# Some Clinical Problems Awaiting Solution by Research

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Confronted as they are every day by patients who are never free from the risks of acute exacerbation and severe nerve damage in the course of years of treatment, clinical leprologists can never be complacent. It is the over-sanguine and superficial observer, be he physician or journalist, who is bemused by the relative successes of sulfone therapy and satisfied with the present state of therapeutic progress. It is not only questions of treatment that bristle with unresolved problems. Whenever a fundamental question is posed on some clinical aspect of leprosy, the only honest answers that can be given at present are at best equivocal and at worst confessions of ignorance.

My object in this paper is to indicate certain obvious and not-so-obvious clinical problems in leprosy that await solution. Many of these problems touch upon the domains of the dermatologist and the neurologist; most of them concern closely the immunologist and the biochemist. All of them present a challenge to some ancillary discipline allied to basic pathology, and all are related more or less directly to the intensely practical "theoretic" questions we

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have been lately considering. My clinical language will perforce be accompanied by pathologic undertones.

## THERAPY

Since, to the physician, the complete restoration of the individual patient to health is the ever-present goal, and since the patient's own desires to this end override any academic discussions revolving around the presence or the morphology of the presumably causative organism, we shall consider first a few problems of therapy.

While the average clinical and bacteriologic improvement in a group of leprosy patients who are apparently similar in all essential respects may be estimated, the variations between patients are considerable, and it is the individual unpredictability rather than the group consistency that is remarkable. Why should this be so?

I have occasionally been struck by the quite obvious lack of correspondence between clinical and bacteriologic improvement. Both the morphologic index and the bacterial index may, in the individual patient, lag many months behind the average, whereas the clinical picture may concurrently improve more rapidly than the average, and vice versa. What is the explanation?

A most pressing problem is the inordinate length of treatment required before clinical arrest of the disease can be expected—from four to eight years in lepromatous leprosy, and two to four in tuberculoid. This long period must somehow be shortened. But how? So far, attention has been concentrated on bacteriostatic or bactericidal agents effective in mycobacterial disease. In the matter of rate of reduction of the BI and MI there is not very much to choose between most of the drugs at present recognized as efficacious, and combinations of such drugs do not appreciably and demonstrably accelerate this rate. Given the lengthy generation time of *M. leprae* and its vulnerability to bacteriostatic agents, should not attention now be diverted to reducing the allergic reaction to mycobacterial antigen and to accelerating the removal of degenerating mycobacteria from sensitized tissues? It may be that proteolytic enzymes and other "opsonizing" agents might facilitate and hasten the removal of effete mycobacteria.

Drugs are rightly evaluated primarily for their effect on multibacillary disease; yet they act also in cases of paucibacillary disease, in which the main pathology is a vigorous tissue response in skin and nerves. In cases of borderline leprosy, not only do normal bacillary forms disappear rapidly under dapsone, but degenerate mycobacteria also disappear within a few months, and the clinical condition improves concurrently. The drugs appear to supplement or stimulate or potentiate some innate factor. In tuberculoid disease, drugs accelerate the normal tendency to spontaneous regression and repigmentation. How is this result achieved? Can we learn something from the cases of spontaneous regression of leprosy lesions that will point the way? Is it significant that such lesions may disappear even when the lepromin test is negative?

Another problem concerns the apparent inaccessibility of *M. leprae* in certain situations. So-called relapse or recurrence in lepromatous leprosy is probably due in the main to reactivation from foci of living bacilli in deep organs and between nerve fibers. When skin lesions are inactive, superficial nerve trunks may remain tender for long periods. Normal bacilli are recoverable from lesions in Glisson's capsule and the Kupffer cells and from nerves years after clinical arrest of leprosy. Are they invulnerable, or simply inaccessible?

Why do antileprosy drugs, often in minute doses, precipitate or provoke a recurrence of acute exacerbation in lepromatous leprosy? What is the active agent? Is it the drug, or a metabolite, or some antigen from degenerating *M. leprae*? The reaction occurs usually within 48 hours of the exhibition of the drug, and attempts at desensitization with a soluble sulfone (as for sulfone dermatitis) may be successful.

Is it possible that antigenic material released from degenerating mycobacteria, and as yet unstained and unidentified by standard procedures, is responsible for both local and generalized tissue sensitization?

Another problem: in lepromatous disease, generalized worsening may occur during standard treatment, with the more or less

sudden appearance of new lesions and an extension of the old. Or, perhaps after two or three years of treatment, and when all normal bacilli and all or nearly all degenerate forms have disappeared from the routine smears, a crop of small fleshy nodules may suddenly appear in the skin, containing innumerable morphologically normal *M. leprae,* in a kind of miniature incubator. Where do they come from, why do they appear, and why do they multiply?

Reactivation of nonlepromatous disease may occur also in the course of treatment, accompanied or not by increase in the numbers of *M. leprae.* Such exacerbations in major tuberculoid disease may be characterized by the sudden appearance of *M. leprae* (often in clumps of a dozen or so) and a temporary negativity of the lepromin test. What is the immunologic explanation of these events?

When the continuation of antileprosy treatment is impossible or inadvisable by reason of persistent exacerbation in lepromatous leprosy, the clinical condition may gradually improve, and concurrently fragmented *M. leprae* may progressively disappear from all sites smeared. If it could be ascertained without doubt that normal bacilli were no longer present in such patients, it might be ethically justifiable to withhold specific antileprosy drugs and observe the result. Can we ever be sufficiently certain?

