Immunologic Suppression in Leprosy and its Relation to Lepromatous Disease

Research on the suppression of immunity in leprosy has recently led to several interesting developments. Two general areas are involved: (a) attempts to produce an experimental disease that is more extensive and severe than the usual infection with Mycobacterium leprae in the foot pads of normal mice; and (b) attempts to explore the immunologic phenomena in lepromatous patients that lead to the absence of lepromin reactivity.

Earlier attempts to enhance the foot pad infections in the mouse were largely unsuccessful. Suramin, a compound that enhances growth of tubercle bacilli in the mouse, had no effect on M. leprae infections in the mouse. Cortisone, which also promotes the multiplication of M. tuberculosis in the mouse, had only a limited effect on the growth of M. leprae; it prevented some of the loss of bacterial viability that normally occurs in the plateau phase, but it did not increase the numbers of bacteria significantly. Some other procedures that are capable of producing more pronounced immunologic deficit do not allow the mice to survive long enough for decisive experiments with M. leprae. Thus the radiomimetic drug cyclophosphamide (cytoxan), when used in doses needed to enhance other mycobacterial infections, killed the mice in about one month. Also thymectomy of newborn mice usually causes "runting" and death in two to three months. The thymus is necessary for the normal development of the lymphoid tissues in neonatal mice.

In adult mice, thymectomy by itself does not have such a profound effect, but if the

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Thymectomy is followed by heavy x-irradiation lymphoid tissues do not regenerate but the immunologic depression develops. In this procedure transduction of syngenic bone marrow is given to protect the mice against the otherwise fatal effects of irradiation on the myeloid system: lymphocytic elements are present in the bone marrow transduction, but they are apparently unable to develop properly in the absence of a thymus. Some of these thymectomized-irradiated mice die in the first few weeks, but the survivors live for approximately normal life spans. The immunologic depression is manifested by poor antibody response to many antigens and markedly delayed rejection of skin grafts from foreign lines of mice.

Thymectomized-irradiated mice have now been employed to excellent advantage by Rees and co-workers to study infections by other routes as well. Their findings after foot pad inoculations have been confirmed. In thymectomized-irradiated mice inoculated in the foot pad, bacillary multiplication occurs at first at approximately the same rate as that in normal mice. However, at the time when the logarithmic phase of growth is terminated, at about 1 × 10⁶ bacilli per foot pad in normal mice, bacillary multiplication continues in thymectomized-irradiated mice. Although multiplication gradually slows, the population eventually reaches a level of 10⁷ to 10⁸ bacilli, or about 10 to 100 times that in normal mice. Furthermore, solidly staining, presumably viable, bacilli continue to be present. Late in the course of these infections bacillary invasion of nerves becomes frequent, and there is an interesting spread to the other peripheral sites, that is, uninoculated foot, ears, and nose, and invasion of lymph nodes and bone marrow as well.

The immunologic story seems to be that the normal mouse reacts to the presence of M. leprae in the foot pad when it reaches a level of about 1 × 10⁶ bacilli, and most of the bacilli are then killed. Presumably the reaction is mediated by the infiltrate of lymphocytes and macrophages that appears at about this time. (Mice that have been well vaccinated with BCG are able to react to a lower number of M. leprae and thereby impose a lower plateau.) Thymectomized-irradiated mice respond only imperfectly at this time, merely slowing the multiplication rather than stopping it. The continued multiplication of bacteria leads to invasion of nerves, and eventually enough bacteria enter the local lymphatic and vascular pathways to seed the other peripheral sites effectively.

When thymectomized-irradiated mice are inoculated intravenously with large numbers of M. leprae, the infection generalizes much more quickly. Approximately 10¹⁰ M. leprae can be harvested from one mouse 19 months after infection, about 95 per cent of the yield coming from ears, nose, and foot pads. Significantly, the histopathologic findings in these intravenously inoculated mice resemble very much those seen in human lepromatous disease. In the heavily infected foot pads tissue (Virchow) cells are frequent, and bacilli are often found in perineural and Schwann cells of nerves. The involvement of skin may be comparable in all respects to that in human disease, and there may even be marked epidermal flattening and a "clear zone" where bacilli are
very few. Micro-colonies of bacilli in the voluntary muscle fibers are a prominent feature. The muco-perichondrium of the nose may be heavily infected and bacilli shed into the mucus.

