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The Influence of Immunosuppression and Immunodeficiency on Infections with Leprosy and Tuberculosis*

Leprosy and tuberculosis are chronic mycobacterial infections, both characterized by a spectrum of clinical presentation and pathological findings which are now known to be determined by the nature of the host's immune response to the infection. Although the two infections differ extensively in their rates of development, organ predeliction, and histopathology, the immunological defense mechanisms they elicit in their hosts are probably very similar. Therefore it is very likely that any immune defects responsible for the most severe polar forms of the two diseases are also similar.

The spectrum of disease

Leprosy. The Ridley and Jopling scale[1] in its present form includes:

TT = polar tuberculoid
BT = borderline tuberculoid
BB = borderline
BL = borderline lepromatous
LLs = subpolar lepromatous
LLp = polar lepromatous

TT is the high-resistant form of leprosy, characterized by few well-demarcated skin lesions and localized peripheral nerve involvement. The histopathology of the TT lesion shows granulomata of epithelioid macrophages with surrounding lymphocytes and very few *Mycobacterium leprae* organisms.

LLp is the low-resistant end of the leprosy spectrum, characterized by *M. leprae* dissemination causing widespread disease with organ involvement. There are multiple poorly demarcated skin lesions, and histopathology shows the absence of granulomata. The leproma lesion contains *M. leprae*-laden macrophages but no lymphocytic infiltrate. LLp sera contain high titers of antibody to *M. leprae* and various autoantibodies.

Leprosy has a very long incubation pe-

* This review was written in 1983 by Nicola Hilary Strickland while a third year student at Green College, University of Oxford, England. It won first prize in the annual competition sponsored by the British Leprosy Relief Association (LEPRA) for essays on various aspects of leprosy. We take pleasure in publishing this review. Miss Strickland's present address is: Flat 16, Norham End, Norham Road, Oxford OX2 6SG, England.

[1] Ridley, D. S. Histological classification and the immunological spectrum of leprosy. Bull. WHO **51** (1974) 451–465.

riod, often of many years. Classically, the first lesion is of "indeterminate leprosy" which usually heals spontaneously, but about 25% of the cases enter the clinical spectrum as one of the unstable borderline forms. A patient's position on the spectrum may change as the disease progresses, tending to move toward the lepromatous pole if untreated and toward the tuberculoid pole if treated.

Tuberculosis. The Lenzini scale[2] includes:

RR = polar reactive
RI = intermediate reactive
UI = intermediate unreactive
UU = polar unreactive, anergic

The spectrum is similar to that found in leprosy, except that the extreme polar forms of tuberculosis do not persist as they do in leprosy because extreme RR is rapidly self-curing, and extreme UU is rapidly fatal without treatment.

RR is the high-resistant form of tuberculosis characterized by granulomatous lesions with epithelioid cells and surrounding lymphocytes, which are successful in eliminating *M. tuberculosis* organisms.

UU is the low-resistant form of tuberculosis characterized by dissemination of *M. tuberculosis* and widespread organ involvement. The sera contain high antibody titers.

Decreased cell-mediated immunity

It is now well established that the fundamental immunological defect in lepromatous leprosy and unreactive tuberculosis is the lack of cell-mediated immunity (CMI) to *M. leprae* and *M. tuberculosis,* respectively. The defective CMI becomes progressively more marked on descending the disease spectra, being virtually absent in LLp leprosy and in UU tuberculosis.

The major evidence for lack of CMI in lepromatous leprosy and in unreactive (anergic) tuberculosis is as follows: There is an absence of granuloma formation in the lesions. Lymph nodes show depleted T cell areas (paracortex and intermediary sinuses). Lepromin or tuberculin delayed-type hypersensitivity (DTH) skin tests are negative. *In vitro* tests of CMI to *M. leprae* or *M. tuberculosis* are negative, e.g., lymphocyte transformation test (LTT), lymphocyte-induced macrophage activation and inhibition of macrophage migration tests. Mice which have had their CMI obliterated by thymectomy and X-irradiation develop a lepromatous type of disease when inoculated with *M. leprae,* and develop uncontrolled systemic tuberculosis when inoculated with *M. tuberculosis.*

It is interesting that drug treatment in leprosy and tuberculosis, which is accompanied by a decrease in the number of mycobacterial organisms, is associated with the progression of the disease type toward the more high-resistant polar type (TT or RR); whereas the absence of drug therapy and the accompanying proliferation and dissemination of the mycobacteria leads to progression of the disease toward the low-resistant pole (LL or UU). This seems to indicate that the continued presence of the mycobacterial organisms is in some way important in depressing the host's cellular immunity. This could account for the observations by Pearson[3] that well-documented LLp patients, treated with leprosy chemotherapy for up to 24 years and with no evidence of viable organisms for many years, developed recurrences of leprosy upon stopping treatment and, curiously, the initial lesions showed clinical BT features. The appearance of the lesions gradually moved down the scale until they became florid LLp lesions, presumably as the *M. leprae* organisms re-emerged and multiplied.

The "delay" hypothesis[4] was an early idea put forward to explain the lack of CMI in leprosy and tuberculosis. It proposes a delay in onset of the specific cell-mediated immune response to the mycobacteria which increases toward the low-resistant poles of the disease spectra. The delay is so long in LLp leprosy and UU tuberculosis that CMI never appears. This hypothesis is an unsatisfactory explanation, particularly in leprosy where most patients initially present

[2] Lenzini, L., Rottoli, P. and Rottoli, L. The spectrum of human tuberculosis. Clin. Exp. Immunol. **27** (1977) 230–239.

[3] Pearson, J. M. H. The epidemiology and some implications of sulphone-resistant leprosy. Abstract in Int. J. Lepr. **47** Suppl. (1979) 318.

[4] Rook, G. A. W. Immune responses to mycobacteria in mice and men. Proc. R. Soc. Med. **69** (1976) 442–444.

with an indeterminate form of the disease which shows some evidence of effective CMI and then progress toward a polar form. If the disease progresses toward the lepromatous pole, then it appears that the CMI which the patient possessed initially must gradually be lost.

Thus it appears most likely that the defect in CMI operating in leprosy and tuberculosis is due to the development of an immunodeficiency or immunosuppression mechanism. It is important to remember that any patient presenting with clinical leprosy or tuberculosis, even of the most resistant polar type (TT, RR), must still lack normal CMI since the vast majority of individuals exposed to either of these diseases develops only subclinical infection.

The mechanism of immunodeficiency implies that there is a physical absence or primary malfunction of some component of the cell-mediated immune response. On the other hand, a functional immunodeficiency of CMI could arise as a result of an immunosuppression mechanism, so that although the intact cell-mediated immune response pathway is present, its normal function is suppressed.

