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Growing Points in Leprosy Research

(2) Epidemiology

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In spite of limited progress in leprosy epidemiology over recent years, the opportunities for new and potentially fruitful approaches are now good. The need for further epidemiological work arises mainly from the failure, so far, to achieve the primary prevention of leprosy on any meaningful scale by any of the means theoretically available, including the interruption, by means of environmental changes, of its transmission. Re-awakened interest in the nose as the likely source of infection in leprosy, new information on the probable survival time of *Myco. leprae* outside the body, epidemiological similarities between leprosy and tuberculosis, and anthropological methods for measuring contacts between leprosy patients and their family and social circles, are points which should help in the design and conduct of studies of the environmental and other factors, besides *Myco. leprae* itself, involved in leprosy transmission. The potential value of lymphocyte transformation testing as a way of identifying those infected by *Myco. leprae* calls for further intensive study, much of it by epidemiological means. Another field in which the epidemiologist must collaborate with workers in different disciplines is in assessing the effectiveness of chemotherapy, whether by sulphones or newer preparations such as rifampicin, and in keeping the question of antibiotic resistance in leprosy under review.

The Committee on Advances in Epidemiology of the Tenth International Leprosy Congress in Bergen, 1973, concluded that there had been few major developments in the epidemiology of leprosy in the previous five years. Its forecast for the future, however, was more optimistic, reflecting the real new opportunities for epidemiological work in leprosy that now exist. Many of the potential openings depend on testing and exploiting recent technical developments and progress in other disciplines. In this respect, leprosy is in the same position as many other chronic diseases for which population-based study methods are appropriate—that further progress depends largely on working links between epidemiologists and those with other skills, the contribution that the epidemiologist on his own can now make being rather limited.

Leprosy Control

What can and ought to be done by epidemiological methods is largely determined by the present world leprosy position, and the interpretation of what has been achieved since the widespread introduction of the sulphones in the late 1940s and early 1950s.

Without doubt, many assumed that sulphones would be effective not only in treating patients with clinically manifest leprosy, but also in preventing the spread of the disease to others. This hope was partly based on the decline in tuberculosis observed in many (mostly economically developed) countries after the introduction of streptomycin. This particular comparision was, of course, inappropriate since mortality from tuberculosis in many of the Western countries concerned had been falling for some years before streptomycin became available. Vital statistical data on tuberculosis and leprosy for countries where both were endemic were simply not available at the start of the antibiotic era, but it is unlikely that similar changes in tuberculosis mortality were occurring in these non-Western countries. Circumstances in which comparisons between the two diseases may or may not be helpful need careful thought; an example is discussed later.

At all events, the phrase "leprosy control" has, by common usage, come to have at least two different meanings, and the resulting confusion has created difficulties that are only now being resolved.

On one hand, the term has been applied to mass treatment programmes whose chief objectives have been the detection and treatment of as many people with leprosy as possible, the potential benefit to the *individual patients* concerned being the reason for these programmes. There is little doubt that these schemes have generally succeeded in their main purposes, by providing treatment for those who would otherwise not have received it, and in most cases by reducing the prevalence of the disease. Nevertheless, only limited efforts have been made formally to assess the impact of mass case detection and treatment. While information on bacteriological changes following sulphones is available, comparatively little has been done to measure clinical and social costs and benefits. This subject, developing rapidly in relation to other diseases and the health services of many countries, assumes much more than academic importance with the arrival of rifampicin, the first bactericidal anti-leprosy antibiotic. For, vastly expensive as this drug is compared with dapsone, the indications are that it may have to be used for much shorter periods than the latter. If established, this development could mean potentially large savings in long-term projects based on dapsone, and the ability to divert resources into other health services. These changes are, of course, not by any means certain, but their possibility is something that leprosy epidemiologists with interests in applied aspects need to be aware of in the coming years—and if they do occur, the cause of integrating leprosy services into general health services will be considerably advanced. There are, of course, many schemes around the world that could study problems and developments in this field.

On the other hand, "leprosy control" has been used in a primary preventive sense to suggest that leprosy incidence (i.e. the rate at which new cases appear) might also decline as a result of treating established cases; in this instance, it is the benefit to *those at risk but hitherto unaffected* that is under consideration. Whether or not mass treatment programmes have accomplished this as well as helping those with clinical leprosy is still an open question. On the whole, however, the consensus view is that incidence has not declined in areas where such programmes have been in operation.

