Immunology, Epidemiology and Social Aspects of Leprosy
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EPIDEMIOLOGY OF LEPROSY

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1. Introduction

The control of leprosy through a better understanding of the epidemiology of the disease is beset with several problems, some relating to the inadequacy of the tools for use in the field, and others resulting from the peculiarities of the disease itself. Furthermore, the lack of standard terminology for defining the disease and its classes, the need for long-term investment in efforts, and the generally low priority given to the disease in several countries have added to the frustration of the epidemiologist in this field.

2. Distribution of Leprosy in Space and Time

2.1 *Geographic distribution*

The geographic distribution of leprosy in the world is shown in Figure 1. The estimated total number of leprosy patients in the world varies from 10 to 12 million. The last estimate made by WHO in 1975, was about 10.6 million (Sansarricq, 1981). Since then, in spite of variations in certain countries, the total estimate for the world appears to remain at about the same level.

Of the estimated cases, Asia contributes to the largest share with about 62 per cent, followed by Africa with about 34 per cent, South America with about 3 per cent, and the rest of the world with about 1 per cent. However, in terms of intensity of the disease in the population, that is, mean prevalence by continent, the problem is about

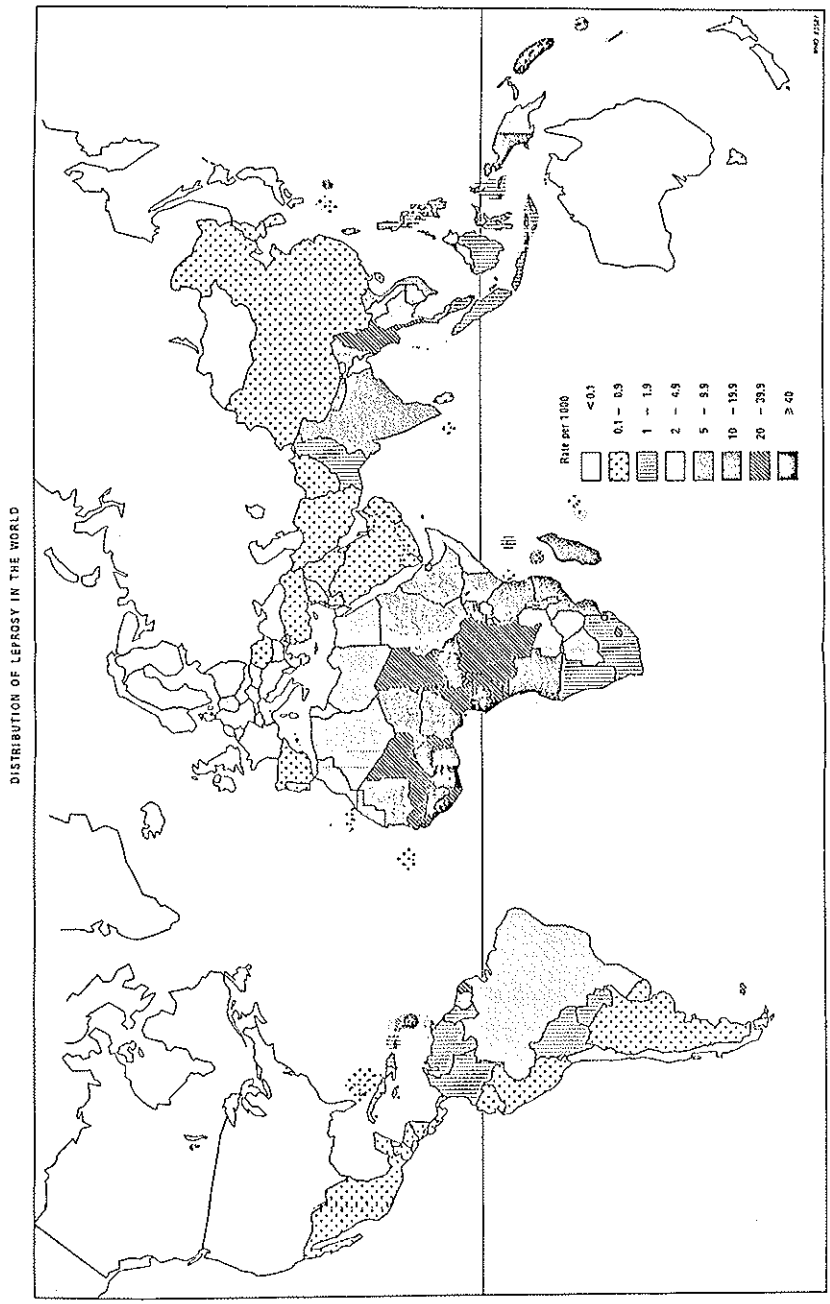
DISTRIBUTION OF LEPROSY IN THE WORLD
Rate per 1000
< 0.1
0.1 – 0.9
1 – 1.9
2 – 4.9
5 – 9.9
10 – 19.9
20 – 39.9
≥ 40