General depression of CMI. The specificity of the depression of CMI in leprosy and tuberculosis is open to question. While patients near the unreactive poles (lepromatous leprosy and anergic tuberculosis) are regularly found to be unresponsive to *M. leprae* and *M. tuberculosis,* respectively (as assessed by negative DTH tests), a large proportion of them also show variable depression of other T cell-dependent immune responses. For example, skin sensitization by dinitochlorobenzene (DNBC)[5] and picryl chloride[6] was found to be diminished in lepromatous patients. Similar results have been obtained with a number of other tests of CMI in lepromatous patients, e.g., delayed skin allograft rejection[7]. However, the data vary considerably between studies. Turk and Waters[8] reported that lepromatous patients can respond to another skin sensitizer: keyhole limpet hemocyanin (KLH). It seems possible that generalized deficiency of cell-mediated immune responses could be the result, not the cause, of the disease process in lepromatous leprosy and unreactive tuberculosis. This might be accounted for by the destruction of T cell-dependent areas of lymph nodes, seen histologically to be almost completely replaced by mycobacteria-laden macrophages at this end of the disease spectrum. It is worth mentioning that tests of skin sensitization and graft rejection may be difficult to interpret in lepromatous patients whose skin is diffusely infiltrated. Negative results in such tests may not necessarily reflect underlying changes in the host's immune system.

There is certainly no evidence to suggest that the nonspecific deficiency in CMI seen in patients with low-resistant forms of leprosy or tuberculosis can be accounted for by any congenital general failure of T lymphocyte differentiation (such as diGeorge's syndrome or Nezelof's syndrome). Mycobacterial patients have no past history of increased susceptibility to viral or fungal infections, as would be expected if they had a pre-existing widespread deficiency of CMI.

A viral role?

In seeking to understand the possible influence of immunosuppression and immunodeficiency on leprosy and tuberculosis, it may be instructive for us to consider the recently recognized acquired immunodeficiency syndrome (AIDS), which is apparently also characterized by a severe defect in general CMI developing gradually in a previously healthy individual. The lack of CMI renders the AIDS sufferer susceptible to a number of opportunistic infections and tumors (notably Kaposi's sarcoma). AIDS develops exclusively in a small number of high-risk groups, mainly composed of male homosexuals, recipients of multiple blood tranfusions, and blood products, e.g., he-

[5] Waldorf, D. S., Sheagren, J. N., Trautman, J. R. and Block, J. B. Impaired delayed hypersensitivity in patients with lepromatous leprosy. Lancet **2** (1966) 773–776.

[6] Bullock, W. E. Studies of immune mechanisms in leprosy. N. Engl. J. Med. **278** (1968) 298–304.

[7] Han, S. H., Weiser, R. S. and Kau, S. T. Prolonged survival of skin allografts in leprosy patients. Int. J. Lepr. **39** (1971) 1–6.

[8] Turk, J. L. and Waters, M. F. R. Cell-mediated immunity in patients with leprosy. Lancet **2** (1969) 243–246.

mophiliacs, intravenous drug abusers, and Haitians.

The epidemiological data best fit the hypothesis[9] that AIDS is caused by an as yet unidentified infective agent (presumably viral*) which is transmissible by intimate contact or blood inoculation. The occurrence of AIDS only in certain risk groups could be explained by the variation in host susceptibility to the infecting agent, as seen in leprosy and tuberculosis. This hypothesis would predict that, as in leprosy and tuberculosis, many healthy people have already been exposed to the infective agent but they do not develop clinical disease because they have a normally functioning immune system. It is proposed that AIDS is itself an opportunistic infection which only causes clinical disease in those individuals who are already immunocompromised in some way. The one characteristic which all the AIDS risk groups may have in common is pre-existing chronic immunosuppression or immunodeficiency of CMI. Many factors which might give rise to such an immunological defect have been suggested: infection by a new strain of cytomegalovirus (CMV) or hepatitis B virus; parasitic infection; retrovirus associated with human T cell leukemia; infection with multiple sexually transmitted diseases from numerous sexual partners; parenteral contact with sperm or leukocytes; use of "recreational" drugs, e.g., nitrite compounds; use of steroid creams; etc. However, it appears that no single one of these factors applies to all AIDS-affected members of all the risk groups.

If the defect in CMI affecting leprosy and tuberculosis patients does pre-date infection with the mycobacteria, then one would be justified in looking for factors which might previously have caused the immune defect in all patients subsequently contracting the clinical disease. No such common factor is evident, however. At one time, an increased incidence of hepatitis B antigen (HBAg) was described in lepromatous leprosy (LL) patients[10]. This does not appear to be a valid association because the LL patients studied were institutionalized, while the control group were outpatients. An equally high incidence of HBAg was found in institutionalized borderline patients. A subsequent study of LL outpatients by Samuel, *et al.*[11] did not find any increased incidence of HBAg. Patients who are treated with immunosuppressive drugs (such as corticosteroids) to depress their CMI, in conditions such as post-renal transplantation to prevent graft rejection, are known to develop active tuberculosis infection more often than do untreated individuals[12]. It is usually assumed that steroid-induced CMI reduction predisposes to reactivation of old quiescent tuberculosis lesions in these patients, but it could also render the patient more susceptible to a new infection from environmental *M. tuberculosis*. Of course iatrogenic exposure to steroids is uncommon in the histories of the vast majority of tuberculosis and leprosy patients (although steroids are therapeutically employed in leprosy purposely to suppress the transient increase in CMI associated with type 1 reactions).

Many studies of AIDS patients have documented various abnormalities of CMI, including: cutaneous anergy (e.g., to tuberculin); T lymphopenia; and, notably, a decrease in the normal ratio of peripheral T helper lymphocytes:T suppressor lymphocytes (Th:Ts) measured as $OKT4^+$:$OKT8^+$ subsets defined by monoclonal antibodies. If this decrease in the Th:Ts ratio were characteristic of the depressed CMI in AIDS, it would provide a useful diagnostic marker for the syndrome. However, Pinching, *et al.*[13] investigated 97 symptom-free homosexuals and found that a high pro-

[9] Levy, R. A. and Ziegler, J. L. Hypothesis: Acquired immunodeficiency syndrome is an opportunistic infection and Kaposi's sarcoma results from secondary immune stimulation. Lancet **2** (1983) 78–81.

* Editor's Note: Since this essay was written, a viral etiology has, of course, been established for AIDS.

[10] Blumberg, B. S., Melartin, L., Lechat, M. and Guinto, R. S. Association between lepromatous leprosy and Australia antigen. Lancet **2** (1967) 173–176.

[11] Samuel, I., Samuel, D. R. and Godal, T. Hepatitis-associated antigen in leprosy. Abstract in Int. J. Lepr. **41** (1973) 565.

[12] Millar, J. W. and Horne, N. W. Tuberculosis in immunosuppressed patients. Lancet **1** (1979) 1176–1178.