The other area of research has involved the permissiveness of the lepromatous patient's immunologic capacity. As is well known, lepromatous patients fail to react to lepromin, but they react normally to suspensions of many other mycobacteria, including tubercle bacilli (reviewed in 13). However, carefully controlled studies indicate that lepromatous patients have decreased sensitivity to tuberculins.20 The tuberculin reaction is, of course, the classic example of delayed-type hypersensitivity, and the studies have now been made of the lepromatous patient's ability to develop delayed-type sensitivity to chemicals. Normal persons are not sensitive to these substances, but they may be sensitized easily by exposure through the skin. It was found that lepromatous patients were markedly deficient in their ability to develop sensitivity to picric acid21 and dinitrochlorobenzene.22 Apparently the situation is similar to that seen in other diseases with immunologic deficits; the ability to develop a new sensitivity is definitely impaired, even though the ability to manifest a preexisting sensitivity may persist.

Lymphocyte transformation in cultures in vitro from peripheral blood is a closely related phenomenon. When antigens to which the patients are sensitive (e.g., tuberculins) are added to cultures of white cells, a limited percentage of the small lymphocytes transform into large blast-like cells that are capable of mitosis. Another class of substances, such as phytohemagglutinin (PHA) and streptolysin O (SLO), causes a large fraction of the cells of normal persons to transform in a similar process. It has now been reported that most patients with lepromatous leprosy have markedly impaired lymphocyte transformation to PHA15 and to SLO.23 Defective lymphocyte transformation has previously been observed in chronic lymphatic leukemia. Hodgkin's disease, acquired agammaglobulinemia, and in ataxia telangiectasia (see 12 and 17 for references). These conditions are also marked by other immunologic deficiencies, including impaired ability to develop delayed sensitivity. More recently depressed lymphocyte transformation to PHA has been observed in infants with congenital rubella.24 At first sight congenital rubella appears to be a more obvious parallel to lepromatous leprosy, because it also is an infectious disease characterized by some of the features of immunologic tolerance. However, it is now suggested that the action of rubella virus is a direct one, since it can cause impaired lymphocyte transformation when added directly to cultures of normal cells.25 Lymphocyte transformation in leprosy continues under investigation and a better notion of the mechanism involved should be gained soon, since the procedure is relatively simple and rapid.

Clarification of these immunologic phenomena is obviously important for the understanding of lepromatous disease. The very long persistence of leprosy bacilli after they have been killed by effective drugs seems to be a related phenomenon. Ridley suggests that in treated lepromatous patients those with borderline features rid

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themselves of bacilli more rapidly than do those with pure lepromatous disease.\(^6\) Perhaps unrelated is the well-known observation that erythema nodosum leprosum is much more frequent in patients with pure lepromatous disease.

These two areas of immunologic research in leprosy\(^6\) are, of course, related. The mice have been shown to develop lepromatous disease when treated by a procedure (thymectomy and irradiation) that produces a profound and long-lasting immunologic depression, and the immunologic depression in lepromatous patients has been more clearly delineated by well-known immunologic procedures.

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**Leprosy and Tuberculosis**

Analogies between leprosy and tuberculosis have been cited often, but are important enough to warrant repetition for emphasis in the interest of progress in each field. Differences between the two will probably prove of equal significance, and in the long run knowledge of these may be more effective in promoting advances in understanding.

The current issue of *The Journal* points up a number of elements in common in tuberculosis and leprosy, particularly in the fields of immunology, epidemiology and chemotherapy. Similarities in mycobacterial etiology and to some extent in a granulomatous type of pathologic tissue response are familiar facts, and a great deal of attention is given to immunologic features as reflected in the tuberculin, lepromin and lepoin reactions, and cross reactions that occur throughout the mycobacterial field in skin sensitivity and induced serum antibody response. Analogies in epidemiologic investigation are likewise familiar. Studies of contact infection are basic in each field. Sharma's paper on household infection in the current issue of *The Journal* is a noteworthy example. In practice the methods developed in surveys for leprosy are the ones first used with corresponding objectives in tuberculosis. This is not because of any fundamental priority in thinking in tuberculosis, but rather because the tools used in tuberculosis surveys, particularly the tuberculin test and x-ray examination, are more readily applied, and more effective in diagnosis in the early stages of tuberculosis, than the procedures available in leprosy.

The therapeutic and socially important product of epidemiologic and case-finding surveys, viz., separation of the infected from the well, for the protection of the latter, is well exemplified in each disease, but it is notable that the recognition of contagious and practice of quarantine in leprosy far antedated practice in tuberculosis. The lepromas of antiquity and the Middle Ages came hundreds of years before the sanatoria for tuberculosis, which