FIG. 1

three times as intense in Africa as it is in Asia. Almost one billion people in the world live in high endemic areas where the prevalence of leprosy is at least one per 1000.

In countries where leprosy is endemic, the prevalence rates show marked variations, with rates ranging from below one per 1000 to over 50 or more per 1000. Considerable variations in prevalence are known to exist within countries and even between adjacent areas. In fact, the uneven nature of the distribution of the disease appears to be a characteristic of leprosy.

An interesting feature of leprosy is the geographic variation seen in the occurrence of lepromatous leprosy, as indicated by the proportion of lepromatous cases over total cases, and often expressed as lepromatous rate. This rate varies from below 5 per cent to over 70 per cent in different parts of the world.

2.2 *Age Distribution*

Leprosy is known to occur at all ages, ranging from early infancy to very old ages. The youngest case seen by the author was in an infant of two and a half months, where the diagnosis of tuberculoid leprosy was confirmed by histopathology. Occurrence of leprosy, presumably for the first time, is not uncommon even after the age of seventy.

Figure 2 shows the age-specific incidence rates in a part of South India where leprosy is highly endemic. The pattern is very similar to that seen in many high endemic areas, where there is a clear peak at ages 10-14, followed by a depression which in turn is followed by a rise and a plateau covering ages 30-60. The bimodal curve in high endemic areas suggests the possibility of two distinct experiences, one among children and the other among adults. In the absence of specific immunological tools to measure subclinical infection, one can only speculate on the assumption that the disease occurrence parallels the acquiring of infection. Even so, it is difficult to accept that a large number of persons in high endemic areas acquire infection and disease for the first time at a late age. There are two possible explanations for this. One is that the incubation or latent period is very long in a proportion of infected individuals, resulting in manifestation of disease late in their lives, possibly somewhat similar to endogenous reactivation in tuberculosis. The other explanation is that leprosy in adult life in endemic areas is often the result of re-infection or superinfection among individuals who had previously been infected

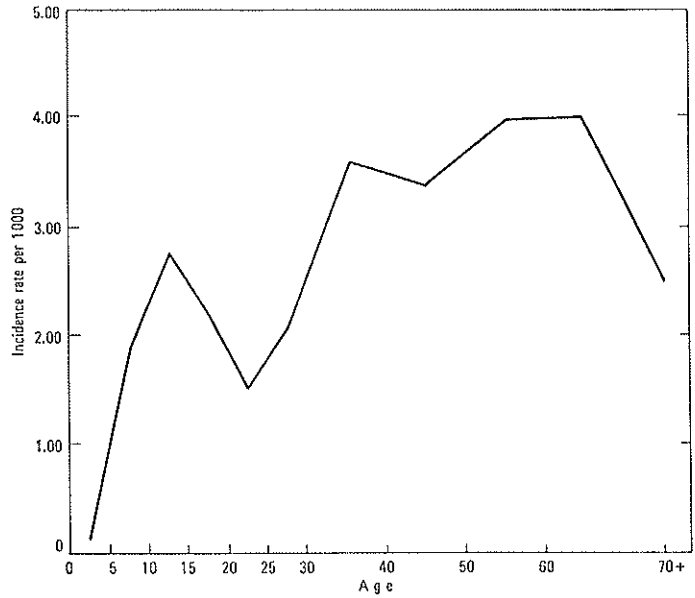

FIG. 2. Age-Specific Incidence of Leprosy in South India.