[13] Pinching, A. J., McManus, T. J., Jeffries, D. J., Moshtael, O., Donaghy, M., Parkin, J. M., Munday, P. E. and Harris, J. R. W. Studies of cellular immunity in male homosexuals in London. Lancet **2** (1983) 126–130.

portion of them showed exactly the same abnormalities of depressed CMI as those found in AIDS, including similarly decreased Th:Ts ratios. In fact, decreased Th:Ts ratios are not pathognomonic of AIDS (or its prodrome), but are also seen in various other circumstances likely to be associated with decreased CMI, such as after many common infections, after iatrogenic immunosuppression, and after exposure to multiple antigens.

In a study of T-cell subsets in 22 leprosy patients, Bach, *et al.*[14] found that the ratios of peripheral blood $OKT4^+$:$OKT8^+$ cells (Th:Ts) were normal in tuberculoid patients and in lepromatous patients without recent erythema nodosum leprosum (ENL). Several larger studies are needed, using treated and untreated patients who have had leprosy for varying periods of time, before we can really interpret these data meaningfully. However, the normal Th:Ts ratio does perhaps seem to indicate that neither polar type of leprosy patient has the same generalized defect of all cell-mediated immune responses seen in AIDS patients. One would not necessarily expect to detect changes in overall Th:Ts ratios in leprosy or tuberculosis if their basic defect in CMI affects only the small numbers of peripheral Th and/or Ts cells specific for the mycobacterial organism.

Some recent work by Pelton, *et al.*[15], using the measles virus as a model, has provided a clue concerning the mechanism whereby viruses may exert immunosuppressive effects. I have used this mechanism to propose a theory (discussed below) in which virus infection could cause specific immunosuppression of the host's cell-mediated immune response to *M. leprae* or *M. tuberculosis* in leprosy and tuberculosis, respectively.

The measles virus infection in man has been known to induce transient impairment of CMI since loss of tuberculin skin hypersensitivity during a natural measles virus infection was observed early this century. One explanation for this phenomenon could be the direct infection of lymphoid cells by the virus, which in some way renders them immuno-incompetent. Several studies have revealed the presence of the measles virus in lymphocytes during acute infection, as judged by immunofluorescence and by direct recovery of the virus. It has also been demonstrated that the majority of T lymphocytes possess receptors for the measles virus[16].

McFarland[17] looked at the effect of measles virus infection of the immunological function by measuring antibody synthesis in a hapten-carrier system in mice, and demonstrated that only the T helper cell activity was depressed. He showed that measles infection in mice does not result in a generalized depletion of T cells, and suggested that the immunosuppression arises as a result of the measles virus selectively infecting a functionally important subpopulation of lymphocytes.

This suggestion is supported by the results of Pelton, *et al.*'s recent study[15] using infectious center assays to show that only a small percentage of human T lymphocytes (5.6%), and an even smaller percentage of human B lymphocytes (0.96%), support measles virus replication. Pelton, *et al.* showed that the measles virus suppressed the specific antibody response of cultured human tonsil lymphocytes to a diphtheria toxoid antigen challenge, provided that the cells were infected with the virus within 72 hours of antigen challenge. However, measles virus infection of the lymphocyte cultures which were already spontaneously secreting antibody (B lymphocytes taken from patients with systemic lupus erythematosus) did not result in immunosuppression.

These findings suggest that the measles virus causes immunosuppression by a selective effect exerted only during the inductive phase of the immune response. Thus, the functionally important subpopulation

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[14] Bach, M., Wallach, D., Chatenoud, L. and Cottenot, F. T cell subsets analyzed by monoclonal antibodies in leprosy patients. In: *Immunological Aspects of Leprosy, Tuberculosis and Leishmaniasis.* Humber, D. P., ed. Amsterdam: Excerpta Medica, 1981, pp. 273–275.

[15] Pelton, B. K., Winsome, H. and Benman, A. M. Selective immunosuppressive effects of measles virus infections. Clin. Exp. Immunol. **47** (1982) 19–26.

[16] Valdimarrson, H., Agnarsdottir, G. and Lackmann, P. J. Measles virus receptors on human T lymphocytes. Nature **255** (1975) 554–556.

[17] McFarland, H. F. The effect of measles virus infection of T and B lymphocytes in mouse. I. Suppression of helper cell activity. J. Immunol. **113** (1974) 1978–1983.

of lymphocytes proposed by McFarland to be selectively infected by the measles virus could well be those lymphocytes undergoing the inductive phase of the immune response to the antigen being tested.

I would speculate that such a virus-mediated immunosuppression mechanism might operate in polar low-resistant tuberculosis and leprosy patients at the time of their initial infection with mycobacteria. We know that both these mycobacterial infections have a higher incidence in populations living under poor socio-economic conditions associated with poor housing, overcrowding, and malnutrition. These are precisely the factors predisposing to increased susceptibility to multiple viral infections. Under such circumstances, chances are probably reasonably high that an individual may be suffering a viral infection at the same moment in time that he is exposed to infection with *M. tuberculosis* or *M. leprae.* The virus could then cause specific immunosuppression by the exact mechanism outlined in the experiments just described: the virus would act during the inductive phase of the body's immune response to the invading mycobacterium to produce a state of selective immunosuppression specific for that infecting mycobacterial organism.

Viruses other than measles are known to infect T cells and to suppress their function (e.g., rubella, mumps, herpes simplex and, possibly, influenza), so even a mild or subclinical viral infection, perhaps unrecognized by the patient, might suffice to create a state of immunosuppression to *M. tuberculosis* or *M. leprae.*

Improvements in the socio-economic conditions of a population are known to be associated with a decline in the incidence of both tuberculosis and leprosy which, if the above suggestion is correct, would be expected from the concomitant decrease in the incidence and transmission of viral infections in the community.

Helper T cells

It now seems clear that the balance of current evidence favors the view that the defect in CMI in low-resistant LLp leprosy and UU tuberculosis is predominantly specific for the invading mycobacterium. It has been well documented in many studies that in the early stages of either lepromatous leprosy or unreactive tuberculosis, patients who are unable to mount a cell-mediated immune response against antigens of the specific infecting mycobacterium are still quite capable of showing normal CMI toward other T cell-dependent antigens, e.g., they give positive skin tests to coccidiodin or histoplasmin antigens. As discussed earlier, it seems highly likely that the nonspecific depression in CMI seen in many leprosy and tuberculosis patients at the polar low reactive end of the spectra may arise in more long-standing cases of the disease as the T cell-dependent areas of lymphoid tissue become replaced by mycobacteria-laden macrophages.

A theoretically simple way of explaining the host's specific cell-mediated unresponsiveness (tolerance) to the particular mycobacterium is to propose that there is a specific immunodeficiency of all helper T cells responsive to the antigenic determinants of that organism. This immunodeficiency or "clonal deletion" of the specific helper T cells might be due to a physical absence of such T cells in the host, or to an intrinsic immune defect in the cells preventing them from functioning normally. The deletion or defect need not necessarily apply to the helper T cells themselves. It could affect soluble mediators acting specifically on the helper T cell subset. It is very difficult to directly prove that clonal deletion is the mechanism operating since this would mean demonstrating the physical absence (or presence in an inactive state) of a subset of antigen-specific cells. We would have no way of experimentally detecting such an absence or inactive presence. The nearest one can get is to prove that other possible mechanisms which might be responsible for the specific deficiency of CMI, such as immunosuppression by suppressor cells, are not operating. In some instances specific clonal deletion and T suppressor cells may coexist, if the role of the latter is not immunosuppression of the mycobacterium-specific T-helper cell response.

