

## 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 leprolin 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 casefinding 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 contagion and practice of quarantine in leprosy far antedated practice in tuberculosis. The leprosaria of antiquity and the Middle Ages came hundreds of years before the sanatoria for tuberculosis, which

had their origins in the middle of the nineteenth century.

Mass surveys and the identification of groups at risk had their inevitable sequels in attempts to ward off infection and disease in the healthy persons exposed. Success in vaccination against other diseases raised the hope of comparable measures in tuberculosis. The culmination of many studies in this field was the development of BCG, which came to be accepted as a practical product for immunization against tuberculosis. It is interesting to note that BCG prophylaxis in tuberculosis has remained controversial, in spite of a worldwide experience covering millions of BCG vaccinations. The success of specific drugs, on the other hand, in the therapy of tuberculosis soon raised the possibility of drug prophylaxis in that disease, and now chemoprophylaxis with isoniazid has become a widely practiced procedure. Some reference to BCG vaccination and chemoprophylaxis in tuberculosis is made in the news columns of *THE JOURNAL* (page 101).

Largely on the tuberculosis model, the two procedures, BCG inoculation and chemoprophylaxis—the latter with the leprosy-specific DDS, rather than the tuberculosis-specific isoniazid—have become of great interest as preventive measures against leprosy infection. Attention has been called frequently to studies in this field in editorials and other publications in *THE JOURNAL*.<sup>1</sup>

In the field of chemotherapy itself the analogy is very close. While the major drug in the treatment of tuberculosis today is isonicotinic acid hydrazide (isoniazid, INH), it will be recalled that the first breakthrough in the drug therapy of tuberculosis came with the introduction of sulfonamides in the treatment of experimental tuberculosis, in the nineteen-thirties, in the wake of initial studies on sulfanilamide and re-

lated compounds in other, more acute infections.<sup>2</sup>

These studies, carried out in several countries, led to productive investigations by Feldman, Hinshaw and associates on the use of the drug Promin (p,p'-diaminodiphenyl sulfone-N, N-didextrose sulfonate) in both experimental tuberculosis and clinical tuberculosis in man. The success of these trials led directly to the classic studies of Faget and associates at Carville, Louisiana, with Promin in leprosy. Before this, after early studies in England and France on the chemotherapeutic effect of 4,4'-diaminodiphenyl sulfone (DDS) on acute coccal infections, Rist in Paris (1939) noted its bacteriostatic effect on tubercle bacilli *in vitro* and in experimental infections. But toxic effects in man led to the prompt disuse of DDS in human tuberculosis. With the development of better methods of administration, Cochrane and associates found that DDS in small nontoxic doses was effective in leprosy. Others, stimulated first by Cochrane, achieved significant results. Oral use followed and has remained the standard treatment in the therapy of leprosy with DDS.<sup>3</sup>

The brief review above is set forth to show how closely studies of the chemotherapy of tuberculosis and leprosy have been intertwined. It is noteworthy that coincidentally with the investigations noted above several studies were made of the action of sulfones and sulfonamides on other mycobacteria. Thus a concept was established of some degree of specificity of drugs of this class for microbes of the mycobacterial genus. In the current issue of *THE JOURNAL* studies by Hastings and Trautman are reported, dealing with the value of the well known antituberculosis drug streptomycin in association with DDS in the treatment of leprosy.

One more element of mutual significance

<sup>1</sup>See Rees, R. J. W., BCG vaccination against leprosy. *THE JOURNAL* **34** (1966) 186-190; Yoshie, Y., United States-Japan Leprosy and Tuberculosis Conference, *THE JOURNAL* **34** (1966) 311-313; and Guinto, R. S., Chemoprophylaxis and BCG vaccination against leprosy. *THE JOURNAL* **34** (1966) 313-316.

<sup>2</sup>For review, see Long, E. R., *The Chemistry and Chemotherapy of Tuberculosis*, Williams & Wilkins Co., Baltimore, 1958, pp. 304-314.

<sup>3</sup>For review of this fast moving history see Doull, J. A. Sulfone therapy of leprosy. Background, early history and present status. *THE JOURNAL* **31** (1963) 143-160.

in the pathogenesis of the two diseases may be noted briefly. In tuberculosis, thanks in part to experimental studies carried out over many years by Lurie, a role of heredity and inborn constitutional factors in resistance and susceptibility has become recognized. In leprosy too, although with perhaps less precision, susceptibility appears to be conditioned by inborn factors. Up to the present time the concept appears to be held chiefly with respect to susceptibility to one or other of the polar types of leprosy, rather than to the disease itself, although the latter possibility has not been discarded. Pioneering efforts, still far from a definitive state, to tie the development of leprosy with certain hereditarily determined blood markers are noted in a paper by Lechat and associates in this issue of THE JOURNAL.