and whose immune response to leprosy had become inadequate as they grew older. In either case, in the absence of a specific method for identifying sublinical infection and strain variations of *M. leprae*, the hypotheses will remain untested.

2.3 *Sex distribution*

Although leprosy affects both sexes, in most parts of the world males are affected more frequently than females, often in the ratio of 2:1. This preponderance of males is observed in as diverse geographic situations as India, Philippines, Hawaii, Venezuela and Cameroon. Doull *et al*, from their studies in the Philippines, have also pointed out that the difference was a true difference due to higher incidence among males, and not due to differing duration of disease for the two sexes.

2.4 *Clustering of leprosy*

The more frequent occurrence of leprosy in certain clusters, particularly family clusters, is well recognized. However, the most debated point is whether this is due to the clusters sharing the same environment or the same genetic predisposition, or a combination of both. The occurrence of leprosy in clusters has been particularly observed in low endemic areas, and well documented in Norway and Louisiana.

2.5 *Time trends in leprosy*

Just because leprosy as a disease has a chronic course, it is often assumed that the epidemiological situation in any area remains static. In fact, the epidemiological situation is capable of a considerable amount of dynamic changes, and the factors that influence these changes are many. Both long-term and short-term trends have been studied with regard to occurrence of leprosy.

2.5.1 *Long-term trends*

In Northern Europe, continental United States, Venezuela, Japan and Hawaii, there have been well-documented studies on decline in incidence of leprosy leading gradually to virtual disappearance of the disease in the native-born population. In northern Europe the peak was reached in medieval times, with the decline occurring last in Norway during the 19th century (Irgens, 1980). Careful analyses of declining incidence rates in Norway, Hawaii and Japan reveal several features which are similar to those of tuberculosis under similar circumstances, including (a) a gradual increase in the mean age at onset of disease over time, (b) a decrease in age-specific incidence rates within successive cohorts associated with a fall in the mean age at onset, and (c) a gradually increasing proportion of the lepromatous type over a period of time among incidence cases.

2.5.2 *Short-term trends*

Among short-term trends the well-documented leprosy epidemic at Nauru Island in the Pacific is unique in many ways (Wade and Ledowsky, 1952). It showed that, although leprosy is generally an endemic disease, occasionally it is capable of reaching epidemic proportions when conditions are favourable. The disease was probably

introduced into Nauru for the first time in 1912 by a patient from the nearby Gilbert Island. By 1920 there were four known cases, and by 1924 at least 24 per cent of the population of 1200 were known to have been affected. The sudden increase followed an epidemic of influenza. The disease started declining after 1927 and by 1952 only 4 per cent of the population were affected, and this had declined to less than 1 per cent by 1981. Less dramatic outbreaks have been reported from Eastern Nigeria, New Guinea and the Pacific Islands of Ponape and Truk.

The short-term outbreaks reported so far have certain common features. They include occurrence of disease in an unselected manner throughout the community irrespective of age, sex and household contact status, and the type of leprosy which was mostly tuberculoid with a high tendency for spontaneous healing.

2.6 *Occurrence of deformities*

The occurrence of deformities in leprosy is one of the important concerns about the disease. About one-fifth to one-third of leprosy patients develop deformities of varying degrees. Deformity in leprosy is not only permanent, but in many instances also progressive even after the disease has become inactive. This is largely due to the component of sensory loss that occurs with the disease. The proportion of deformity is higher in lepromatous leprosy than in non-lepromatous leprosy, resulting from the progressive nature of the former type. In addition to physical deformities, and mainly as a result of them, leprosy patients in many societies suffer from an additional burden of social disability due to the stigma attached to the disease.