There is some evidence suggesting that *M. leprae*-reactive helper T cells are physically present in lepromatous patients but are nonfunctional due to lack of the appropriate lymphokine-mediated triggering

mechanism. Haregewoin, *et al.*[18] found that lepromatous leprosy T cells exposed to *M. leprae in vitro* failed to show a proliferative response, and failed to produce the lymphokine interleukin 2 (IL2). In contrast, when these T cells were cultured in the presence of IL2-rich medium (a T cell conditioned medium) they responded to *M. leprae* by proliferation. These findings indicate that T lymphocyte unresponsiveness in lepromatous leprosy may result from a deficiency of IL2 production rather than from a lack of *M. leprae*-responsive T cells.

Role of suppressor cells

Is the immunosuppression exerted by suppressor cells relevant to the etiology and pathology of leprosy and tuberculosis? This is a question which has become increasingly important over the last decade since it has become established that subpopulations of suppressor T lymphocytes form an integral part of the normal homeostatic mechanism regulating normal immune responses. We could easily propose that malfunctioning suppressor cells are responsible for the failure of an effective immune response in lepromatous leprosy or unreactive tuberculosis. For example, overproduction of suppressor cells, or inappropriate suppressor cells, could cause immunosuppression of the host's cell-mediated immune response at the lepromatous leprosy/anergic tuberculosis end of the spectra. Alternatively, failure to generate suppressor cells, or nonfunctional suppressor cells, could lead to the inability to damp down an inappropriate immune response, perhaps accounting for the excessive antibody production seen in lepromatous leprosy and anergic tuberculosis.

Ellner has demonstrated that patients with active pulmonary tuberculosis possess two types of suppressor cell—T lymphocytes (T_γ^+) bearing IgG Fc receptors[19], and adherent monocytes[20]—which independently suppressed the *in vitro* proliferative response to a specific antigen (tuberculin purified protein derivative). The T_γ^+ suppressor cells were present in tuberculin high-responder patients; whereas adherent monocyte suppressors were the dominant suppressor cells in anergic patients (defined by negative tuberculin skin tests). Thus, opposite polar types of tuberculosis seem to be associated with the predominance of different suppressor cell types, but we do not know whether these suppressor cells predispose to the particular clinical tuberculosis types or are merely their sequelae. Ellner[20] also found that depleting adherent suppressor cells from the peripheral blood mononuclear cells of anergic (tuberculin low responder) patients enhanced their T lymphocyte *in vitro* proliferative response to tuberculin by a mean of 24.4-fold. If it does turn out that immunosuppression by these adherent monocyte suppressors is the fundamental cause of anegric-type tuberculosis, then their elimination *in vivo* would obviously become a priority in the treatment of tuberculosis.

Several groups of workers have investigated the role of suppressor cells in leprosy and have produced some conflicting results whose interpretation is controversial. Two of the opposing sets of data are considered here in some detail. Mehra, *et al.*[21] have developed an *in vitro* assay system which measures the ability of Dharmendra lepromin antigen to induce the suppression of the proliferative response to the mitogen concanavalin A (ConA) of peripheral blood mononuclear cells from leprosy patients. Suppression occurred using cells from lepromatous and borderline patients but not from tuberculoid leprosy patients or from normal controls. Two cell populations were found to be responsible for this lepromin-induced *in vitro* suppression: a) an adherent cell—presumed to be from the macrophage series, and b) a nonadherent T lymphocyte. The T lymphocyte population was characterized further[22, 23] and all of the suppressor

[18] Haregewoin, A., Godal, T., Mustafa, A. S., Belehu, A. and Yemaneberhan, T. T-cell conditioned media reverse T-cell unresponsiveness in lepromatous leprosy. Nature **303** (1983) 342–344.

[19] Kleinhenz, M. E. and Ellner, J. J. as quoted by Chaparas, S. D. Immunity in tuberculosis. Bull. WHO **60** (1982) 447–462.

[20] Ellner, J. J. Suppressor adherent cells in human tuberculosis. J. Immunol. **121** (1978) 2573–2579.

[21] Mehra, V., Mason, L. H., Fields, J. P. and Bloom, B. R. Lepromin-induced suppressor cells in patients with leprosy. J. Immunol. **123** (1979) 1813–1817.

[22] Mehra, V., Mason, L. H., Rothman, W., Reinherz, E., Schlossman, S. F. and Bloom, B. R. Delineation of a human T cell subset responsible for lepromin-induced suppression in leprosy patients. J. Immunol. **125** (1980) 1183–1188.

activity was found to reside in a 20–30% subset of human T cells, characterized by the markers TH_2 and OKT8 (recognized by horse anti-thymocyte globulin and a monoclonal anti-T cell antibody, respectively)[22], and *in vivo* by the surface markers Ia and FcR[23].

Mehra's group believe that their findings support the theory that selective immunological unresponsiveness to *M. leprae* in lepromatous leprosy is due to immunosuppression exerted by the T suppressor cells on the cell-mediated response.

Certainly this immunosuppression theory appears capable of accounting for some puzzling features of leprosy[24]. For example, both clinically "lepromatous" and "tuberculoid" lesions may co-exist in a single individual with borderline leprosy. Borderline patients are in an unstable leprosy state. The dimorphous lesions could be explained by proposing that the quantitative ratios of effector cells (promoting an efficient CMI response against *M. leprae*) to suppressor cells (inhibiting the CMI response) may vary in different parts of the body at a given instant in time. The relative balance of cell types could be reflected by the clinical appearance of the lesion: lepromatous, indicating suppressor cell excess, and tuberculoid, indicating the predominance of effector cells at that site. The patient's disease will ultimately evolve toward one or other of the leprosy polar types, depending on whether it is the suppressor or effector cells which finally predominate.

Suppressor cells also provide a theoretically convincing way of explaining the specific unresponsiveness of lepromatous leprosy patients to *M. leprae* and yet their ability to respond to *M. tuberculosis* (tuberculin). These two mycobacterial species share about 30 crossreacting antigenic determinants, so how is it that lepromatous leprosy patients are unresponsive to these antigens on *M. leprae* and yet are apparently able to recognize the same antigens when they appear on *M. tuberculosis*? If this is true then clearly one cannot suggest that the clones of T cells recognizing these cross-reacting antigens have been deleted in lepromatous leprosy patients. The problem could be resolved by postulating the existence of a single antigenic determinant, unique to *M. leprae,* which is capable of activating specific suppressor cells. These suppressor cells would then inhibit effector cells (probably T helper cells) from responding to the other antigenic determinants of the *M. leprae* organism. This unique "suppressor determinant" on *M. leprae* would be absent on *M. tuberculosis,* so the suppressor cells would not be generated on infection with the latter organism, and the patient's effector cells would be able to respond to the other crossreacting antigenic determinants present on the mycobacterium.

