Leprosy—A Model for the Understanding of Chronic Granulomatous Disease

In the past, leprosy as a disease has largely been regarded as noncontributive to the general knowledge of medicine despite recognition of the biologic principle that all disease processes are inter-related and knowledge from each should be contributive to the understanding of disease processes generally. Thus, in the field of infectious granulomas, the study of tuberculosis has been pre-eminent, has contributed much to the understanding of the infectious granulomata and of cellular immunity and hypersensitivity. It has been the classical model for the study of the immunopathology of this group of diseases.

Growing familiarity with, and understanding of leprosy now promise contributions to understanding in areas where the classical model is deficient. Indeed, leprosy presents as an unusually broad spectrum of immunopathologic processes. As this awareness grows it becomes evident that understanding in leprosy has the potential for contributing much to the understanding of many other diseases while at the same time benefiting from knowledge of these other entities. Remarkably, this potential is little recognized. It is the purpose of this presentation to elaborate the concept of a previous editorial (THE JOURNAL **37** (1969) 80-81) and stimulate awareness of the possibilities, utilizing as examples only a portion of the spectrum of disease manifestations known as leprosy.

The immunopathologic spectrum of leprosy. The effective defense mechanism in leprosy, as is generally the case in the infectious granulomata, consists in the phagocytosis and intracellular destruction of the pathogen by macrophages. The broad immunopathologic spectrum of leprosy presents two extreme polar types, the tuberculoid and the lepromatous, with a great number of patients manifesting varying combinations and degrees of the major characteristics of these two polar types. These characteristics may be contrasted as follows:

Tuberculoid	*Lepromatous*
Localized, well-defined, circumscribed lesions	Extensive, diffuse, poorly-delimited lesions
Few bacilli demonstrable	Myriads of bacilli
Intense macrophage (epithelioid) cell response with effective phagocytosis and disposal of bacilli	Abundant macrophage (foam cell) response, with efficient phagocytosis but ineffectual disposal of bacilli
Lepromin reaction (cellular hypersensitivity) positive	Lepromin reaction negative
Granulomatous inflammation	True granuloma generally absent
Circulating (humoral) antibodies insignificant or poorly demonstrable	Humoral antibodies (to polysaccharides) readily demonstrable
Immunologic "reactional" exacerbations characterized primarily by reactions of cellular hypersensitivity	Immunologic "reactional" exacerbations (e.g., erythema nodosum leprosum) characterized primarily by the reactions of immediate type (anaphylactoid) hypersensitivity.
Effective accelerated therapeutic response to specific therapy	Sluggish therapeutic response

Comparative immunopathology. In comparative immunopathology, the lepromatous conglomeration of characteristics is of contributive interest because a comparable state is uncommon in human tuberculosis and little recognized in mycotic infections. The tuberculoid and a portion of the interlying spectrum of leprosy is comparable to the total spectrum usually presented by tuberculosis. Within itself leprosy, therefore, encompasses a broader immunopathologic spectrum. Therefore the tuberculin test is useful as a diagnostic tool whereas the lepromin test is usually regarded as being nondiagnostic. In fact, the lepromin test (Fernández reaction) is suggestively diagnostic for that portion of the spectrum of leprous manifestations which compares to the total spectrum of tuberculosis. It is not responsive to the lepromatous conditions just as the tuberculin test would probably be similarly unresponsive in the event that a lepromatoid segment were included in the spectrum of response seen in tuberculosis. The lepromin test, therefore, should not be regarded as a diagnostic disappointment but as a tool that helps reveal and elucidate an otherwise inadequately recognized portion of the granulomatous immunopathologic spectrum. Comparatively, it may also be noted that the disseminated, often fatal, fungus infections have many lepromatoid characteristics while evanescent systemic mycoses often have tuberculoid manifestations. These inter-relationships seem worthy of extended study and leprosy provides the model having the greatest range that is presently available.

In lepromatous leprosy there is no evident lack in macrophage ability to phagocytose the infective agent. The pathogens proliferate apace and are phagocytosed by yet more phagocytes till in typical lepromatous lesions there are large masses of bacilli-laden cells which appear on section as broad sheets lacking the classical granulomatous structure. Similar circumstances are not often seen in human tuberculosis though there is a parallel to be found in the form of tuberculosis known as the "Yersin" type and seen in some experimental animals. In the human, a morphologically lepromatoid form of tuberculosis may occur when tuberculous infection takes place in a subject long treated with steroids or antimetabolites which interfere with macrophage digestive ability. Similar deficient and ineffective inflammatory response is seen in systemic mycotic infections occurring in patients who have been under like therapy. Comparative study of both the therapeutically debilitated models and the leprosy model should provide insight into mechanisms of debilitation in cellular immunity. As noted, the leprosy model shows strong contrast between the effectiveness of cell disposal of the leprosy bacillus. The tuberculoid macrophages do this chore well and no foam cells appear. The lepromatous cells, however, are markedly deficient in ability to break down and dispose of the bacilli. Bacillary lipid debris accumulates in the cells giving them a foamy structure. This debris stains with various lipid stains and studies of such cells suggest similarities with the storage phenomena seen in the lipidoses. Since in the latter entities inherent defects in cell enzyme systems seem to be responsible, the comparative studies suggest that the "immunologic" defect in lepromatous leprosy may in part at least be a cellular enzymatic deficiency which is not present in those patients who respond to the leprosy bacillus with the tuberculoid reaction. One finds, therefore, in the leprosy model a relation to the lipidoses and leprosy seems to present a bridging model for the study of the relationship of cellular enzymes to the processes of cellular immunity.