Differences, however, in contrast to similarities, are striking. These are conspicuous in the case of the mycobacteria themselves. The tubercle bacillus thrives *in vitro* and is obviously infectious for experimental animals, while the leprosy bacillus, which is still assumed rather than proved by all tests to be the cause of leprosy, has not been cultured *in vitro*, at least to the satisfaction of all concerned, and transmission of infection to laboratory animals has so far proved impossible except in immunologically conditioned mice or on a limited scale as in the foot pads of normal mice.

Tissue culture is a more fruitful method for comparing artificial culture of the two organisms, but here again the differences are significant. Tissue culture of tubercle bacilli is accomplished with sufficient ease so that the procedure can be used for specific study of allergy and immunity, while thus far tissue culture of leprosy bacilli has simply yielded a few optimistic reports.

Metabolic and structural differences between mycobacteria that are easily grown and mycobacteria that are difficult to culture by any method, such as *M. lepraemurium*, are being analyzed in great detail by Hanks and his associates in the hope that clues leading to the eventual artificial culture of the *M. leprae* will be disclosed.<sup>4</sup> From the knowledge so obtained have come a variety of leads, throwing light, for

example, on such problems as the predilection of the lung to tuberculous infection, and the relative insusceptibility of the lung to leprosy.

In at least two other ways tuberculosis and leprosy are widely different in their pathogenesis. Necrosis of tissue, in the form of "caseation," is the rule in tuberculosis, and the exception in leprosy. Caseation and its frequent sequel, softening, are basic factors in the spread of tuberculosis within the body and to other persons in the outside world. The necrotic and softening tuberculous infiltrate in the lung, by far the commonest site of progressive tuberculosis, discharges infectious material into the bronchial tree, where it is aspirated into previously noninfected parts of the lung or discharged as sputum that may infect others. Even in visceral tuberculosis elsewhere than in the lung, caseation and softening are prime factors in the spread of tubercle bacilli by way of the blood and lymph.

The picture in leprosy is in sharp contrast. The granulomatous lesions of the polar forms, which vary from a histiocytic type in the lepromatous infiltrate to an epithelioid-cell type in the tuberculoid lesion, are alike in the fact that there are but minor regions of necrosis (except in the so-called nerve abscesses of tuberculoid leprosy, in which necrosis may be massive). In progressive pulmonary tuberculosis ulceration of the gastrointestinal tract, secondary to caseous and ulcerative tuberculosis of the lung, is common. The gastrointestinal tract is close to immune, on the other hand, to leprosy infection.

In passing, another important distinction may be noted. In the diffuse lepromatous form of leprosy acid-fast bacilli are abundant in the large phagocytic cells. A substantial portion of the weight of the skin may consist of leprosy bacilli. In tuberculosis, in contrast, it is commonly difficult to find acid-fast bacilli in cells, or even in solid caseous masses. They may be cultured from such tissues, to be sure, and they become visible in large masses once softening has developed. In tuberculoid leprosy bacilli

<sup>4</sup>See Hanks, J. H. The cultivation of *Mycobacterium leprae*. Search for a rational approach. Internat. J. Leprosy **33** (1965) 563-569. (Part 2)

usually are not found in cells. At least in histopathologic preparations they appear to be extracellular.

The pathogenesis of caseation has been long debated, and is not yet settled. Ischemia of the central portions of tubercles is admitted to be a factor, but experts lay far greater stress on the effect of allergy in modifying the nature of the tuberculosis infiltrate. Allergy in tuberculosis may be intense, and it is not implausible to think of both caseation and softening as Arthus-like phenomena. The allergy of leprosy is less well defined, and does not appear to be a significant factor in bringing about necrosis. The varying character of allergy in leprosy is a long story, too complicated for discussion here. Leiker has called attention to some of its complexities in the major polar forms of leprosy in this issue of *THE JOURNAL*.

Finally a vital difference in the pathogenesis of the two diseases lies in the predilection of leprosy for the involvement of peripheral nerves. Tuberculosis has no

such tendency. In fact the most conspicuous contrasting elements in the pathogenesis of the two diseases are the tendency of the tuberculous lesion to caseate and soften, and the leprotic lesion to infiltrate nerve trunks, with resultant anesthesias and sensory and motor defects leading directly and indirectly to deformities. The central nervous system, however, escapes in leprosy, while the brain is not infrequently involved in tuberculosis.

These contrasting features have been cited repeatedly, and discussed competently, in the texts and journals concerned with leprosy, and with a degree of detail not possible here. But it seems worth while to keep them in perspective, for they are intimately concerned in the mechanisms of propagation and spread of the etiologic agents of the two diseases within the human body, and in transmission and "take" of the infections in other persons. In these features presumably lie clues for discovery of new and important facts on the nature of the causative mycobacteria.—E. R. L.