Some recent work by Rook and Stanford[25] on the crossreacting antigenic determinants of mycobacteria, now seems to make it unnecessary for us to resort to this "suppressor determinant" hypothesis. It appears that in fact lepromatous patients and anergic tuberculosis patients do not respond to the common mycobacterial antigens either *in vivo* (by necrotic skin test responses) or *in vitro.* Therefore, the ability of lepromatous leprosy patients to respond to other mycobacterial species is due to their ability to recognize the species-specific antigenic determinants, rather than to a lack of immunosuppression of their response to their shared antigenic determinants. This also means that we cannot exclude the possibility that clonal deletion affecting T cells reactive to the shared mycobacterial antigens exists in lepromatous leprosy and anergic tuberculosis patients.

This leaves us with the problem of explaining what the TH_2^+/OKT8$^+$ cell subset identified by Mehra's group are doing in LLp patients, if they are not suppressing T effector cell response to *M. leprae* antigens. One possibility is that they might arise as an incidental secondary phenomenon in response to the excessive mycobacterial an-

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[23] Mehra, V., Convit, J., Rubinstein, A. and Bloom, B. R. Activated suppressor T cells in leprosy. J. Immunol. **129** (1982) 1946–1951.

[24] Bloom, B. R. and Mehra, V. The pathogenesis of lepromatous leprosy. In: *Immunological Aspects of Leprosy, Tuberculosis and Leishmaniasis.* Humber, D. P., ed. Amsterdam: Excerpta Medica, 1981, pp. 128–137.

[25] Rook, G. A. W. and Stanford, J. L. The heterogeneity of the immune response to mycobacteria and the relevance of the common antigens to their pathogenicity. Ann. Immunol. (Inst. Pasteur) **132D** (1981) 155–164.

tigen load present in disseminated polar lepromatous leprosy.

It is important to remember that demonstrating the presence of suppressor cells in laboratory experiments in no way proves that these cells were behaving in an abnormal manner in the host. It will be extremely difficult to establish whether suppressor cells are a primary mechanism responsible for the pathogenesis of leprosy or tuberculosis, or whether they are merely a secondary consequence of established disseminated disease.

There is no doubt that suppressor cells can arise as a secondary phenomenon in systemic disease. Numerous animal studies[26, 27] have demonstrated that heavy systemic loads of mycobacterial antigens, produced by injecting mice intravenously with large doses of BCG or *M. lepraemurium,* trigger the generation of both lymphocyte and macrophage types of suppressor cell, which have nonspecific effects on CMI. Similarly, in man it is known that suppressor cells, activated by antigen and exerting nonspecific immunosuppressive effects, are often found late in disseminated infections, e.g., with protozoa (malaria, leishmania), nematodes, and bacteria. In cases where removal of these suppressor cells has been achieved, it has not altered the course of the disease. Perhaps activation of suppressor cells is just a normal immunological response to an increasing load of pathogen invading the host.

Other workers (Nath, *et al.*[28, 29] and Stoner, *et al.*[30]) have been unable to confirm Mehra, *et al.*'s findings. Nath, *et al.*'s initial experiments[28] employed a protocol which was similar in design to that of the Mehra study, but differed in some details (as discussed later) and yielded apparently opposite results. In this system T lymphocyte suppressor activity was marked in tuberculoid patients and weak in lepromatous patients. Nath's group were able to reproduce their results using co-cultures from HLA-D-matched donors[29].

It is possible that these contrasting findings from the two groups are not necessarily incompatible if we take into account that there were differences in the experimental protocols used which may have had a highly significant effect on the results. Comparing the experimental procedures described by the authors in the lymphocyte proliferation response assays, we find several discrepancies including: a) differences in the nature of the *M. leprae* antigen preparations (Nath's group used autoclaved *M. leprae* antigen, Mehra's group used Dharmendra lepromin antigen), b) the times at which the proliferation responses were measured, c) the concentrations of ConA mitogen used, and d) the treatment status of the leprosy patients studied. There are two particular criticisms which apply to the experiments by Mehra, *et al.*: a) they did not use HLA-matched cells, and b) the relevance of their antigen preparation is questionable. Dharmendra lepromin is prepared by extraction with chloroform and ether. Unfortunately, such treatment with organic solvents may very easily reveal antigenic determinants which are not normally exposed during clinical *M. leprae* infection. Thus, it seems possible that determinants which are not naturally specific to *M. leprae* could be triggering the suppression observed by Mehra, *et al.* This matter could be settled by performing control experiments with other organisms treated in the same manner, yet none is documented in the authors' papers.

Nath[31] interprets her group's findings as support for the following argument: T suppressor cells are generated during strong cell-mediated immune responses in high-resistant tuberculoid leprosy patients as part of

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[26] Watson, S. R. and Collins, F. M. Development of suppressor T cells in mice heavily infected with mycobacteria. Immunology **39** (1980) 367–373.

[27] Bullock, W. E., Carlson, E. M. and Gershon, R. K. The evolution of immunosuppressive cell populations in experimental mycobacterial infection. J. Immunol. **120** (1978) 1709–1716.

[28] Nath, I. and Singh, R. The suppressive effect of *M. leprae* on the *in vitro* proliferative responses of lymphocytes from patients with leprosy. Clin. Exp. Immunol. **41** (1980) 406–414.

[29] Nath, I., van Rood, J. J., Mehra, N. K. and Vaidya, M. C. Natural suppressor cells in human leprosy: The role of HLA-D-identical peripheral lymphocytes and macrophages in the *in vitro* modulation of lymphoproliferative responses. Clin. Exp. Immunol. **42** (1980) 203–210.

[30] Stoner, G. L., Touw, J., Belehu, A. and Naafs, B. *In-vitro* lymphoproliferative response to *M. leprae* of HLA-D-identical siblings of lepromatous leprosy patients. Lancet **2** (1978) 543–547.

[31] Nath, I. Immunology of human leprosy—current status. Lepr. Rev. Special Issue (1983) 31S–45S.

the normal effective immune response to *M. leprae* infection. The lack of these normal T suppressor cells in lepromatous leprosy could be responsible for some of the pathological features of this form of disease, such as unwanted excessive antibody production and erythema nodosum leprosum (ENL) reactions which, one might imagine, could arise as a direct consequence of absent normal immunosuppression.