3. The Prevalence Pool

The prevalence pool of leprosy in a population in general is in a constant flux resulting from inflow and outflow. The inflow is contributed to by the occurrence of new cases, relapse of cured cases, and immigration of cases. The outflow is mainly through cure, death, and emigration of cases. Of the various factors that influence the prevalence pool, the importance of spotaneous inactivation of disease and mortality are less well recognized.

3.1 *Inactivation of Disease*

Where leprosy treatment facilities exist, inactivation or cure due to specific treatment is an important mode of elimination of cases from the prevalence pool. Even in the absence of specific treatment, a majority of patients, particularly of the tuberculoid and indeterminate types, tend to get cured spontaneously. A study in Culion Island in the Philippines showed that, among children, self-healing occurred in 77.7 per cent of cases (Lara *et al*, 1956). A later study in South India involving long-term follow-up of a high endemic population (Noordeen, 1975) showed that, among newly detected tuberculoid cases of all ages and both sexes, the rate of inactivation was 10.9 per cent per year, the bulk of inactivation in the study being spontaneous (Table 1).

TABLE 1 – *Inactivation of tuberculoid leprosy by age*

Age group in years	Total cases	No of cases inactive	Inactivation Rate per year %
0–9	47	24	14.6
10–19	72	24	9.5
20–29	41	18	12.5
30–39	45	14	8.9
40–49	30	11	10.5
50 and over	35	12	9.8
TOTAL	270	103	10.9

3.2 *Mortality in Leprosy*

Mortality in leprosy is often considered unimportant because the disease is rarely an immediate cause of death. However, leprosy patients are exposed to increased mortality risks due to the disease's indirect effects. In a study in Cebu, Philippines (Guinto *et al*, 1954), it had been found that the mortality rate for lepromatous patients was four times more than that of the general population, and that the situation for non-lepromatous patients was very similar to that of the general population. A comparative study of lepromatous patients,

non-lepromatous patients, and general population from the same rural area in South India (Noordeen, 1972) showed that the standardized death rate for lepromatous patients was three and a half times that of the general population, the non-lepromatous patients themselves having a mortality risk which was twice that of the general population (Figure 3). In that population, leprosy was found to contribute to about 1 per cent of all deaths.

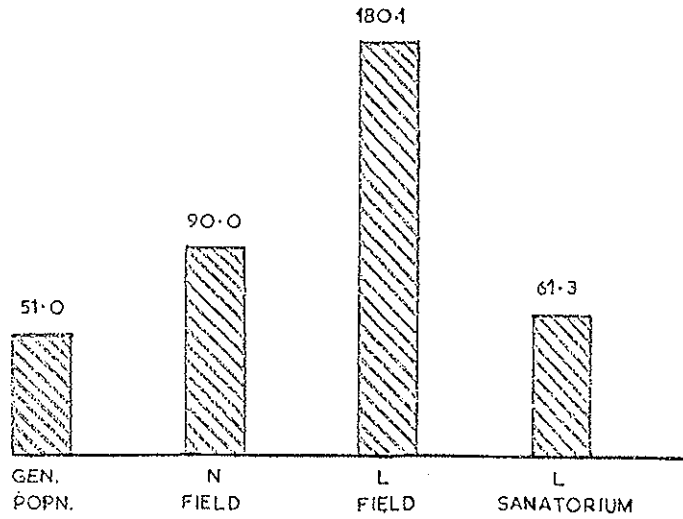

FIG. 3. Standardized death rates (per 1000 for 6 years) among general population, non-lepromatous cases (N) from the field, lepromatous cases (L) from the field, and lepromatous cases from the sanatorium.