If we assume, therefore, that primary prevention is not likely to be achieved by the chemotherapy of overt disease (and this is the only safe assumption in the absence of firm evidence), what other possibilities are there? First, vaccination;

the results of the three major BCG trials are now well-known. In Uganda (Brown, Stone and Sutherland, 1968; Stone and Brown, 1973), protection against leprosy by BCG is about 80%, in New Guinea (Scott and Wigley, 1966; Russel, 1973) about 50%, and in Burma (Bechelli *et al.*, 1970, 1973 *a, b*) about 20%. (Different levels of protection occur at different ages; the figures given are for all ages studied.) These results refer to tuberculoid disease; virtually no information on protection against lepromatous disease is available. Overall, it is difficult to assess the impact that BCG (which most health services probably want to use against tuberculosis anyway) would have on leprosy incidence. The development of a specific anti-leprosy vaccine is obviously desirable, but not very likely at present.

Secondly, chemoprophylaxis is effective in reducing leprosy incidence (Dharmendra, Noordeen and Ramanujam, 1965, 1967; Noordeen, 1969), but calls for the long-term administration and taking of dapsone in doses which (in leprosy patients, at least) are associated with the development of resistance. As a means of preventing leprosy in isolated (e.g. island) communities, chemoprophylaxis may be effective and feasible (Sloan *et al.*, 1971), but its long-term effectiveness and practicability in endemic areas is obviously doubtful.

Finally, leprosy workers suprisingly often overlook the historical lesson that the modification of environmental factors favouring the spread of infectious diseases has been successful in their prevention much more frequently than individually-directed measures (such as immunization). Indeed, this has already happened with leprosy, in so far as the disease disappeared from previously endemic areas (such as Northern Europe) for reasons which, though quite unclear, were almost certainly nothing to do with steps taken by, or directed at, specific individuals in the population at risk. In fact, one of the great advantages of identifying and modifying the environment in which an infectious disease spreads is that changes can often be made (e.g. in water supplies) which do not require the active participation of the whole population. It is to this area of study that leprosy epidemiology is now increasingly turning, through studies of the way in which leprosy is transmitted, and of factors associated with susceptibility or immunity to the clinical disease.

Transmission

The often-quoted assertion that leprosy is transmitted by prolonged, intimate skin-to-skin contact has never been tested. This postulated view of the mode of spread was probably largely derived from the obvious cutaneous clinical signs of the disease. That *Myco leprae* can be recovered from several tissues has been known for a number of years, but it is only recently that interest in the nose and nasal secretions as sources of infection has been re-awakened. Thus, Pedley (1970, 1973) has convincingly demonstrated that not only are insignificant numbers of bacilli shed from the intact skin of lepromatous patients (they are shed from broken skin lesions—these, however, are unusual) but that very large numbers are shed from the nose and upper respiratory tract; the acid-fast bacilli concerned have been identified as *Myco. leprae* (Rees and Ridley, 1973). Moreover, it also appears (Barton *et al.*, 1973) that the clinico-pathological changes in the nose are often more advanced than might be expected from the extent and degree of neural and cutaneous involvement.

Together, these findings begin to build up a composite picture for the possible mode of spread of leprosy that has not hitherto been available, at least on the

basis of scientific evidence (Davey and Rees, 1973). For not only do they suggest a source of infection—they also offer a potential explanation for the apparent failure of chemotherapy in overt disease also to assist with the primary prevention of leprosy in endemic areas. The early lepromatous patient, shedding millions of *Myco. leprae* from nasal lesions disproportionately advanced compared with other manifestations of the disease, may perhaps infect as many people in his family and social circle as he can before he is diagnosed; his treatment may by then be largely irrelevant so far as his ability to spread the disease further is concerned. On this basis, the only way in which chemotherapy could prevent as well as cure would be if a high proportion of lepromatous patients, often with little or nothing in the way of skin manifestations, were diagnosed at the early stages of nasal involvement—from a practical viewpoint, a difficult task.

Spread involves not only a source of infection, but also a portal of entry. Here, analogies with tuberculosis may be helpful. Clearly, *Myco. leprae* could be spread by sneezing, coughing, spitting and unhygienic nose-cleaning methods—in many respects, therefore, by way of droplets as in tuberculosis. In this context, therefore, the figures in Table 1, showing great similarities in bacterial loads from the nasal secretions and sputum of patients with lepromatous leprosy and open tuberculosis respectively are of considerable interest. Clearly, the portal of entry could still be the skin, but equally, *Myco. leprae*-laden particles could also be inhaled or swallowed. Table 2 compares attack rates for the two diseases in household contacts; again, the figures are of the same general order, especially in the younger age-group. Clearly, these comparisons prove nothing, but they do suggest, really for the first time, scientific ways of studying leprosy transmission,

TABLE 1

Mean numbers (log_{10}) of viable Myco. leprae. *and* Myco. tuberculosis *in nose-blows or sputum*

Organism and source	No. of observations	Mean (log_{10})
Myco. leprae 24-h nose-blow output	13	6.95
Myco. leprae single nose-blow	17	6.84
Myco. tuberculosis 12-h sputum output	107	7.69

Adapted from Rees and Meade (1974).

