Some Aspects of the Epidemiology of Leprosy

On the Relationship of Leprosy and Other Mycobacterial Diseases

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Soon after Hansen's discovery of \( M. \) leprae and Koch's discovery of \( M. \) tuberculosis a relationship between the two diseases was considered. In 1924, Sir Leonard Rogers (19), in a Croonian Lecture on leprosy researches, stated: "It is now well established that native races in Central Africa, Oceania and America, among whom some of the highest leprosy rates are found, have very low percentages of positive tubercul reactions." This statement was illustrated by a table showing leprosy rates and percentages of positive reactions to tubercul (von Pirquet). Rogers concluded that mild tuberculosis may give some protection against leprosy and that tuberculosis might be one factor in the extinction of leprosy in Europe. Very little attention has been paid to this remarkable observation. BCG vaccination was tried as a treatment for leprosy, but interest rapidly disappeared after it seemed evident that BCG vaccination was ineffective and that it might provoke leprosy reactions.

In 1941 the hypothesis of an antagonism between leprosy and tuberculosis was revived by Chaussinand (4,5). His evidence, although mainly circumstantial, has stimulated other workers to further studies on the subject. In the next twenty years many papers on the immunologic relationship between the two diseases were published. It was shown that the prevalence of positive lepromin reactors is higher in tubercul-positive than in tubercul-negative individuals and that a very high percentage of negative lepromin reactions can be converted into positive by BCG vaccination. This suggests an increase of resistance to \( M. \) leprae by tuberculosis infection or by BCG vaccination.

Other investigators, however, failed to find a correlation between the response to lepromin and to tubercul. They found also that leprosy may develop in tubercul-positive individuals, that tuberculosis and leprosy are often found in the same individual, that high rates of leprosy occur in areas with a high tuberclesis index, and that after tuberclosis infection or BCG vaccination some individuals remain lepromin-negative. Although some relationship between the two diseases obviously exists, the practical value of the observations remained questionable. The evidence pointed against a simple antagonism between the two diseases.

In the meantime much progress had been made in the field of immunologic research on tuberculosis. Tuberculins had been purified. Studies in many parts of the world had revealed the presence of important nonspecific factors influencing the size of the tuberculin reaction: Whereas previously all reactions to tuberculin measuring 6 mm. or more had been regarded as evidence of infection with \( M. \) tuberculosis, it was shown that in many areas reactions of even 6-12 mm. had to be regarded as nonspecific. Many leprologists who have investigated the immunologic relationship between leprosy and tuberculosis have largely neglected the studies in tuberculosis. Nonpurified tuberculins have been used, and insufficient attention has been paid to the storage of tubercul, to adherence of tuberculo-protein to the wall of containers, to leakage of syringes, and to training in injection and reading techniques. With respect to the lepromin reaction, frequently nonstandardized lepromins have been used and investigators have not standardized their technique of injection and reading of reactions. Consequently many older studies are difficult to assess.

In 1954 a study on the relationship between leprosy and tuberculosis was carried...
out in West New Guinea by Leiker (13) applying WHO criteria to tuberculin testing and using a standardized lepromin. In this study a highly significant correlation between the prevalence of leprosy and the tuberculin index was found. The epidemiology of leprosy, however, could not be explained simply by a straight forward antagonism between the two diseases. Some of the findings may be summarized as follows:

1. New born babies do not react to lepromin. It is concluded that at birth resistance to \textit{M. leprae} is nil.

2. In most children the size of the lepromin reaction gradually increases while they are growing up. Most children develop some resistance to \textit{M. leprae}.

3. In some children the lepromin reaction rather suddenly becomes strongly positive; this was found to happen frequently in households with open cases of leprosy. After a close follow-up of these children in a small proportion of their typical self-healing, "childhood leprosy" lesions have been found. Leprosy infection appears to be one factor for conversion of the lepromin reaction. In a great number of children, however, a simultaneous conversion of the tuberculin reaction was found and the conversion of the lepromin reaction was ascribed to infection with \textit{M. tuberculosis}.