It is highly likely that several subsets of suppressor cells with different regulatory roles may be present simultaneously and at different stages of a clinical tuberculosis or leprosy infection. For example, some suppressor subsets might be suppressing various CMI effector functions, while others could be suppressing antibody production by B lymphocytes. We might expect some suppressor cell subsets to be of physiological, and others of pathological, significance. We need to identify and characterize these different subsets accurately, and try to establish a) which, if any, is of primary importance in the pathogenesis of tuberculosis or leprosy—by exerting excessive or inadequate immunosuppression on the specific cell-mediated immune response, and b) which arise merely as immunoregulatory processes secondary to established mycobacterial infection. At present, most workers studying suppressor cells in the mycobacterioses are looking at nonspecific suppressor effects (e.g., lepromin/*M. leprae*-induced suppression of a mitogenic response), perhaps of dubious relevance to the *in vivo* immune response effector mechanisms in these diseases. It seems likely that we will only succeed in identifying the relevant suppressor cells when we assay specific suppression of the relevant *in vivo* effector systems.

As mentioned earlier, the identification of a suppressor cell subset which plays a primary role in the pathogenesis of mycobacterial disease would greatly influence our approach to treatment. We would hope to find some way of eliminating these harmful suppressor cells. Ideally, it might prove possible to destroy the suppressor cells by using injections of monoclonal antibodies specific for a cell marker unique to the suppressor subset. One could speculate that a cytotoxic drug could be conjugated to these monoclonal antibodies, thereby "targeting" the drug's action onto the suppressor cell subset only. Theoretically, such *in vivo* elimination of the pathological suppressor cells might allow the patient to recover adequate CMI to effect self-cure.

Defective macrophage function

The idea that a defect in some aspect of macrophage function contributes to the host's inefficient immune response in tuberculosis and leprosy has often been put forward. It seems a reasonable suggestion in view of the numerous mycobacteria-laden macrophages/histiocytes found histologically in the lesions and lymph nodes of patients with polar lepromatous leprosy and unreactive tuberculosis. Attempts to demonstrate defective macrophage function in mycobacterial disease are severely hampered by our lack of knowledge concerning the characterization of normal cell types and the effector functions in the adherent monocyte (macrophage) cell series. Numerous criteria have been documented which demonstrate the heterogeneity of the macrophage series, suggesting the existence of functional subpopulations of macrophages. The functional differences between subpopulations appear to represent sequential stages of macrophage maturation and environmentally induced differentiation. It is possible that the different functional subpopulations of macrophages may differ in their microbicidal activity, e.g., *M. lepraemurium* are killed more readily by bone marrow-derived macrophages than by normal peritoneal macrophages[32]. Indeed, peroxidase activity, which may well be important in the macrophage's killing mechanism, shows marked changes in subcellular distribution in macrophages of different maturity: it is present in the lysosomes of monocytes recently derived from bone marrow macrophage stem cells but is absent from mature tissue macrophages. Thus the kind of macrophage in which the mycobacteria proliferate could well affect the outcome of the infection. We could speculate that perhaps different subpopulations of macrophages (as yet uncharacterized) are

[32] Alexander, J. and Smith, C. C. Growth of *M. lepraemurium* in non-stimulated and stimulated mouse peritoneal-derived and bone marrow-derived macrophages *in vitro*. Infect. Immun. **22** (1970) 631–636.

infected in the different clinical types of tuberculosis and leprosy.

It has been shown[33] that a large percentage of macrophages in the lesions of tuberculosis are immature and recently monocyte-derived. In contrast, most of the macrophages in the lesions of lepromatous leprosy are not recently monocyte-derived. A study by McKeever, *et al.*[34] of disseminated leprosy of the armadillo showed that *M. leprae* organisms were found only in peroxidase-negative (presumably mature) macrophages, and were absent from the peroxidase-positive (immature) minority of macrophages. The relative maturity of the macrophages infected by the mycobacteria could be significant in determining not only the competence of their killing mechanism but also their sensitivity to activation by lymphokines. Mature tissue macrophages take at least 24 hours longer than immature monocytes to become microbicidal *in vitro* in response to lymphocyte activiation[35].

Although it had been assumed for a long time that macrophages were the effector cells which destroy mycobacterial organisms, true killing of *M. leprae* by macrophage cultures *in vitro* has only fairly recently been demonstrated[32]. We still do not know which of a variety of microbicidal mechanisms is responsible for mycobacterial killing, so even if a defect in one of these mechanisms were detected, it would be difficult to evaluate its significance with respect to leprosy or tuberculosis.

M. tuberculosis is known to be able to inhibit fusion of phagasomes with lysosomes in nonactivated macrophages[36], possibly due to secretion of ammonia by the organism, or due to polyanions present on its surface. Perhaps susceptibility of a patient's macrophages to this process correlates with the clinical spectrum of tuberculosis. The blockade of phagosome-lysosome fusion in *M. tuberculosis*-parasitized macrophages is relevant only if the lysosomal contents are involved in killing the organisms. (The killing process is now thought to involve the production of superoxide.)

Even less is known about the killing of *M. leprae* in macrophages. Early claims by Beiguelman[37] that macrophages from lepromatous patients specifically failed to lyse autoclaved *M. leprae in vitro* have since been refuted by other studies. Also, it was subsequently shown[38] that *M. leprae* did not survive or replicate any better in lepromatous macrophages than in tuberculoid or healthy macrophages *in vitro*.

The precise intracellular location of an organism is likely to affect its susceptibility to the killing mechanism. It has been shown[39] that *M. leprae* is able to escape from the macrophage phagosome and probably multiplies free in the cytoplasm where it might not be exposed to the conventional macrophage killing mechanisms.

We could propose a multitude of defects in macrophage function which might exist in different individuals, ranging from a defect in the processing/presentation of antigen by macrophages to T cells to a defect in macrophage activation or the macrophage killing process. The whole picture is complicated by the existence of functional macrophage subpopulations. It will remain virtually impossible to elucidate any defect in macrophage function which may be discovered in lepromatous leprosy or unreactive tuberculosis patients until the subpopulations and normal functions of the macrophage series have been better characterized.

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[33] Dannenberg, A. M., Ando, M. and Shima, K. The turnover of macrophages and its relation to their activation and antimicrobial immunity in primary BCG lesions and those of re-infection. J. Immunol. **109** (1972) 1109–1121.

[34] McKeever, P. E., Walsh, G. P., Storrs, E. E. and Balentine, J. D. Electron microscopy of peroxidase and acid phosphatase in leprous and unaffected armadillo macrophages: A macrophage subpopulation contains peroxisomes and lacks bacilli. Am. J. Trop. Med. Hyg. **27** (1978) 1019–1029.

[35] Cohn, Z. A. The activation of mononuclear phagocytes. Fact, fancy and future. J. Immunol. **121** (1978) 813–816.

[36] Armstrong, J. A. and Hart, P. D. Phagosome-lysosome interactions in cultured macrophages infected with virulent tubercule bacilli. Reversal of the usual nonfusion pattern and observations on bacterial survival. J. Exp. Med. **142** (1975) 1–16.

[37] Beiguelman, B. Leprosy and genetics. Bull. WHO **37** (1967) 461–476.

[38] Samuel, D. R., Godal, T., Myrvang, B. and Song, Y. K. Behavior of *Mycobacterium leprae* in human macrophages *in vitro*. Infect. Immun. **8** (1973) 446–449.

