CORRESPONDENCE

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Ir Genes and Leprosy

To The Editor:

The evidence for genetic factors influencing susceptibility to leprosy needs to be examined more critically than was done by Dr. Hastings in his editorial "Transfer Factor as a Probe of the Immune Defect in Lepromatous Leprosy" (IJL **45** [1977] 281-291). Dr. Hastings has adopted a new name ("the leprosy Ir gene hypothesis") for the old theory that lepromatous leprosy patients have a genetically-determined inability to mount a cell-mediated immune response to *M. leprae* infection. At present, the new name adds little to the theory, except perhaps respectability, since Ir genes have been defined in relation to immune responses to synthetic polypeptides in inbred strains of animals ([3]), but not yet in relation to disease susceptibility in man ([9, 18]).[1]

More than 40 years ago Rotberg ([16]) postulated a genetic factor (the N factor) possessed by normal individuals which enabled them to acquire strong Mitsuda reactivity upon natural exposure to *M. leprae* or in response to repeated lepromin testing. He suggested that persistently negative individuals who were susceptible to lepromatous leprosy lacked the "N factor." Then in the early 1960's Beiguelman ([1]) obtained data indicating that a negative Mitsuda reaction was somewhat more frequent among children whose parents were born negative. He suggested that the basis for this observation was a lyser or nonlyser macrophage, the nonlyser phenotype being inherited as a recessive trait ([2]).[2] With advances in our understanding of the mechanism of cell-mediated immunity, the "genetic defect" theory has been put into more refined terms. The focus has now shifted to the T lymphocyte and the hypothesis has been advanced by Godal *et al.* ([10]) that a defective immune response (Ir) gene may be the basis for the defective T cell function.

What is the evidence for the leprosy Ir gene hypothesis? Transfer factor could be a useful probe of the immune defect in lepromatous leprosy were its mechanism of action known. However, as it is not, the fact that transfer factor is effective in the treatment of lepromatous leprosy tells us next to nothing about the nature of the immune defect. Other evidence in favor of the Ir gene hypothesis is equally tenuous. Current theory requires than an Ir gene should be linked to the HLA complex. Yet, as Dr. Hastings notes, there are no convincing associations of leprosy susceptibility with HLA antigens. Promising results were recently obtained from family studies which suggested that HLA-linked genes control the host response to *M. leprae* ([7]). However, while further studies by the same group ([6]) have confirmed this finding for tuberculoid leprosy, an association of lepromatous leprosy with HLA could not be confirmed.

[1] An exception to this statement may be the case of susceptibility to ragweed pollen allergy which seems to be under HLA-linked Ir gene control ([13]).

[2] It must be cautioned in interpreting such data that Mitsuda reactivity is acquired by the majority of the population in an endemic area between the ages of 5 and 15 years ([11]). Therefore, if comparisons between groups of children are to be valid, the groups must be carefully age-matched.

Although there is little, if any, evidence available to support the leprosy Ir gene hypothesis, there is now substantial evidence against it:

First, it has now been shown by histological methods that about 80% of the patients originally classified as polar lepromatous have actually passed through a borderline phase ([14, 15]). These patients comprise the indefinite or subpolar lepromatous group. It is clear then that the large majority of lepromatous patients do have the genetic capacity to mount a cell-mediated reaction to *M. leprae*. Apparently, this reactivity develops too late and is subsequently overwhelmed by the progressive infection. The Ir gene hypothesis is not even required to explain the other 20% of lepromatous patients. A slightly longer delay in the cell-mediated reaction would explain it equally well.

Second, twin studies probably provide the best evidence for some type of genetic influence in leprosy susceptibility. Yet, at the same time, they seem to rule out the genetic defect theory. In the most thorough study ([4]), 37 of 62 pairs of monozygotic twins were found to be concordant for leprosy. However, at least 4, and possibly 5 of these 37 were discordant for leprosy type, i.e., one of the twins had lepromatous leprosy and the other one had tuberculoid leprosy. Again, it is evident that individuals who must have the genetic capacity to respond to *M. leprae* infection with cell-mediated immunity have nevertheless developed the lepromatous form of the disease.