4. In the older age groups the average size of the lepromin reaction in tuberculin-positive individuals was significantly larger than in tuberculin-negative individuals.

5. New Guinea offered the rather exceptional situation of providing study areas which were free or nearly free from leprosy and tuberculosis. It was found that the great majority of adults in these areas showed positive lepromin reactions (and negative tuberculin reactions), although conversion to positivity occurred on the average at a later age as compared with areas with a high prevalence of tuberculosis. It is concluded that apart from leprosy and tuberculosis other factors influence the size of the lepromin reaction. The conversion may be caused also by other mycobacterial infections, and not necessarily with pathogenic mycobacteria.

6. Although most adults had developed a weakly to strongly positive lepromin reaction the average size of reactions still increased after BCG vaccination, suggesting that not all adults had reached a maximal resistance to \textit{M. leprae}.

7. Most, but not all tuberculin-negative individuals became lepromin-positive after BCG vaccination. Of the tuberculin-positive adults, a few were found to be lepromin-negative and remained negative after BCG vaccination. It was concluded that some individuals are not capable of developing resistance to \textit{M. leprae}.

8. The size-frequency distribution histograms of lepromin reactions of positive tuberculin reactors, of BCG-vaccinated individuals, and of leprosy patients show a wide variation in size of the lepromin reactions, suggesting that there is a quantitative element in the factor or factors determining the degree of resistance which individually can be developed.

The conclusions can be summarized as follows. Most people possess a "potential resistance" to \textit{M. leprae}. This potential resistance is developed into "effective resistance" after infection with various types of mycobacteria. Some individuals do not possess a potential resistance or have a weak potential resistance only. These individuals are consequently not capable of developing sufficient effective resistance and after infection with \textit{M. leprae} are liable to develop a particular form of leprosy. The findings can be explained by the hypothesis that potential resistance is dependent on a genetic factor, according to Spickett (22) with a single dominant gene, with a penetrance of 70 per cent. Studies of the skin reactions of leprosy patients and healthy subjects to other mycobacteria suggest that the absence of this genetic factor also influences the response to other mycobacterial antigens (14).

It has been found that the average size of nonspecific tuberculin reactions is smaller in lepromatous patients than in tuberculoid patients and healthy subjects. Lepromatous patients also respond, on the average, with smaller reactions than tuberculoid and healthy subjects, to a suspension of \textit{"Mycobacterium 875"}, which differs from \textit{M. leprae} and \textit{M. tuberculosis}. McKinley (17) found that reactions to old tuberculin in
leprosy patients in the Philippines were less frequently positive than in healthy subjects. Similar findings have been reported from tests with the Lleras Acosta (14) strain from South America. Rutgers (18) has found that the average size of reactions to BCG is smaller in lepromatous patients than in healthy subjects. These findings support the hypothesis that leprosy patients are not only less capable of reacting to M. leprae, but are also less capable of reacting to other mycobacteria. The genetic deficiency causes a lesser resistance to the whole family of mycobacteria, although the degree of lesser resistance to different mycobacteria may vary. This hypothesis is supported too by immunologic as well as epidemiologic data, in particular from areas with a very high prevalence of leprosy combined with a very low type rate.

Congo (7-19). Prevalence rates of 6.9 per cent, with a type rate of 2 per cent only, have been found in some areas. In other areas with a prevalence rate of 4.4-6.5 per cent the type rate was higher (9 per cent). In 37,442 people, only two cases of tuberculosis have been found. Swerts (20) concluded: "It seems that the impregnation with Hansen's bacillus precedes that with Koch's bacillus."

Uganda (21). In the West Nile lowlands prevalence rates of 1.1-5.3 per cent have been found, as compared with prevalence rates of 0.6-1 per cent in the highlands. In the former very few cases of tuberculosis have been seen, which is explained by little contact with civilization, whereas more tuberculosis was found in the highlands, because of labor elsewhere.

Eastern Nigeria (22). In 1941 a prevalence rate of leprosy of 12.1 per cent with a type rate of 8.8 per cent was found in villages in Owerri. Lowe (23) states, "A few tuberculosis cases have been seen, but a definite opinion has been formed that tuberculosis is not common in the area." Davey (24) stated, "No case of tuberculosis was encountered in 2500 people seen."