Other aspects of the leprosy model in brief. It has long been recognized that the skin lesions of leprosy appear predominantly on the extremities, face and buttocks, and there has been much speculation as to the reasons for this localization. It now seems of interest to recognize that the leprosy bacillus, being an organism of low virulence and invasive power, requires every advantage in order to establish leprous lesions. More vigorous pathogens may cause tissue damage and lesions almost wherever they land, but the leprosy bacillus succeeds best where natural barriers have already been breached. The long-known concept of *locus minoris resistentiae* thus seems to play a

significant role in that even slight increase in vascular permeability caused by pressure, irritations, etc., provides such opportunity for localization. Through its chronicity and need for such localization advantages, leprosy presents as a further model for the study of the relationship of such factors to the localization of disease.

It has also been long known that a major characteristic of leprosy is the involvement of peripheral nerves by the infection. This is so characteristic that it is largely responsible for the fact that leprosy is probably the greatest single crippling disease now existent. Again, there has been much speculation as to the reasons for this "predilection" for nerves. This, too, commends itself to study for not only would greater knowledge enhance the effectiveness of treatment but would probably result in greater understanding of the anatomy and physiology of these nerves. May it be that the leprosy bacillus spreads in perineural lymphatics and intraneural spaces, just as first infection tuberculosis spreads from the peripheral Ghon component to the hilar lymph nodes? In second infection tuberculosis such lymphatic spread is stopped, but in lepromatous leprosy it continues, if indeed this is the mechanism of nerve involvement. Why?

As a sequel to nerve involvement there is marked damage to bones of the extremities, and again much crippling and deformity results. Part of this osseous damage is explainable by secondary osteomyelitis, pressure atrophy, etc., but there are resorptive changes that defy such explanation. On the other hand, secondary to the neural involvement there is seen to be marked vascular alterations in the extremities. These seem to result in some of the reorganization of bone that takes place. Again, leprosy—and there is plenty of it—presents as an interesting and useful model to help in the understanding of the dynamics of bone pathology.

Finally, the social model. As populations age and individuals live longer, chronic diseases assume increasing importance in many areas. So does social reaction and attitudes to such chronic debilitations.

Of all disease, leprosy has attracted the greatest social reaction, unfortunately most of it in the form of horror, rejection and general opprobrium. It presents, therefore, as a model for study in also this area. Perhaps some understanding of the reaction to leprosy, extreme though it often is, may carry over into a better understanding of society and individuals and also to other chronic, deforming diseases.

In such an attempt we have formulated, as follows, a disease characterization that would seem most likely to call forth the extreme opprobrium to which leprosy has been subjected.

1. The disease manifestations should be *externally manifest*, i.e., readily recognized.
2. It would have an *insidious onset*, not appearing dangerous at first but perhaps easily confused with some other mild disease. This would give it opportunity to wax and develop—and to spread while yet unrecognized.
3. The disease would have a *prolonged course and be nonfatal.*
4. It would be *progressively deforming and crippling.* Perhaps no better way of achieving this can be conceived than of involving the peripheral nerves and setting up a series of sequellae involving vascular and bone damage in the extremities and face.
5. It would have a *long incubation* period. The sufferer, and society would then often not recognize its origin and primitive society especially might well conclude that such horror must be a special punishment from heaven for unusual wrongdoing.
6. The disease would have a *fairly high incidence.* A rare disease would be unlikely to provoke continuing opprobrium. An extremely common disease would not readily subject its victims to ostracism since too large a segment of society would be involved.
7. Its occurrence would be associated with a *low standard of living.* Societies with this status are more likely to be limited educationally and to foster superstitions and irrational beliefs.

It is evident that the above characterization is merely a summation of major characteristics of leprosy. It is also clear that none of the characteristics mentioned are

exclusive to leprosy. However, the total constellation of characteristics is unique to leprosy and leprosy therefore becomes the example of most extreme social opprobrium in most societies where it exists and this horror carries over into societies where its incidence may be low or diminishing.

Conclusion. It seems evident that leprosy, long neglected as a research and study model, presents many unique aspects covering broad fields of medical interest. As these are recognized and mined for their contribution to medical understanding much can be expected that will be beneficial to the sufferers from the disease and much understanding can be expected that will help also in the understanding of other disease. —O.K.Skinsnes