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EDITORIALS

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Immunity to Leprosy and the Mitsuda Reaction

In the leprosy field there are two chief ways of looking at the immunology of the disease. Neither view is complex, but many workers are familiar with only one and consequently they fail to appreciate the logical consequences of the other.

Figure 1 sketches view A, which might be called the leprologists' view because it is the traditional one in leprosy. It is strongly influenced by the Mitsuda test results. Uninfected persons are thought to fall into two groups—the vast majority who are Mitsuda positive, when tested, vs the small minority who are Mitsuda negative. When Mitsuda-negative persons (or those whose reactions would be negative if they were tested) become infected with *Mycobacterium leprae,* they (and only they) develop multibacillary disease. When Mitsuda-positive persons (or those whose reactions would be positive if they were tested) become infected with *M. leprae,* most escape clinical disease, but some develop paucibacillary disease. In Figure 1 the results for a *M. leprae* soluble antigen skin test are largely hypothetical. They refer to a test indicating delayed-type hypersensitivity to *M. leprae* antigens and peaking at 24–72 hours; the results are based on what would be expected in other chronic diseases, especially tuberculosis. In reality, it is not yet known whether a skin-test antigen can be prepared that has the requisite sensitivity to detect most infections with *M. leprae* without a confusing degree of crossreactivity with other organisms. The results shown for serologic tests with *M. leprae* antigen are also largely hypothetical. Results with Abe's indirect fluorescent antibody test[1] suggest that *M. leprae*-infected, clinically normal persons have detectable specific antibody for *M. leprae,* but the problems of specificity are very difficult to solve in view of possible crossreaction with unknown determinants (not represented in the suspensions used for absorbing the serum). Just now much hope is pinned on some form of a serologic test that would employ the phenolic glycolipid of Brennan[2] because of the unique chemical structure of its sugars and the presence of antibody to the glycolipid in many leprosy patients.

Figure 2 sketches view B, which might be

[1] Abe, M., Minagawa, F., Yoshino, Y., Ozawa, T., Saikawa, K. and Saito, T. Fluorescent leprosy antibody absorption (FLA-ABS) test for detecting subclincal infection with *Mycobacterium leprae.* Int. J. Lepr. **48** (1980) 109–119.

[2] Hunter, S. W., Fujiwara, T. and Brennan, P. J. Structure and antigenicity of the specific phenolic glycolipid antigens and a related diacylphthiocerol in secretions from *M. leprae.* Int. J. Lepr. **50** (1982) 591–592.

called the immunologists' view. It is based on experience in other diseases of man and on results in experimental animals immunized with *M. leprae*. Uninfected persons are all regarded as being Mitsuda positive when tested (although positive to varying degrees). The intradermal injection of integral lepromin is regarded as an immunization, and a positive Mitsuda test is regarded as a manifestation of delayed-type hypersensitivity in the form of an immune granuloma developing around persisting antigen. The full development of sensitivity to *M. leprae* requires about four weeks in animals and in man; thus the timing of the usual reading. When previously uninfected persons are infected with *M. leprae*, the vast majority acquire immunity but some develop paucibacillary disease. A few of those infected develop tolerance or unresponsiveness rather than sensitization and go on to develop multibacillary disease. The reason that these few humans develop tolerance is not established, but in mice, which are normally Mitsuda positive, tolerance (and Mitsuda negativity) can be induced by intravenous injection of *M. leprae*.[3] For sensitization of mice, the intradermal route is much more effective. The subcutaneous route is relatively ineffective for the induction of sensitivity or tolerance. Thus a process in man can be imagined that involves establishment of an early infection in a non-immunogenic locus, with eventual feeding of antigen intravenously and resultant tolerance. Other invoked mechanisms involve the immunosuppressive action of other infectious agents, e.g., measles virus, or of protein-deficient diets.

In recent years a particular form of view A has been expressed by Convit and colleagues[4] as an *M. leprae*-specific defect in macrophages, viz., an inability to digest *M. leprae* and thereby an inability to present *M. leprae* antigens for the sensitization of T cells. The macrophages are thought of as being normal as regards BCG, so that when they are confronted with a mixture of live BCG and heat-killed *M. leprae*, they ingest both species of bacilli, become activated by the BCG, and consequently process and present *M. leprae* (and BCG) antigens normally to T cells.

By view A, Mitsuda reactivity is considered to be genetically controlled. An interesting consequence may be that genetic studies of families will show linkage of lepromin reactivity with antigens of the major histocompatibility complex.

By view B, tolerance is viewed as an accident of infection. A consequence may be that it is possible to prevent infection by efficient immunization by an effective route (perhaps heat-killed aqueous *M. leprae* vaccine administered intradermally in adequate dosage) at an early age before natural exposure to *M. leprae*.