Before we leave the question of therapy, the question may be asked: why should 3 per cent of deeply pigmented African patients evince sensitivity to dapsone (as shown by fixed or other eruptions), whereas the comparable figure among the lighter hued is one-thirteenth of this?

## NEUROLOGY

The overwhelming importance of nerve damage in leprosy has been sufficiently stressed, but fundamental clinical problems remain, some of which will be briefly indicated.

The restriction of nerve damage to certain peripheral nerves is noteworthy, but these nerves are involved much more extensively than is generally realized, as is shown by radioscopic visualization of the perineurial lymphatics. The sites of maximum clinical changes—enlargement, hardness, tenderness—are well known, but *M. leprae* are also present at other sites in the nerve trunks. What factors are common to the sites of predilection to make them particularly susceptible to damage?

Recent work on tagged isotope migration in axons, and distal arrest of the shunt at sites of recognized maximal predilection, may have a bearing on the polyneuritis of leprosy. The possible influence of temperature, trauma, and anatomic vulnerability deserves study.

Another line of probably profitable investigation concerns the similarities between experimental allergic encephalitis and polyneuritis, the polyneuritis of leprosy and the neuritides of the Guillain-Barré type. Perhaps one day it may be possible to embrace these diverse concepts in one unitary pathology, and determine the role of all possible factors on local antigen-antibody confrontation associated with some biochemical mycobacterial component.

An intriguing clinical feature of the polyneuritis of leprosy is the persistence of local nerve tenderness years after the disappearance of activity in the skin lesions and of distal neurologic changes. The *nervi nervorum* may be exposed to a lower threshold of painful stimuli by reason of antecedent ischemia and progressive fibrosis. Is this so?

The appearance of peripheral neuritis during treatment, or its exacerbation, the apparently fortuitous involvement of nerve modalities in any proportion and to any degree, the relative failure of corticosteroids to modify substantially the neural inflammation, the unpredictable results of nerve decompression (unlike decompression in the carpal tunnel or pedal tunnel syndromes)—all raise problems that call for investigation.

## ACUTE EXACERBATION

The management of acute exacerbation may tax to the utmost the patience and resource of both victim and medical attendant.

Its occurrence raises problems of intri-

guing interest. It may occur spontaneously and with no obvious precipitating cause in the untreated leprosy patient, or its onset may be postponed until well into the fourth year of successful therapy, when *M. leprae* are represented by rare collections of acid-fast dust in routine smears. Its duration, also, is variable—from a single brief self-limiting attack to one of the most exhausting and distressing of progressive conditions known to man. Its management ranges from the simplest to the most demanding. Anti-inflammatory agents, such as the antimonials and the antimalarials and chlorpromazine, sometimes act like a charm, and sometimes fail to act at all.

The theoretic problems raised by acute exacerbation as exemplified particularly by erythema nodosum leprosum are similarly wide-ranging.

Curiously, if ENL is a local sensitization phenomenon in which the panniculus bears the brunt of the reaction, why should it occur only in the completely Mitsuda-negative lepromatous patient? Why does it not occur in the patient with reactional tuberculoid disease whose lepromin reaction is temporarily negative?

Again, ENL never occurs in those forms of leprosy that clinically most closely resemble sarcoidosis, whereas in the latter condition erythema nodosum occurs at some stage in perhaps 30 per cent of cases.

Again, ENL has clinical features that place it at one extreme of the erythemata occurring in a great variety of toxic, bacterial, spirochetal, fungal and parasitic infections. Why the differences, and what accounts for them?

There are numerous close parallels between ENL in leprosy and the withdrawal panniculitis after corticosteroid therapy in such conditions as rheumatoid arthritis. In fact, the resemblances are so close as to suggest that recurrence and exacerbation of ENL during withdrawal of corticosteroids may be more closely related to suprarenal disturbance than to local tissue sensitization.

The tissue changes of progressive lepra reaction are occasionally reversible, the hard, dark, glistening, tender integument becoming almost normal. This is difficult to explain if these changes consist of post-inflammatory fibrosis and tissue destruction.

## MISCELLANEOUS CLINICAL PROBLEMS

This brief reference to some of the baffling problems confronting the clinical leprologist may be rounded off by posing a few deceptively simple questions.

Why is the skin lesion of leprosy typically hypopigmented in deeply-pigmented persons?

Why do leprosy lesions seldom occur in the inguinal region, in the axillae, on the scalp or in a narrow transverse band in the lumbosacral region, even though the rest of the body may be occupied by confluent lepromatous macules? Even when smears from those sites are highly positive, no obvious changes in the skin are present.

Why does leprosy often appear first during late pregnancy or after parturition? What is the precise nature of any hormonal factor involved?

Why is the gynecomastia of lepromatous leprosy sometimes unilateral? And why are the breast tissue, the areola and the nipple involved alone or in any combination?

Why, in view especially of the histologically demonstrable changes in the terminal fibrils, is local irritation so noticeably absent in leprosy lesions?

Does cutaneous pigmentation affect susceptibility to contract leprosy, or augment the tendency toward spontaneous regression, or decrease the lepromatous/tuberculoid ratio?

Why is leprosy as an infection so hard to catch and so easy to cure? If the allergic component were as simple to control and eliminate as *M. leprae* is apparently rendered incapable of multiplying *in vivo,* then many of our most pressing problems could be well on the way to solution, even though fundamental questions remain for the present unanswered.

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