[39] Evans, M. J. and Levy, L. Ultrastructural changes in cells of the mouse foot-pad injected with *M. leprae*. Infect. Immun. **5** (1972) 238–247.

Some interesting work by Convit, *et al.*[40] has recently demonstrated that lepromatous macrophages are capable of digesting *M. leprae* when appropriately activated. This group showed that intradermal injection of a mixture of heat-killed *M. leprae* with viable BCG resulted in an epithelioid granuloma induced by the BCG which also eliminated the *M. leprae* organisms. Sixty-two percent of their patients with active LL or BL were vaccinated with the killed-*M. leprae*-BCG mixture and subsequently showed features of increased CMI, both on histopathological criteria and on clinical examination (reversal reactions with tuberculoid characteristics)—32% of the group became skin-test positive to soluble *M. leprae* antigen.

The hypothesis favored by Convit to explain their findings is that a primary deficiency in the processing and/or presentation of *M. leprae* antigens by nonreactive macrophages in lepromatous patients leads to an inadequate immunological response to *M. leprae*. Using the mixed injection containing BCG triggers the activation of the lepromatous macrophages, which are then able to digest *M. leprae* and process/present *M. leprae* antigens in the appropriate manner to elicit an effective *M. leprae*-specific CMI.

Nevertheless, one cannot rule out the possibility that it is not the defective lepromatous macrophages which are being activated by this experimental protocol. It could be that the BCG antigen activates a less mature, recently monocyte-derived subpopulation of healthy macrophages, which could be present in lepromatous patients but not normally responsive to *M. leprae* antigen alone. The simultaneous injection of *M. leprae* with BCG may force this BCG-activated subpopulation of macrophages to digest *M. leprae* as well under these circumstances.

Whatever the mechanism of the response, Convit, *et al.*'s findings promise to have important consequences for the future treatment and immunoprophylaxis of leprosy. The secondary reactions occurring in their immunotherapy trial were no worse than those seen with conventional drug therapy, and were well controlled with small doses of corticosteroids or thalidomide (depending on severity). Convit and his co-workers are carrying out a preliminary trial of immunoprophylaxis in over 2500 leprosy contacts in highly endemic areas of Venezuela,[40] and their results so far are encouraging. They have shown that vaccination with the *M. leprae*-BCG mixture induces an immunological conversion to positive skin reactivity to soluble *M. leprae* antigen which is clearly superior to that induced by BCG alone in the control group. The superiority of the response was judged by the percentage of conversion reactions, their strength (diameter of induration), and their persistence at eight months as compared with two months. Obviously, the only absolute criterion by which to assess accurately the efficacy of a preventative vaccine for leprosy would be to record the incidence of new leprosy cases during an observation period of at least ten years. For leprosy, this would be such a formidable task that positive skin reactivity tests have been used instead to assess immunity status. Clearly the trial data will only be valid if skin reactivity does accurately parallel effective CMI to *M. leprae* infection.

Genetic factors

We could invoke genetic regulation to explain why only a minority of those exposed to leprosy and tuberculosis contract clinical disease, and why the host responses to infecting mycobacteria vary so much—resulting in the diverse clinical presentations of tuberculosis, and especially of leprosy. We could postulate that there is a genetic defect in lepromatous leprosy and unreactive tuberculosis patients which renders them unable to respond efficiently to the mycobacterial antigens. There is no clear-cut evidence that genetic factors play a really major role in regulating the immune response to leprosy or tuberculosis, but a number of studies do indicate that the genotype does have some, probably minor, influence on the spectra of these two diseases.

Well-conducted twin studies should provide a useful means of investigating whether there is a genetic predisposition to a partic-

[40] Convit, J., Aranzazu, N., Zuniga, M., Ulrich, M., Pinardi, M. E., Castellazzi, Z. and Alvardo, J. Immunotherapy and immunoprophylaxis of leprosy. Lepr. Rev. Special Issue (1983) 47S-60S.

ular disease. Monozygous twins share exactly the same chromosomes, whereas dizygous twins share an average of half their genes. Thus, if a trait is genetically determined, a higher "concordance rate" is expected in monozygotes than in dizygotes.

Tuberculosis twin studies have been more conscientiously carried out than leprosy twin studies with respect to the major biases which often weaken the results of such twin studies. Comstock[41] analyzed the data of the Prophit tuberculosis twin study, using multivariate methods to standardize for a large number of variables, and concluded that there was a significant, but small, difference of 5% in the concordance rates for tuberculosis infection in monozygous twins as compared with dizygous twins.

The best documented of the leprosy twin studies is that of Chakravartti and Vogel[42]. They found that of 21 pairs of monozygous twins, 11 pairs were concordant (both twins having lepromatous leprosy) and 10 pairs were discordant (4 of these pairs had 1 twin with lepromatous leprosy and the other twin with tuberculoid leprosy, while the other 6 pairs had 1 twin with lepromatous leprosy and the other twin without leprosy). In 8 dizygous pairs included for comparison, 2 pairs were concordant for lepromatous leprosy, while the other 6 pairs were discordant for lepromatous leprosy, with 1 twin affected with lepromatous leprosy and the other without. The authors interpreted their data as providing strong evidence in favor of genetic factors underlying the susceptibility to leprosy infection, since there was a high concordance rate for leprosy among monozygotes as compared with dizygotes.

Unfortunately, the protocol used in this study can be criticized for several reasons. It is clear that not all of the twin pairs in the population under study have been included in the data since there were almost three times as many more monozygous twins than dizygous; whereas one expects at least two thirds of the twin pairs to be dizygotes if all twin pairs in a population are recorded. Such a failure in "ascertainment" leads to exaggerated concordance rates, since it is the unusual similarities which are recognized in the community. Also, accurate zygosity diagnosis to distinguish monozygotes from dizygotes (e.g., using blood markers) is essential, since relying on a subjective similarity assessment is biased in favor of increased monozygous concordance rates. It is far more likely that a genetic factor would be involved in determining susceptibility to one or the other clinical polar form of leprosy (reflecting competence of host CMI) rather than in controlling a susceptibility to any type of leprosy infection, as suggested by these authors. However, in view of the experimental biases mentioned above, it is not possible to draw convincing conclusions about genetic predisposition to a particular leprosy type from the study data. Perhaps the finding to which we should really pay most attention is the existence of the four leprosy type-discordant (lepromatous/tuberculoid) monozygous twin pairs, since the occurrence of the two different polar leprosy types in individuals with identical genotypes (and, it is assumed, comparable histories of exposure to leprosy infection) establishes that the lepromatous response to *M. leprae* infection is not determined solely by genetic factors.

Therefore, twin studies have so far suggested that genetic factors play a small part in susceptibility to tuberculosis, but have not yet established whether a genetic influence is important in leprosy.