View A is commonly justified by the experience reported by Dharmendra and Chatterjee.[5] In that study, people in an Indian village were examined for leprosy 15–20 years after they had been tested with integral lepromin. A high attack rate of lepromatous leprosy was observed in those who had been Mitsuda negative. No lepromatous disease was seen in persons who had been Mitsuda positive. The authors concluded that the Mitsuda reaction has great prognostic value and that persons with a negative Mitsuda reaction are more likely to develop disease, especially of the lepromatous type. Objection may be raised, however, on the ground that Mitsuda-negative persons were, at the time of testing, already infected with *M. leprae* and immunologically committed to tolerance rather than immunity. Although the population studied was described as healthy at the time of the skin tests, no bacteriological examinations were described, and the time of onset was not given for the leprosy found 15 or 20 years later. Indeed, in 16 persons who were negative on repeated testing (three tests in total), eight developed lepromatous disease. Unfortunately no information on the age distribution of the subjects was included (see below).

Technical objection might be raised to the presentation of the two views in Figures 1

[3] Shepard, C. C., Walker, L. L., Van Landingham, R. M. and Ye, S-Z. Sensitization or tolerance to *Mycobacterium leprae* antigen by route of injection. Infect. Immun. **38** (1982) 673–680.

[4] Convit, J., Ulrich, M. and Aranzazu, N. Vaccination in leprosy—observations and interpretations. Int. J. Lepr. **48** (1980) 62–65.

[5] Dharmendra and Chatterjee, K. R. Prognostic value of the lepromin test in contacts of leprosy cases. Lepr. India **27** (1955) 149–152.

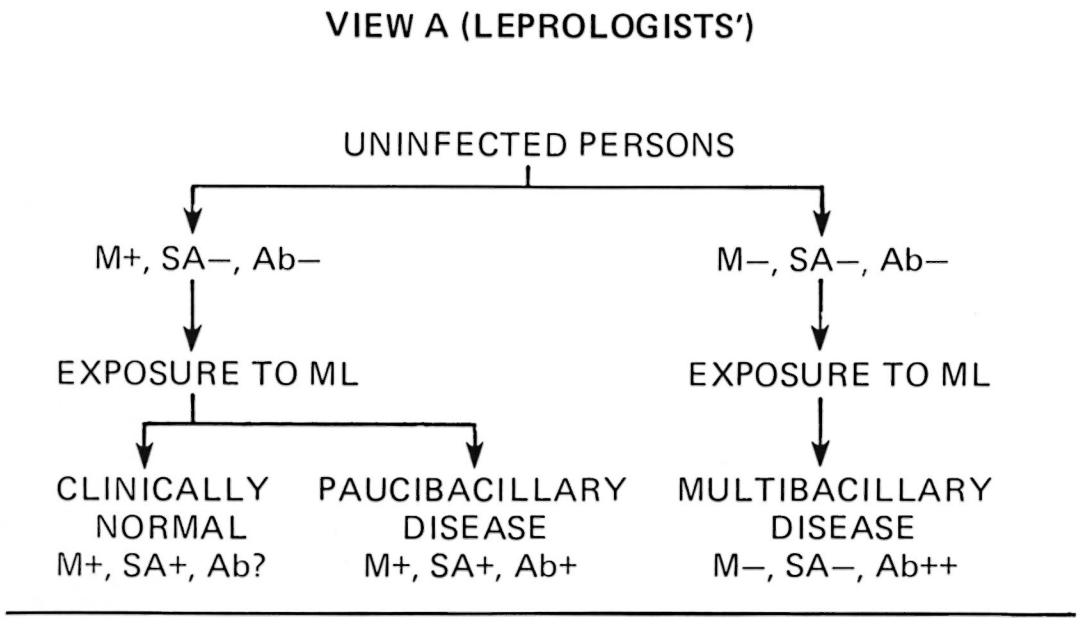

FIG. 1. View A (leprologists') of the immunology of leprosy.

and 2 on the basis that the division of the population into Mitsuda positive and Mitsuda negative is overly neat. From a practical standpoint, the potency of integral lepromin (the concentration of the *M. leprae*) is adjusted to give distinct positive reactions in fully tuberculoid patients (without an excessive incidence of local ulcerations) and negative reactions in fully lepromatous patients. In recent years a concentration of 1.6×10^7 *M. leprae* per 0.1 ml intradermal injection has been widely used. Because of possible variability in normal persons, a larger dose might be needed to obtain positive reactions in nearly all (e.g., greater than 95%) normal uninfected persons. It may be, however, that such a dose would cause an unacceptable amount of ulceration. With lepromin of the concentration now used, this problem has been avoided by repeated testing. With current antigens, three or four repeated tests in negative reactors are apparently required to define Mitsuda negativity in clinically normal populations. The results of Dhamendra and Chatterjee[5] support the view that such negative persons should then be examined bacteriologically as well as clinically.