4. Transmission Factors

4.1 *General Considerations*

There are several constraints in studying the transmission of leprosy. Unlike many other communicable diseases, in leprosy there is considerable difficulty in identifying the three reference points that are involved in the transmission of the disease, these being the onset points of exposure, infection and disease. The problem with the onset point of exposure relates mainly to the clear identification of the source of infection, which is not always easy. The problem with the onset point of the disease is related mainly to the insidious nature of the onset of the disease in most instances. The identification of the point of onset of infection is the most important and most difficult problem in the study of transmission. Although the future in this area appears to be very promising with the availability of specific and sensitive tests, at present there is no test dependable enough to measure sub-clinical infection with sufficient sensitivity and specificity for use in epidemiological studies. Until such a test becomes available the epidemiological picture of leprosy will remain incomplete.

4.2 *Reservoir of Infection*

The only known reservoir of infection in leprosy is the human being. However, a naturally occurring disease with organisms indistinguishable from *M. leprae* has also been detected among wild armadillos in parts of Southern United States (Walsh *et al*, 1981), though the epidemiological significance of the animal is generally considered to be negligible. Among human beings it is the lepromatous cases that carry the largest load of organisms, with the maximum load reaching over seven billion organisms per gram of tissue. Patients of non-lepromatous leprosy carry a very much smaller bacillary load, probably not exceeding one million organisms in total. In addition to clinically identified cases, occurrence of AFB in the skin (Figueredo *et al*, 1949; Chatterjee, 1976a) and nasal mucosa of healthy subjects (Chacko *et al*, 1979) have also been reported. The evidence that the AFB found on such "carriers" is *M. leprae* is not conclusive, although there is some evidence that persons who carry such AFB have a higher chance of developing the disease as was found during their follow-up (Chatterjee *et al*, 1976b).

4.3 *Portal of Exit of* M. leprae

The two portals of exit of *M. leprae* often described are the skin and the nasal mucosa. However, the relative importance of these two portals is not clear. It is true that the lepromatous cases show large numbers of organisms deep down the dermis. However, whether they reach the skin surface in sufficient numbers is doubtful. There is no doubt that when lepromatous patients have ulcers from the breaking down of nodules, or when they have other breaks in their skin, large numbers of organisms could be discharged. It is also possible that, apart from breaks in the skin, small numbers of organisms escape to the surface of the skin along with sweat and sebaceous secretions. Regarding the nasal mucosa, its importance had been recognized as early as 1898 by Schaffer (1898), particularly that of the ulcerated mucosa. The quantity of bacilli from nasal mucosal lesions in lepromatous leprosy has been demonstrated by Shepard (1960) as large, with counts ranging from 10,000 to 10,000,000.

4.4 *Portal of Entry*

The portal of entry of *M. leprae* into the human body is not definitely known. However, the two portals of entry seriously considered are the skin and the upper respiratory tract.

With regard to the respiratory route of entry of *M. leprae*, the evidence in its favour is on the increase in spite of the long held belief that the skin is the exclusive portal of entry. Rees and McDougall (1977) have succeeded in experimental transmission of leprosy through aerosols containing *M. leprae* among immune-suppressed mice, suggesting a possible similarity among humans.

4.5 *Subclinical Infection in Leprosy*

Although reliable tools for a routine study of subclinical infection in leprosy have yet to be made available, limited studies based on measuring immune-response in healthy subjects have indicated that a much larger proportion of persons exposed to leprosy than those seen with the clinical expression of the disease acquire infection.

Godal in 1973 was the first to measure CMI response through the lymphocyte transformation test among different categories of persons exposed to leprosy. He found that the test was showing a gradation of

response among Europeans visiting Ethiopia according to the period of their stay and their proximity to leprosy patients. Contacts of leprosy patients also showed a high rate of response to LTT.

With regard to the humoural antibody response, Abe (1980) has applied his indirect fluorescence (FLA-ABS) test among different categories of the population of Okinawa. The test was found not only to be positive in 100 per cent of polar lepromatous and borderline lepromatous patients, 88 per cent of borderline tuberculoid patients and 77 per cent of polar tuberculoid patients, but also positive to the extent of 92 per cent among household contacts. None of the heatlhy non-contacts or patients with pulmonary tuberculosis were positive to the test.