Third, very recently studies in this Institute have tested directly the hypothesis that unresponsiveness to *M. leprae* is genetically determined ([20]). This was done by measuring the responses to *M. leprae* in the lymphocyte transformation test (LTT) of normal siblings of polar, indefinite, and borderline lepromatous patients, and at the same time determining the relationship of the normal and lepromatous sibling within the HLA region by the mixed lymphocyte reaction (MLR). We have found that the large majority of normal siblings, in contrast to the lepromatous group, respond positively to *M. leprae*. Furthermore, those normal siblings who were HLA-identical to the lepromatous patient responded as well as the HLA-nonidentical ones. We have concluded that the specific T cell unresponsiveness characteristic of lepromatous leprosy is not genetically determined.

It nevertheless seems probable that a genetic influence on leprosy susceptibility does exist, but that, as in the case of tuberculosis susceptibility, it has a complex multifactorial basis. In fact, the magnitude of the concordance for leprosy in monozygotic and dizygotic twins is very similar to that found for tuberculosis concordance in twin studies of tuberculosis susceptibility ([14]). It is also worth noting that tuberculosis shows a spectrum of disease analogous to that of leprosy ([12]), and that transfer factor has also been useful in treating progressive drug-resistant tuberculosis ([17]). Yet, to my knowledge, no one has seriously proposed a "tuberculosis Ir gene."

While a degree of genetic influence seems probable, some of the evidence frequently cited as indicating the existence of genetic factors in leprosy susceptibility may not be evidence at all:

1. *Family clustering of leprosy cases.* This observation misled Danielssen and Boeck ([5]) who erroneously concluded that leprosy was a hereditary disease. It is still possible that we may be misled by this observation. It could be explained as well by the intensity and/or duration of the exposure to *M. leprae* as by the genetic defect theory.

2. *Differing patterns of leprosy in different ethnic groups inhabiting the same area.* These observations need not be due to genetic factors unless all environmental factors are equivalent. Do the two groups have similar social habits and nutritional levels? Do they have comparable socio-economic status? Do they have similar incidences of other diseases in each age group? It would seem to be quite difficult at present to sort out these environmental factors from whatever genetically-influenced difference in susceptibility to different types of leprosy may exist in different ethnic groups. It must also be remembered that such genetically-determined influences as do exist may operate at quite a different level than by direct control of the cell-mediated immune response to *M. leprae*.

3. *The specificity of the defect.* This fact does not imply a genetically-determined unresponsiveness, and can be explained by a desensitization theory. Lepromatous patients seem to be unresponsive to all antigens of

M. leprae which are capable of evoking a cell-mediated response, not just one antigen (or determinant) as might be predicted by the Ir gene hypothesis. This total unresponsiveness can be explained by a desensitization to all *M. leprae* antigens, such as may be caused by the antigen overload associated with the massive infection.

4. *The persistence of the defect.* This fact does not constitute evidence for a genetic etiology of the immune defect because bacilli are now known to persist indefinitely in the body. The permanence of the defect may also be a reflection of the profound effects of a mycobacterial infection which encompasses the entire reticuloendothelial system, including the bone marrow ([19]).

5. *The pre-existence of the defect.* The pre-existent unresponsiveness is indicated by the data of Dharmendra and Chatterjee ([8]). However, the lepromin negativity of those individuals destined to develop lepromatous leprosy is equally well explained by a) lack of exposure, b) "inappropriate" exposure (i.e., underexposure, overexposure, or exposure by the wrong route), or c) immunosuppression during the time of exposure (e.g., by malnutrition, intercurrent infection, pregnancy, etc.) as by a genetically-determined unresponsiveness. That the pre-existence of the defect has been given so much weight in favor of a genetic etiology may be due to the fact that the unwarranted assumption is made that the pre-existent unresponsiveness and the persistent post-infectious unresponsiveness have the same basis. In fact, they may have quite different causes, neither one of them being genetically determined. The pre-existent unresponsiveness may result from the conditions listed above. The persistent post-infectious unresponsiveness, in contrast, is most likely due to the ravages of the infection itself. As has been noted, in approximately 80% of lepromatous cases there is proof of a period of responsiveness between two different periods of unresponsiveness, i.e., the transient borderline phase of indefinite lepromatous leprosy.

In view of the paucity of evidence currently available to support the leprosy Ir gene hypothesis, Dr. Hastings' tentative conclusion that, "there is little hope in attempting immunization of prelepromatous individuals with *M. leprae*" is certainly premature. It would seem at present that his alternative hypothesis which postulates that in some way control mechanisms have gone awry in lepromatous patients may provide a more plausible etiology for the immune defect of lepromatous leprosy.

—Gerald L. Stoner, Ph. D

Armauer Hansen Research Institute
P.O. Box 1005
Addis Ababa, Ethiopia

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