Northern Nigeria (25). The lowest prevalence of leprosy has been found in the city of Katsina. The leprosy index increases toward the periphery, in Katsina 0.8 per cent leprosy, against 2-2.6 per cent around Katsina and 2.8-3.8 per cent in the periphery. Collard (1) carried out a tuberculin survey in and around Katsina. In the city and in a 10-mile zone around Katsina 45 per cent positive reactors were found. In the next 10 mile zone the percentage of positive reactors was 27 per cent and in a further 10 mile zone only 18 per cent.

Brazil (7). In Campanha the prevalence of leprosy was 0.23 per cent and the morbidity rate of tuberculosis 10.8 per cent, with a mortality rate of 4 per cent. In Missões the prevalence of leprosy was 0.75 per cent and the morbidity rate of tuberculosis 2.9 per cent, with a mortality rate of 1.6 per cent. Similar findings have been reported from other provinces.

Nauru (25-29). In this famous epidemic of leprosy, a prevalence rate of 30 per cent was found. Zieman (cited by Chaussinand (4)) recorded that in 1909-1910, of 4,177 patients who were hospitalized, only five showed pulmonary tuberculosis.

Although the methods of survey in these reports have not always been satisfactory according to modern concepts, the findings strongly suggest that high prevalence rates of leprosy with low type rates coincide with low prevalence rates of tuberculosis. In studies in New Guinea (11) the prevalence rates of leprosy are based on intensive population surveys and for testing with tuberculin the WHO criteria were applied. A statistically highly significant correlation between prevalence of leprosy and the percentage of positive tuberculin reactions has been found (Table 1). New Guinea offered a rather unusual opportunity to study epidemics of leprosy very closely. It has been possible to trace the history of the disease in the communities in detail. A study of the literature revealed that all epidemics that have been reported present a similar pattern as follows.

1. Epidemics of leprosy have been reported exclusively from isolated communities with a low level of hygiene and other factors favorable for the transmission of infectious diseases.

2. In many epidemics there is evidence that leprosy is of recent origin in the community. In New Guinea definite proof of a recent introduction has been found in all communities studied.
3. The prevalence of tuberculosis is invariably low.

4. The epidemic presents a characteristic pattern:

(a) Soon after introduction of the disease the prevalence rate increases rapidly, but a great majority of the cases are of the mild, self-healing tuberculoid type, with only one or a few small lesions.

(b) The disease is not focalized around the few lepromatous or borderline patients; many cases are found in families without open cases of leprosy, suggesting a highly susceptible population and in the majority of new patients, transmission after incidental superficial contact with the few infectious patients.

(c) The child rate is relatively low. Adults seem to be nearly as susceptible as children.

(d) After the prevalence rate has reached a peak, the incidence of new, mild tuberculoid cases decreases, but regularly one or a few more progressive type, new cases are seen, resulting in a decrease in prevalence and an increase in type rate.

(e) Gradually the new cases occur relatively more frequently among the contacts of positive patients than in families without open cases and the disease becomes more focalized.

(f) The incidence of new cases in adults decreases and new cases occur relatively more frequently in young children. The child index increases.

(g) Gradually the pattern becomes similar to that of other areas with a longer history of leprosy.

The course of epidemics of mild tuberculoid leprosy can be explained as follows: In every community a small proportion of the people have little or no potential resistance. These individuals are likely to develop a progressive form of leprosy after infection with *M. leprae*. Because of the small number of these susceptible individuals and of the few sources of infection in the community at the beginning of an epidemic, the number of progressive cases will rise only slowly. In a community with little leprosy, little tuberculosis and other mycobacterial infections, there are, however, many individuals who have potential resistance to *M. leprae*, but who have not yet developed effective resistance. If these individuals, before they are infected with other mycobacteria, are infected with *M. leprae*, mild forms of leprosy may appear. In these individuals effective resistance to *M. leprae* is developed by the leprosy infection, which acts like a vaccination, and the type of leprosy will be benign, self-healing tuberculoid. The chances that a potentially resistant individual will become infected with *M. leprae* are many times greater than that a person lacking potential resistance will be infected. Consequently the type index will be low.