In addition to the above, skin tests with various preparations of lepromin, and more recently with soluble antigens from *M. leprae*, have also provided useful information on the occurrence of sub-clinical infection, although the specificity of these tests, particularly of the integral lepromin, has been rather questionable. Zuñiga *et al* (1982), using the soluble skin antigen prepared by a method developed by Convit, have found that the skin test positivity in a part of Venezuela was 19 per cent among non-household contacts and 48 per cent among household contacts.

4.6 *Method of Transmission of Leprosy*

The exact mechanism of transmission of leprosy is not known. At least, until recently, the most widely held belief was that the disease was transmitted by contact between cases of leprosy and healthy persons. More recently the possibility of transmission by the respiratory route is gaining ground.

The term "contact" in leprosy is generally not clearly defined. All that we know at present is that individuals who are in close association or proximity with leprosy patients have a greater chance of acquiring the disease. However, it is the definition of contact by early workers with qualifications such as "skin to skin", "intimate", "repeated", etc., that has made it appear as if the disease could be acquired only under such conditions, and that the transmission involved some kind of "inunction" or "rubbing in" of the organisms from the skin of affected persons into the skin of healthy subjects.

There is considerable evidence that household contacts of leprosy are at high risk of infection and of disease. A large population-based

study in the Philippines was the first to provide age standardized attack rates for clinical leprosy per 1000 persons/years of observation according to type of primary case. In non-contacts, contacts of "neural" (non-lepromatous) and "cutaneous" (lepromatous) cases, the attack rates were 0.83, 1.6 and 6.23 per 1000 years of observation respectively (Doull *et al*, 1942). Later studies have confirmed this trend as was seen in South India (Table 2).

TABLE 2 – *Incidence by Contact State*

Contact State	Number Exposed	New cases in 5 years	Incidence per 1000 per year	Relative Risk
Non-Contacts	186,047	1,723	1.85	1
Contacts of non-lepromatous cases	11,173	379	6.78	3.7
Contacts of lepromatous cases	1,025	90	17.56	9.5
Contacts of both types	12,198	469	7.69	4.2

An interesting observation with regard to risk for contacts, is the exceptional situation in Europe, where immigrant cases and Europeans, who had returned home after acquiring leprosy in endemic countries, have failed to produce secondary cases among their contacts. There is as yet no plausible explanation for this. The other interesting observation in many studies is the observance of a relatively low rate of conjugal transmission.

In endemic areas, the observance of high risk for contacts should not lead to underestimation of the importance of the non-contact population in terms of their contribution to the total yield of new cases. Even with a relatively low risk, the non-contact population contributes to a larger share of new cases solely because of its large size in comparison with the contact population. Even in highly endemic areas, the contact population contributes to less than 15 per cent of the total population, and even with the increased risk its contribution to the total new cases is less than 25 per cent, the rest of the 75 per cent or so of new cases coming from the non-contact population, which has a relatively low risk.

With regard to contacts of non-lepromatous cases, although they have a low risk relative to contacts of lepromatous cases, their risk is still higher than that for non-contacts. Even with a relatively low infectivity, non-lepromatous cases contribute to as many or more new cases as lepromatous cases. This is because of the much larger proportion of non-lepromatous cases which, therefore, contribute to a much larger share of the total contact population. Thus, the collective potential of non-lepromatous cases as sources of infection should not be underestimated.

5. Factors Determining Clinical Expression After Infection

5.1 *General Considerations*

There is sufficient evidence in leprosy to show that all people who get infected do not develop the disease. The factors that determine clinical expression after infection appear to be as important as the factors that determine infection after exposure. Of the many possible factors that determine clinical expression of disease, a few are discussed below.

