Immunology, Epidemiology and Social Aspects of Leprosy
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# LEPROSY IMMUNOLOGY — SOME ASPECTS OF THE ROLE OF THE IMMUNE SYSTEM IN THE PATHOGENESIS OF DISEASE

by

TORE GODAL

*Laboratory for Immunology,*
*The Norwegian Radium Hospital,*
*Montebello,*
N-0310 Oslo 3, Norway

The immunology of leprosy has been a subject of extensive research for the last 15 years. Important progress has been made in a number of areas, including support for the overall concept that among those who become exposed to *M. leprae*, the great majority appears to develop an effective immune response sufficiently rapidly to arrest *M. leprae* infection before overt clinical disease is precipitated. This I will call subclinical infection. Only in a minority of subjects the disease apparently becomes clinically expressed. Towards the tuberculoid end, considerable evidence suggests that the immune response to *M. leprae* is the major cause of lesions, while towards the lepromatous end of the spectrum, accumulation of vast numbers of bacilli in infiltrating host cells plays an important role.

The precise detection of subclinical infection is of fundamental importance to a more complete epidemiological understanding of leprosy. This has not yet been achieved. However, significant advances have been made recently in this area by development of *M. leprae*-specific serological techniques as pioneered by Abe. More recently the employment of a chemically defined and unique antigen of *M. leprae*, namely the phenolicglycolipid 1 identified by Patrick Brennan and his co-workers, appears promising. In this and related areas the development of monoclonal antibodies is rapidly becoming important to leprosy immunology.

There is no time during this presentation to consider in detail all the different aspects of leprosy immunology. Thus, I will here focus on two aspects: namely, nerve damage in borderline and tuberculoid patients, and the nature of the immunological deficiency in lepromatous leprosy.

Nerve damage in leprosy is of key importance, since this is a major cause of deformity. Deformity often results from loss of sensation and loss of motor nerve function. If one looks histopathologically at damaged nerves in borderline and tuberculoid patients, the regular cablelike structure may be completely broken down by infiltrating inflammatory cells. Actually, there often is granuloma formation within the nerves. A considerable body of evidence suggests that this granuloma formation within the nerves with lymphocytes, macrophage and epithelioid cells results from immunological attack from the host on leprosy bacilli hiding within the nerves. Thus, whenever recognized by the host immune system, T lymphocytes will become attracted to these sites and release various factors called lymphokines, which in turn will attract and activate monocytes to kill bacteria that they will engulf. However, this attack will, as an unfortunate side effect, also distort and damage nerve fibers and function. It is important from a clinical point of view that this type of nerve damage in leprosy may occur very rapidly. This is especially seen in reversal reactions, where there may be a rapid build-up of immunological attack on leprosy bacilli. It is therefore very important to treat such patients adequately as soon as possible; that is, they really have to be considered as emergency cases, otherwise nerve function may be permanently lost.

Let us now turn to lepromatous leprosy. The central question here is; what is going wrong in lepromatous leprosy? Why does the host system fail to attack the leprosy bacilli, which are thriving in the tissues in vast numbers?

It is well known from earlier studies that this immunological defect is remarkably specific to leprosy bacilli. The patient's T-cells may respond strongly to BCG or PPD, but be completely negative to *M. leprae*. Thus, the defect is what we immunologists call antigen-specific. Since it is well known from a large number of studies, including studies on T-cell deficient animals, that it is the T-cell that has the capacity to mediate specific immunity to intracellular bacilli such as the leprosy bacillus, one has for a long time suspected that T-cells play a central role in the defect of lepromatous leprosy. The

mechanisms involved in T-cell activation and T-cell-mediated intracellular killing of mycobacteria have advanced considerably during recent years and allow a more detailed analysis of the defect in lepromatous leprosy. Thus, we will here now first consider the basic concepts of T-cell activation and then discuss recent findings, which suggest more precisely the nature of the defect in lepromatous leprosy.

T-cell response may be subdivided into three parts, the afferent limb or inductive phase, the central or regulatory phase or level, and the efferent limb or effector phase. With regard to the afferent limb, we have known for a number of years that T-cells do not see the antigen alone, but that the antigen is presented to the T-cell by other cells, so-called antigen-presenting cells, which include monocytes, macrophages or dendritic cells. The Langerhans cells of the skin also belong to this cell category.

How antigen-presenting cells interact with T-cells is not yet a fully understood process. It looks like they actually talk to each other, that is to say, it is a mutually dependent, highly sophisticated process. The antigen-presenting cells have on their surface the antigen derived from, in our case, *M. leprae* and high concentrations of HLA-DR molecules, both of which are required for T-cell activation. In addition there is evidence that the antigen-presenting cell produces a factor, interleukin 1 (IL-1), which is required for T-cell activation. However, the production of IL-1, as well as the level of HLA-DR expression, may actually be under T-cell control.

The activation of T-cells leads to two clearly distinguishable phenomena:

(1) some T-cells start to produce a factor required for T-cell proliferation and production of lymphokines. This factor is called interleukin 2 (IL-2).

(2) Other T-cells, will develop receptors for IL-2 and are thereby able to respond to IL-2.

This part of the immune response, the *afferent limb*, sets the stage for T-cell proliferation and interleukin production, which may be called the *central level* of the immune response. The central level may also be called the regulatory level, because T-cells are controlled by other T-cells, so-called suppressor cells, and this regulation is often called the suppressor circuit. These suppressor cells may have the T4 or the T8 phenotype and are thus not limited to T8 cells. Suppressor

cells may interfere with T-cell activation in various ways; for example, by blocking induction of IL-2 receptors or by blocking IL-2 production.

Let us now consider the third part of the T-cell response, the so-called *efferent limb*. How do T-cells effectuate their attack on *M. leprae* and related organisms? It appears that T-cells mainly orchestrate or conduct the attack by production of lymphokines, some of which have chemotactic properties and attract monocytes from the blood into the sites where *M. leprae* has been detected, and other lymphokines (one called macrophage activation factor, MAF, probably identical with γ-interferon) activate the macrophage to kill and digest the bacteria they have internalized.

We may now return to the question of what is going wrong in lepromatous leprosy. It would be apparent that there are many places where things could go wrong:

(1) The antigen-presenting cells may be compromised.

(2) T-cells may lack receptors for *M. leprae* antigens.

(3) Patients may have developed an overwhelming suppressor circuit that could suppress IL-2 receptor induction or IL-2 production. And finally;

(4) There could be a defect in the efferent limb.

Time does not allow a detailed consideration cf the experimental data, which may be in favour of or against any of these possibilities. However, data have steadily accumulated in recent years that provide further evidence that the defect is located at the central or regulatory level. Several investigators, especially Mehra and Bloom, have detected suppressor cells in lepromatous leprosy. Finally, Dr. Haregewoin in Addis Ababa, in collaboration with Salim Mustafa and myself, has shown that lepromatous T-cells fail to produce IL-2, but if given IL-2 from external sources to lepromatous T-cells, the T-cells will now mount a proliferative response to *M. leprae*.

Combined, these findings suggest that suppression of IL-2 production may be of central importance. They are encouraging because they suggest that these studies on the immunological nature of defects, in lepromatous leprosy may lead to new approaches for restoring immunological competence in such patients. Hopefully some day termination of chemotherapy and prevention of drug resistance may become feasible in such patients.

In conclusion, the immune system is of central importance to the pathogenesis of various disease manifestations in leprosy. The main contribution of leprosy immunology so far has been at the conceptual level. But the stage is now set in a number of areas for exploring more direct contributions to leprosy control.

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