>25</sup> The mechanisms which promote the resurgence of DTH leading to reversal reaction are not known. However, reversal of a block in phagosome–lysosome fusion<sup>11</sup> could occur in treated patients if the block is maintained only by metabolically-active bacilli. The 'unblocking' of fusion in macrophages might then provide an important stimulus to *M. leprae*-specific DTH, as the macrophage has an essential role in the induction and expression of sensitized T cells.<sup>26</sup>

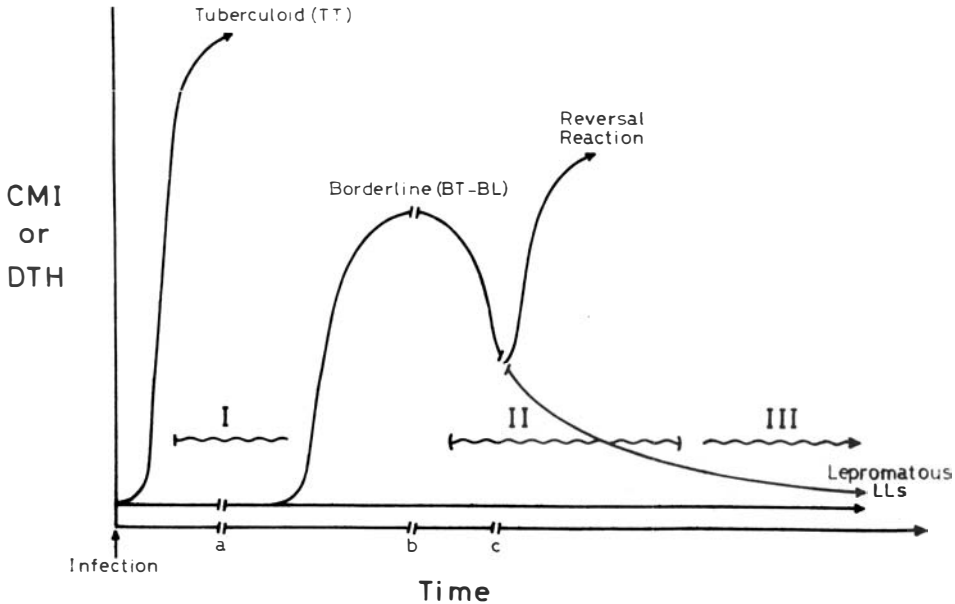
#### LEPROMATOUS LEPROSY (LLs AND LLp)

Leprosy of both the subpolar and polar types represents a fully disseminated infection which encompasses much of the reticuloendothelial system (RES),

including the bone marrow, spleen, liver, and lymph nodes. Subpolar lepromatous leprosy (LLs) includes those lepromatous patients who have downgraded following an earlier borderline stage.<sup>24</sup> Polar lepromatous leprosy (LLp) is distinguished by a merging of the first and final phases of suppression which precludes the emergence of the immunity (or hypersensitivity) which characterizes borderline leprosy.

**PHASES OF SUPPRESSION**

Three major phases of suppression can thus be postulated (Fig. 1). Phase I, or primary suppression, is the phase of suppression which precedes signs of clinical leprosy. When primary suppression is overcome by rising DTH, the typical lesions of borderline leprosy occur. Phase II, or secondary suppression, is the phase of suppression which follows onset of clinical borderline leprosy and permits downgrading toward lepromatous leprosy (subpolar). Following the



**Figure 1.** Phases of suppression which determine the spectrum of leprosy. Three phases of suppression (indicated by wavy lines) could explain the observed spectrum of clinical leprosy. For definition of Phases I, II, and III see text. This diagram is similar to that of Godal *et al.*<sup>27,28</sup> who assumed that the late cell-mediated immune response to *M. leprae* seen in borderline and lepromatous patients was due to a variable lag period prior to attainment of threshold levels of bacillary antigen, rather than to an active suppression as is assumed here. The time scale is not defined because it varies widely in individual patients. The incubation period of borderline leprosy has been estimated to be from 2 to 5 years.<sup>28</sup> The breaks in the time scale serve to emphasize (a) the variable length of Phase I suppression which presumably determines in part the nature of the borderline disease (BT, BB or BL) and which in turn influences both (b) the duration of the active phase of a borderline infection and (c) the time of onset of reversal reaction following the initiation of chemotherapy.<sup>25</sup>

decline in bacillary viability resulting from chemotherapy, secondary suppression may be dramatically reversed with the onset of a reversal reaction. Phase III, or tertiary suppression, is the irreversible suppression of the lepromatous state, both polar and subpolar.

Elucidation of the cellular mechanisms responsible for the observed phases of suppression is hampered by the lack of experimental *M. leprae* infections which parallel the spectrum of human leprosy. However, other mycobacterial infections of mice will continue to provide useful insights into the immunoregulatory events which may underlie the leprosy spectrum.<sup>29-34</sup>

#### COROLLARIES

There are several corollaries to the postulated phases of suppression:

(a) There is no 'innate' level of immunity which is characteristic of each type of leprosy. The widely variable lymphocyte transformation test (LTT) responses and levels of lymphocytic infiltration of the lesions of borderline leprosy<sup>35,36</sup> are not readily accommodated by a static picture of the leprosy spectrum which assumes a steadily declining CMI capacity across the spectrum. These wide variations can rather be attributed to differences between patients who are still in the active phase of a borderline leprosy infection and those in whom secondary suppression has already set in. It seems likely that the active phase is shorter in borderline lepromatous patients than it is in borderline tuberculoid patients because of the much heavier bacterial burden in the former group. Therefore, most borderline lepromatous patients have passed through the active phase of the disease by the time they self-report to the clinic, and, on the average, their lymphocyte transformation responses to *M. leprae* are much lower than those in the borderline tuberculoid group, as are the number of lymphocytes in the lesions.<sup>35, 36</sup>