TABLE 2

Average annual age and sex-specific attack rates for tuberculosis and leprosy in family contacts, S. India

Age	Male		Female	
	Tuberculosis	Leprosy	Tuberculosis	Leprosy
0-4	4.0	4.4	3.8	5.6
5-14	1.8	7.3	1.6	2.1

Adapted from Rees and Meade (1974).

and they are certainly compatible with a mode of spread for leprosy similar to that of tuberculosis. The openings here for the epidemiologist, either in collaboration with the microbiologist, or at least with awareness of work in this field, are obvious. They should also be enhanced by the results illustrated in Table 3, which indicate the likely length of time that *Myco. leprae* can survive outside the body. Prospective incidence studies of leprosy, necessary to elucidate the "risk factors" associated with the onset of clinical disease (Meade, 1971) should obviously consider information of this sort in planning what variables might usefully be studied, and how they could be measured. Table 3 suggests, for example, that since *Myco. leprae* can probably survive 2 or 3 days outside the body, the lepromatous patient and the person he infects need not be in the same place at the same time; Hausfeld (1970) has described how contacts outside (as well as within) the immediate family circle can be measured in ways that could usefully take account of the distribution of survival times of *Myco. leprae* outside the body.

TABLE 3

Survival of Myco. leprae *in dried nasal secretions*

Exposure to drying (Days)	Viability (infectivity for mice, %)	No. of tests
0	100	3
1.0	100	3
1.75	10	2
3.0	0	2
7.0	0	1
10.0	0	1

Mean temperature: 20.6°C; mean humidity: 43.7%.
Rees, 1973 (personal communication).

End-points; Infection and Clinical Disease

One of the leprosy epidemiologist's problems has always been the definition of "end-points" in relation to the onset and diagnosis of leprosy. The appearance or non-appearance of clinical leprosy as an end-point suffers the disadvantages that, first, diagnosis is often difficult, especially in the early stages, and secondly that the appearance of clinical disease is obviously the final stage in a process of infection and its sequelae that may have been going on for many years. The lepromin skin test may (or may not) be of value in forecasting susceptibility to lepromatous disease, but cannot be interpreted, as the tuberculin test can, as an index of previous infection (or artificial protection). Thus, the development of lymphocyte transformation testing (Godal and Negassi, 1973) is of great potential importance. If this technique is as specific for infection by *Myco leprae* as early results indicate, it offers a means whereby those who have been infected can be identified and also of comparing those infected who do or do not go on to clinical disease. A good deal of work needs to be done before the technique can be accepted as valid, and much of it will have to be in the field, the epidemologist working closely with the immunologist. Apart from specificity for *Myco. leprae*, the reproducibility of the technique needs study; assuming these are satisfactory (and that the method can be adopted for field conditions—a difficult, though

probably not impossible task) information on the proportions in endemic areas with positive tests is crucial. For if virtually the whole of a population shows transformation at very early stages (to take a somewhat extreme example) the discriminatory value of the technique would be limited, since all it would really show is that most people have been infected, and the problem of which individuals succumb to clinical disease and which do not would remain. The finding of more gradual changes in positive responses by age, however, with the consequent identification of distinct infected and uninfected groups, might well make the technique as valuable as tuberculin testing in tuberculosis. The possible effects of "superexposure" (Godal and Negassi, 1973), arising from prolonged exposure to lepromatous disease, in giving false negative lymphocyte transformation results clearly calls for intensive study, also in field surveys.

At the same time, the value of clinical disease, or its absence, should not be overlooked as an end-point. What matters to the individual is not whether he has been infected or not, but whether he has clinical leprosy. There are other examples, such as ischaemic heart disease or lung cancer, where the clinical end-point, rather than the pathological, has had to be used (for obvious reasons) without obscuring epidemiological associations between these diseases and their postulated causes.

Resistance to Sulphones

Finally, the leprosy epidemiologist must play an increasing part in studying the emergence of resistance to sulphones. This development has been known for several years, and was to be expected (again, by analogy with tuberculosis) in a monotherapeutic situation. Whether the sulphone resistance problem will become a major one is difficult to foresee; it turns out that because of the very long time-periods needed for reasonably complete data-collection, it is difficult to say whether intervals from the start of chemotherapy to resistance are falling (as many believe they are) and even more difficult to tell whether the incidence of resistance is increasing, and if so, at what rate. Relative youth at the start of treatment, and treatment with low doses of sulphones are associated with the later emergence of resistance (Rees *et al.*, 1973), and it is almost certain that other associations can be identified by properly designed and conducted studies. The whole crucial problem of sulphone resistance is not one that the clinician, microbiologist, epidemiologist or statistician can solve on his own, and is yet another example of the way leprosy research on any particular issue is increasingly involving several disciplines. The same is true of the clinical trials that are now needed (partly, though not entirely, as a result of the growing concern over the potential implications of sulphone resistance) to assess the clinical and microbiological effects of rifampicin, and the most effective ways of using it in a service context.

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