5.2 *Genetic Predisposition*

Although the relative contribution of genetic host factors versus environmental factors is still far from clear, both twin and family studies indicate an important contribution of host genetics to the type of disease developing after infection. Whether genetic factors also contribute to differential susceptibility to infection with *M. leprae*, or to the development of clinical leprosy irrespective of the type, is less clear. There is now ample evidence that HLA-linked genes influence the development of tuberculoid leprosy (de Vries *et al*, 1981) and evidence has recently been presented for HLA-linked control of lepromatous leprosy (van Eden, 1983). These HLA-linked genes do not seem to control susceptibility to clinical leprosy *per se*, but rather to determine the type of disease to develop.

5.3 *Route of Infection*

Recent studies by Shepard *et al* (1982) in the mouse foot-pad model suggest that the route of entry of the organism may, to some extent, determine the occurrence of leprosy. This is based on the

observation that while intradermal administration of killed *M. leprae* sensitizes the animal, intravenous administration of killed *M. leprae* tends to tolerize the animal as studied through skin test reactivity. This also raises the possibility of tuberculoid and lepromatous leprosy being the result of different routes of entry of the organisms.

5.4 *Re-infection*

The occurrence of leprosy, presumably for the first time, in older individuals in endemic areas has raised the possibility of re-infection in these individuals, as it is difficult to believe that they remained uninfected for such a long period in an endemic area. However, this occurrence in the older ages can also be explained by the possibility that the disease in these persons represents reactivation of old undetected primary disease following waning of previous acquired immunity. As there is no evidence of a distinct primary disease occurring in leprosy as in tuberculosis, the hypothesis of re-infection gains some importance. Further, the occurrence of relapse in lepromatous leprosy also suggests, at least in a proportion of relapsed individuals, the possibility of re-infection. There is nothing against these immune deficient inactive patients living in endemic areas succumbing to fresh infection. In the absence of a method for identification of strain variations of *M. leprae*, the hypothesis on re-infection will remain untested.

5.5 *Prior Infection with Other Mycobacteria*

There is some evidence that prior infection with the atypical environmental mycobacteria and possibly *M. tuberculosis* influence the occurrence of leprosy. BCG vaccination itself is known to provide a degree of protection against leprosy as shown in Table 3 (Sundaresan, 1982; Scott *et al*, 1982; Stanley *et al*, 1981; and Tripathy, 1983). This is possibly due to the antigenic overlap between *M. leprae* and other mycobacteria. The varying degrees of protection given by BCG against leprosy in different geographic areas, and the limited protection seen among natural tuberculin positive reactors in the BCG study in Uganda (Stanley *et al*, 1981), support this possibility. Rook *et al*, (1981) have gone further and have suggested that the protective efficacy of BCG in different areas may get enhanced or diminished, depending upon the local environmental mycobacteria, some acting synergistically with BCG and some antagonistically.

TABLE 3 – *Major Field Trials with BCG*

Country	Control			BCG			
Number of Study Subjects	Person-Years	New Cases	Incidence ‰ per year	Person-Years	New Cases year	Incidence 0/00	Protection %
BURMA (28 220)	151 060	831	5.5	151 415	663	4.4	20.4
NEW GUINEA (5 544)	27 100	172	6.3	29 300	100	3.4	46.0
UGANDA (10 990)	42 800	192	4.5	43 300	37	0.9	80.9
INDIA (181 400)	240 000	2 301	9.6	488 000	3 602	7.4	23.0

6. SUMMARY AND CONCLUSIONS

A critical review of the past progress in the field of epidemiology of the disease reveals several features unique to leprosy. These include study of the disease by traditional leprologists often isolated from the mainstream of developments elsewhere, the relative scarcity of hard information in published literature, the extensive use of ill-defined and non-standardized tools such as lepromin for epidemiological reasoning, and the widespread confusion in the application of terminology relating to disease states. Nonetheless, the fact remains that leprosy is one of the most challenging of diseases from the point of view of both its understanding and control.