The nature of the genetic control operating in human tuberculosis is not clear. Animal studies suggest that two separate factors are involved[43]. Numerous authors have reported a restrictive genetic factor operating in syngeneic mice which is not linked to the major histocompatibility complex (MHC). It is associated with an innate ability of the animals' macrophages to inhibit the initial multiplication of *M. tuberculosis* organisms. There also appears to be a MHC-linked factor which may involve a functional defect in the immune response (Ir)

[41] Comstock, G. W. Tuberculosis in twins: A re-analysis of the Prophit survey. Am. Rev. Respir. Dis. **117** (1978) 621–624.

[42] Chakravartti, M. R. and Vogel, F. A twin study on leprosy. Top. Hum. Genet. **1** (1973) 1–123.

[43] Lagrange, P. H. Tuberculosis: Immunological and clinical aspects. In: *Immunological Aspects of Leprosy, Tuberculosis and Leishmaniasis.* Humber, D. P., ed. Amsterdam: Excerpta Medica, 1981, pp. 20–31.

genes of the mouse H-2 complex. It controls the degree of cooperation between macrophages and T lymphocytes, and seems to be associated with defective presentation of mycobacterial antigens by macrophages to T lymphocytes, resulting in failure of the recognition process.

There have been a number of population studies attempting to correlate HLA haplotypes with clinical types of leprosy. No universal pattern has emerged, although evidence is accumulating to suggest that the human HLA-DR region genes may play a role in determining susceptibility to leprosy type. The human HLA-DR region genes correspond to the murine immune response (Ir) genes. Thus, if we were to find that a particular HLA-DR haplotype is significantly associated with an increased incidence of lepromatous leprosy, we could surmise that this HLA-DR haplotype, and the DR antigens it encodes, in some way determine the immunodeficiency or immunosuppression mechanism that we suspect to be responsible for lepromatous leprosy pathology.

A sound research design for testing the HLA linkage hypothesis has been developed by de Vries, *et al.* It is based on a comparison of haplotypes between two or more affected siblings. Mendelian principles dictate that four different haplotype combinations are possible among full siblings. Thus, on the average, the probability is 25% that any two siblings are HLA identical by chance alone. de Vries, *et al.* therefore looked for departures from this prediction, i.e., evidence for a non-random allocation of HLA haplotypes. In the Wardha area of India, they showed that siblings with tuberculoid leprosy inherited HLA-DR2 significantly more often than expected, and their frequency of HLA-DR6 was much less than expected[44, 45]. This suggests that the susceptibility genes for tuberculoid leprosy may be linked to HLA-DR2, and that resistance genes for this type of leprosy may be linked to DR6.

In a different study[46], van Eden, *et al.* compared the HLA haplotypes of 79 unrelated leprosy patients from a Negroid-Caucasoid ethnic group in Surinam (South America) with a matched healthy control group. They found that HLA-DR3 was significantly associated with tuberculoid leprosy and that HLA-DR3 was negatively associated with lepromatous leprosy. Thus possession of HLA-DR3 in this population group apparently predisposed to development of the tuberculoid type of leprosy after infection with *M. leprae,* and conferred resistance to the lepromatous type of leprosy. They also found that HLA-BW22 appeared to be significantly enhanced among tuberculoid leprosy patients, especially among those with polar tuberculoid leprosy. However, in this Surinam population, HLA-DR2 seemed to be associated with leprosy in general (both lepromatous and tuberculoid forms), and this finding agrees with Japanese data[47].

These differences in the HLA associations with leprosy type found in the various population studies seem to argue against the direct involvement of the HLA gene products themselves in controlling the immunity to leprosy. However, one could suggest several explanations to account for the differences in HLA associations. Perhaps there is an, as yet unrecognized HLA-encoded molecule which determines the immune response to leprosy. Predisposition to leprosy may be determined by a non-HLA-encoded cell membrane structure whose gene is linked to the HLA genes. It may be that more than one HLA gene influences the immune response to leprosy (as in the Surinamese population, where both DR3 and BW22 HLA

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[44] de Vries, R. R. P., Mehra, N. K., Vaidya, M. C., Gupte, M. D., Meehra Khan, P. and van Rood, J. J. HLA-linked control of susceptibility to tuberculoid leprosy. Tissue Antigens **16** (1980) 294–304.

[45] van Eden, W., de Vries, R. R. P., Mehra, N. K., Vaidya, M. C., d'Amaro, J. and van Rood, J. J. HLA-segregation of tuberculoid leprosy: Confirmation of DR2 marker. J. Infect. Dis. **141** (1980) 693–701.

[46] van Eden, W., Leiker, D. L., d'Amaro, J.,Schreuder, G. M. T., de Vries, R. R. P. and van Rood, J. J. Leprosy-type specific HLA associations in a negroid population from Surinam. In: *Immunological Aspects of Leprosy, Tuberculosis and Leishmaniasis.* Humber, D. P., ed. Amsterdam: Excerpta Medica, 1981, pp. 276–278.

[47] Sugiyama, K., Izumi, S., Matsumoto, Y., Ohkawa, S., Matsumoto, H., Miyazaki, T., Juji, T. and Maeda, H. Analysis of the immunogenetic background of Japanese leprosy patients by HLA and serum protein allotypes. Abstract in Int. J. Lepr. **48** (1980) 502.

haplotypes were associated with tuberculoid leprosy).

Thus, both the twin study data and the animal experiments suggest that genetic factors do play a small but significant role in determining susceptibility to tuberculosis, although we do not know how they influence the host's responsiveness to *M. tuberculosis*. The evidence so far is less convincing for leprosy. The HLA findings could be more easily explained had they revealed a positive association with the lepromatous rather than the tuberculoid type of leprosy, since it is in the former that there appears to be the maximum defect in the host's cell-mediated immune response to *M. leprae*. It would be interesting to know whether the polar types of tuberculosis show any HLA linkage (HLA-BW15 occurs with increased frequency among patients with tuberculosis in general).

In summary, I have considered how various mechanisms mediating immunosuppression and immunodeficiency may influence infections with leprosy and tuberculosis. The defect in CMI is most marked in the low-resistant polar forms of both diseases. It appears, at least initially, to affect predominantly the host's cellular immune response to the particular infecting mycobacterium. Viruses are known to impair CMI, and there is an interesting comparison to be made between AIDS and the mycobacterioses in this respect. I hypothesize that immunosuppression of the host's CMI to leprosy or tuberculosis arises as a result of a viral infection coinciding with the induction phase of the host's response to the mycobacterial infection. The role of suppressor cells has also been discussed, both the possibility that their presence is responsible for immunosuppression effects and the equally plausible argument that their absence (or malfunction) might account for phenomena such as the excessive antibody production seen in lepromatous leprosy and in anergic tuberculosis. I have considered various mechanisms which may give rise to immunodeficiency in these diseases, including clonal deletion of T helper cells, the lack of appropriate lymphokine secretion, and possible macrophage defects in the intracellular processing and antigen presentation of these mycobacterial organisms. Finally, I have referred to genetic factors which may be important in controlling the expression of these immunosuppression and immunodeficiency mechanisms influencing leprosy and tuberculosis infections.

—Nicola Hilary Strickland