(b) Polar tuberculoid leprosy results when bacilli in the primary focus of infection fail to induce adequate suppression. Some failures of suppression resulting in TT leprosy would likely occur simply because bacilli in the primary focus gain early access to the peripheral lymphon compartment via lymphatic vessels. The relationship of local spread to systemic dissemination would be influenced by the location of the primary focus. Alternatively, some of the individuals who develop tuberculoid leprosy may do so because they have an HLA-linked impairment of their ability to generate suppressor cells in response to *M. leprae*. This could explain the apparent HLA association of susceptibility to tuberculoid leprosy noted above.

(c) The mechanisms underlying the primary suppression are identical in individuals destined to become either borderline or lepromatous patients. However, in borderline leprosy the suppression is interrupted early. In polar lepromatous leprosy it is not interrupted before persistent (tertiary) suppression sets in following complete dissemination throughout the RES. It is important to note that the irreversible suppression follows complete dissemi-

nation of the infection, but does not precede it. In other words, although the lepromatous patient has passed into the irreversible Phase III, in its earlier stages his disease passed through a phase of primary suppression (phase I) which under different circumstances might have been interrupted to precipitate one or the other type of borderline leprosy.

### **Implications for vaccine trials**

Various vaccination strategies have been proposed which derive from their proponents' views on the pathogenesis of leprosy.<sup>17</sup> No matter which of the proposed vaccines is eventually tested, a deduction from this last corollary has implications for the interpretation of the trial data. If it is true that the early stages of suppression are qualitatively identical in individuals incubating borderline or lepromatous leprosy, then it seems possible that an effective anti-leprosy vaccine (ALV) would be able to precipitate subclinical lepromatous leprosy as one of the borderline types. The factors which control the natural evolution of the disease are incompletely understood. However, the balance of suppression *vs.* immunity is influenced by immunological perturbations caused by pregnancy<sup>37</sup> and possibly by such factors as intercurrent infections, malnutrition, injury, and stress in general.

Another important factor could be the distribution of bacilli in the body. In particular, the relative numbers of bacilli reaching the central and peripheral lymphon compartments may be important. It seems likely, therefore, that the intradermal inoculation of an ALV could provide a potent stimulus to the peripheral lymphon compartment and thereby tip the balance in favour of immunity. The evidence obtained by Convit *et al.*<sup>38</sup> for a conversion of Mitsuda-negative indeterminate leprosy to determinate (borderline) leprosy by intradermal inoculation of *M. leprae* combined with BCG supports this possibility.

Thus at certain stages in the evolution of the disease vaccination might precipitate borderline leprosy in individuals who otherwise would have continued to progress silently towards polar lepromatous leprosy.<sup>39</sup> This would complicate the interpretation of vaccine trials because some of these subclinical lepromatous cases in the unvaccinated control group could get safely through the trial period undetected due to the fact that the incubation period of lepromatous leprosy may range up to ten years or more. From a public health point of view, precipitation by vaccination as 'closed' cases those early infections which might otherwise have gone on to become infectious 'open' cases is highly desirable. However, this factor, in itself, will tend to increase the incidence of leprosy in the vaccinated group compared to the control group, and, depending on the incidence of lepromatous leprosy in the trial region, will make the overall protection rate appear less than it actually is. Selection of lepromin-negative individuals for inclusion in the vaccination trial, as would likely be done, would tend to accentuate the problem because individuals in

early subclinical stages of a lepromatous leprosy infection are thought to be found largely in the lepromin-negative group. Unfortunately, subclinical lepromatous leprosy cannot be identified easily by any of the diagnostic methods currently available.

The design of an effective vaccine and a successful field trial of it depends on an understanding of the forces which shape the leprosy spectrum. The concept that three major phases of suppression can account for the complexities of the leprosy spectrum accommodates much of the available evidence. However, further experiments will be required to establish its validity as a basis for design and testing of a leprosy vaccine.

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## Editorial note

### *1. Special issue of Leprosy Review: 'Leprosy and Primary Health Care'*

In one of the later numbers of *Leprosy Review*, **52**, 1981, we are intending to devote the entire number to the urgent and important topic of Leprosy and Primary Health Care. Invitations have already been issued to experts in the international field who may be able to contribute, and it is also hoped to review existing WHO and other documents which may be relevant. Meanwhile we welcome spontaneous contributions, letters or comments from readers who feel they have something to say about a matter which is clearly of enormous importance to the methodology of leprosy control between now and the year 2000.

### *2. News and Notes; Leprosy and the Community; Reviews and Abstracts.*

We apologize for the very short entries under several of these headings in recent numbers of the journal. This is due to pressure on space, mainly from original articles, but it is hoped to catch up with a backlog of interesting material during 1981.

### *3. Vancouver style.*

In the transition period during 1980, we have been far from strict, and not always consistent, in this style of printing, which is now in extensive use by a number of well-known journals. From now on, however, we shall attempt to use it more accurately, and it is therefore essential that contributors submit their manuscripts in this style.

EDITOR