A second objection is more difficult to handle; in fact, it is often ignored in discussions of the significance of lepromin reactivity. This objection has to do with the fact that all infants are Mitsuda negative. Mitsuda reactivity increases both in incidence and size of the reactions through childhood.[6] The mechanism of this age dependency is not known. It does not appear to depend on a general inability of children to develop and manifest delayed-type hypersensitivity, since delayed skin tests to such antigens as tuberculin attain full size in infected or vaccinated children. Other ex-

[6] Leiker, D. L. Studies on the lepromin test. III. Influence of tuberculosis contact and other factors on the lepromin reaction. Int. J. Lepr. **29** (1961) 488–495.

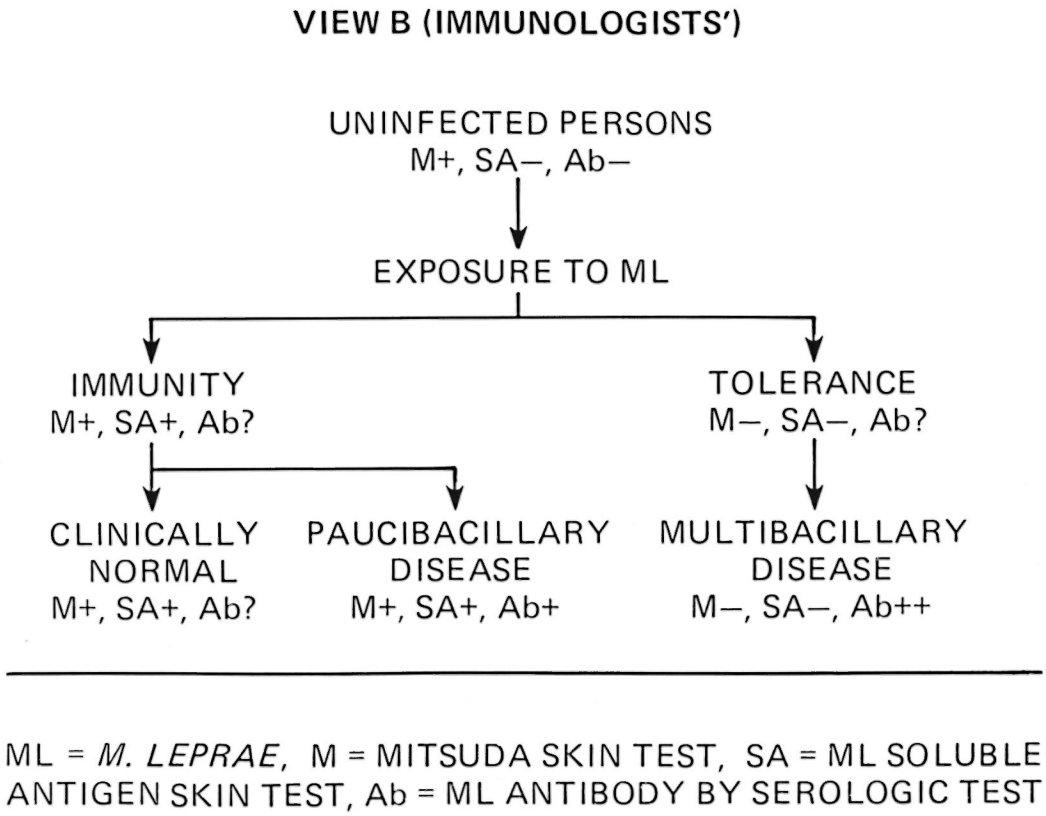

FIG. 2. View B (immunologists') of the immunology of leprosy.

planations can be invoked, e.g., the amount of antigen retained at the site of injection after 28 days is insufficient, or children may have other mechanisms that interfere with the development of an immune granuloma, but there is little evidence to guide us here. A further complication is that young children (younger than six years) often do not develop adult types of leprosy. Rodriguez made the statement[7] "that before the age of 3 years, most children born of leprous parents who show manifest evidence of infection present lesions which signify high resistance to the disease; that between the ages of 3 and 6 years the most common lesions observed indicate, as a whole, relatively low resistance; and that above the age of 6 years the lesions approach the adult types."

To sum up, decisive evidence to select between views A and B does not appear to me to be available now. Each view is relatively simple, however, and involves concepts that seem useful as guides in future studies. The two views are not necessarily mutually exclusive and both mechanisms could operate to some extent. In the meantime, an open attitude seems wise.

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[7] Rodriguez, J. N. Resistance in early childhood. Int. J. Lepr. **17** (1949) 449–455.