The progress in basic research in leprosy in recent years has opened or promises to open a wide vista of opportunities for the epidemiologist. With the imminent availability of dependable and easily applicable immunological tools to measure humoral as well as cell-mediated immune response, the time has now come to formulate appropriate hypotheses to be tested under a variety of conditions

utilizing standardized methodology. The choice of hypotheses to be tested, at least to begin with, should focus on those directly relevant to disease control.

While measurement of infection state through immunological tools, as against measurement of disease state, could be very valuable in identifying risk factors for infection, it should not be forgotten that in leprosy disease determinants after infection are probably equally or even more important than determinants for infection. Again there could be a degree of interaction between these two sets of determinants.

The relationship between infection and disease in leprosy does not appear to be a constant one as seen from the finding that age-specific incidence of infection does not appear to parallel age-specific incidence of disease. For instance, the occurrence of new disease among significant numbers of older adults in high endemic areas cannot be explained simply as resulting from recent infection, as is the case among younger children in the same area. It is difficult to accept that the older individuals who develop the disease had remained uninfected for long periods in such high endemic areas where *M. leprae* infection is so ubiquitous and opportunities for exposure so frequent. Issues such as these need to be studied with appropriate tools to explain better the natural history of the disease and to explore possibilities such as re-infection.

In the past, the study of disease determinants appears to have focused more on genetic predisposition than on other factors. In this context the experience of the host with regard to exposure to other mycobacteria prior to infection with *M. leprae*, and the subsequent experience of the host with regard to repeated doses of *M. leprae* after a primary infection, are questions which need to be studied in some depth. Studies on these need to be carried out not only in high endemic areas, as has been the common practice hitherto, but also in areas where leprosy has a low endemicity and in areas, as in parts of Europe, where autochthonous leprosy fails to occur in spite of the presence of active sources of infection in the immigrant population.

A very interesting feature of leprosy is the variety and gradation of response of the host to *M. leprae*. This response extends from subclinical infection as demonstrated by *in vitro* lymphocyte tests, skin test conversion, serum antibodies, and occurrence of AFB on healthy skin at the one end to lepromatous leprosy at the other end. In between one observes the early monomacular self-healing lesions as well as

well-characterized disease states such as tuberculoid and borderline leprosy. However, the factors that contribute to this wide gradation of response are not clear, whether they are mainly genetic or environmental or a combination of both. While genetic predisposition has been demonstrated both for the tuberculoid and lepromatous leprosy through HLA markers, its importance vis-a-vis the environmental influences is still to be determined. In this context the occurrence of divergent types of leprosy among monozygotic twins, at least among some, is a case in point.

Regarding the transmission process itself, although direct man-to-man transmission is the well accepted view in leprosy, whether through respiratory or skin route, the possibility of extra-human reservoirs existing in close proximity to man cannot be excluded. In any case there appear to have been very few attempts to search for these. The contribution of an extra human reservoir can possibly explain some of the unexplained features of leprosy, such as the very uneven geographic distribution of the disease, the uneven risk of leprosy in different geographic situations even for household contacts, the rapid rise and fall of leprosy in certain situations, and the non-occurrence of secondary cases among contacts of immigrant leprosy cases in parts of Europe.

A major problem facing leprosy research is how to evaluate the efficacy of tools for intervention such as vaccines in a reasonable period of time. The present approach of measurement of outcome through disease occurrence is not only an indirect measure of transmission of infection, but also one that requires follow-up of populations for very long periods of time. Therefore, there is an urgent need to develop tools that could serve as dependable intermediate markers in the measurement of outcome in such intervention trials. In addition there is a need for the development of appropriate epidemiometric models to predict and compare the different methods of intervention, as had been demonstrated by Lechat *et al* (1977) earlier.

Lastly, it should be pointed out that any investment in the study of epidemiology of leprosy can be justified only through its potential utility for disease control, whether direct or indirect. In this connection, an area that needs emphasis is health services research in relation to leprosy. There is also a need to recognize the importance of social and economic aspects of leprosy and to study these by employing an interdisciplinary approach in which epidemiology could play a significant role.

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