Gradually the stock of potentially resistant individuals, who have not yet developed effective resistance decreases. Many people have already acquired effective resistance by a leprosy or tuberculosis infection or by infection with other mycobacteria. The incidence of new mild tuberculoid cases decreases. From time to time some of the few who lack potential resist-
ance will become infected. Consequently the type index increases.

A susceptible stock of population is maintained by immigrants, e.g., marriage partners from other areas and by new born children. Because of the latter, the child index gradually increases. This hypothesis also explains why frequently the incidence of mild tuberculoid leprosy is higher in females as compared with males. Males travel around or work outside the community and have more chance of becoming infected with *M. tuberculosis* than women, who lead a more secluded life. Consequently more men than women have developed effective resistance to *M. leprae*. It also explains why waves of mild tuberculoid leprosy are frequently seen after a population explosion. Most of the new patients are children. The incidence of leprosy in the adults has not significantly changed.

It also explains why epidemics of tuberculoid leprosy have not been reported from the slums of the large cities, but only from isolated communities in rural areas. In the latter, leprosy and tuberculosis are relatively new diseases, whereas in the city tuberculosis is usually already widely spread. This hypothesis is further supported by the findings of Leiker (13) in New Guinea. In patients who had recently shown a mild tuberculoid form of leprosy, the tuberculin index was significantly lower than in patients of the same age group from the same area, but with progressive forms of leprosy, and also lower than of comparable healthy people of the same area.

Finally, the outcome of two BCG trials supports this hypothesis. In Uganda, Kinneir Brown et al. (12) have shown that BCG vaccination offers about 80 per cent protection against leprosy in children. Because in Uganda leprosy in children is usually of a mild tuberculoid type, no conclusions can be drawn about protection against progressive forms of the disease. In New Guinea, Russell (20) and co-workers found a protection rate of about 55 per cent. In New Guinea too the type rate of leprosy in the trial population is very low. It is still puzzling that no significant protection has been found in the WHO trial of BCG in Burma (28). Theoretically it is unlikely that BCG vaccination will protect against progressive forms of leprosy.

**SUMMARY**

Study of the epidemiology of leprosy is seriously handicapped by a lack of reliable and comparable statistics. Conclusions are frequently based on hypothetical elements.

The study of epidemics of leprosy contributes materially to a better understanding of the natural history of the disease.

The concepts that leprosy is feebly contagious, that the disease is usually contracted in childhood, and only after prolonged, intimate contact with strongly bacilliferous patients are incompatible with the findings in epidemics.

No evidence has been found of transmission by other routes than the skin, by insects, or by other vectors. The nutritional status does not seem to have a significant influence on susceptibility to leprosy, nor on the course of the disease. No evidence of different strains of *M. leprae*, differing in virulence, has been found. Poor hygiene does not seem to be the dominating factor in the epidemiology.

The following hypothesis offers an explanation for many epidemiologic findings. Most people, because of a constitutional, probably genetically determined factor, are capable of developing some degree of resistance to *M. leprae*. The potential resistance is converted into "effective" resistance by infection with *M. leprae*. Depending on the degree of potential resistance the disease will be limited to merely a conversion of the lepromin reaction to positive, to mild, localized, self-healing primary tuberculoid skin lesions, or, in a minority, to self-limiting intermediate forms. Progressive types of leprosy are restricted to the small percent of the population lacking the constitutional factor.

Conversion of potential into effective resistance may, however, be induced also by other mycobacterial infections. For example, a tuberculosis infection preceding leprosy infection may thereby prevent the development of nonlepromatous leprosy, in particular the mild tuberculoid forms of the disease. It appears that in epidemics of leprosy the mild tuberculoid cases invariably predominate and that epidemics occur...
rate of tuberculin positivity in children and
leprosy in children as compared with
adults, and the higher percentages of mild
tuberculous leprosy in females as compared
with males, corresponding with a lower rate of tuberculin positivity in children and females.

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