An Epidemiologist's View of Leprosy

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While leprosy has been studied exhaustively by leprologists, it is only recently that persons in other disciplines have given this disease the attention it deserves. Various methods for its prevention and control are now being advocated and tested in the field, and it appears reasonable for an epidemiologist to review the bases of current theories and to examine the evidence for existing hypotheses. This has been done by a review of some of the more recent literature. The conclusion is reached that the anergic, or factor N, hypothesis that has been evolved to relate the lepromin test to the findings in clinical leprosy appears to be the most promising, and that, if this hypothesis can be substantiated, it is unlikely that BCG vaccination can be a very useful tool for prevention. Many possibilities exist for epidemiological and laboratory research into this disease, which in many ways appears to be unique.

INTRODUCTION

Not only were leprosy patients walled up or segregated in the past, but it would be fair to say that the leprologists and the subject of leprosy were also cut off from the main body of medical thought and research. Many pleas have been made, generally in specialist publications read only by leprologists, for research workers in disciplines such as immunology and epidemiology to consider the problems presented by this intriguing and unusual disease. Certainly the current literature contains some new names and new ideas.

This account is by a relative stranger to the subject. With the specific aim of presenting an over-all epidemiological view of leprosy, but using only those parts of the published literature that could be absorbed in a four-week period, I have attempted to look at leprosy from a purely epidemiological aspect. Such a desk-side view in such a short period must be selective and produce an uneven picture. For example, the lepromin test and the possibilities for prevention of the disease with BCG took up a large part of my time and thinking, as neither of these matters has been fully assessed, and both are most interesting and relevant to anyone in epidemiology. However, they are meaningless without some very elementary study of the clinical, bacteriological and general background and of current thought and theories on the subject. This has resulted in some emphasis and omissions that are hard to justify. Some basic observations well known to leprologists have been omitted; this could lead to difficulties in understanding by people who are unfamiliar with the subject. Other apparently simple points have been described in detail, and this could be thought of as undignified and as " padding " by the leprosy expert. It is impossible to avoid either criticism.

From the epidemiological point of view, the standard of published studies on leprosy varies very markedly. Some studies are so incomplete and biased that they must be omitted and ignored. Others are of questionable value, not because of any inadequacy in their purpose or their study design, but because important supplementary information is not included, thus making them difficult to interpret. Some of these works must be included because no other information exists, but I have done so with reservations.

Three independent groups in North America, in the Philippines and in Argentina and Brazil, plus some other investigators in West Africa, India and elsewhere have consistently, over a long period of years, given the lead in thinking and have tried to confirm their hypotheses by field and laboratory studies of an internationally acceptable standard. Some of these findings are contradictory, but in general they are consistent.

It is from the published work of these groups that the major part of the material I have used has been drawn. The references appended to this paper are

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not designed to be a full bibliography of the world literature but are highly selected. In a number of instances, when I was unable to read the original articles for reasons such as lack of time, unavailability of the journals in which they appeared or unfamiliarity with the languages in which they were written, I have relied upon reviews of whole aspects of the leprosy problem. The editorials in the *International Journal of Leprosy* are outstanding in this respect and must have had an enormous influence upon the thinking of workers in this disease.

METHODS OF DIAGNOSIS AND DEFINITION

There is no single test, sign, or finding that can be said to distinguish a person with a leprous infection or illness from the rest of the population. In many patients, by using clinical findings and history (possibly with histological examinations) and, frequently, the demonstration of *Mycobacterium leprae* either in the lesions or the nasal mucosa, the differential diagnosis is not in doubt; no other known disease can show these possibly non-specific findings in the same combination. However, the absence of demonstrable bacilli in many leprous lesions of certain clinical forms and the obscurity of the histology in minimal and transient forms that can be self-limiting and result in spontaneous cure present many problems in definition. It is clear that an experienced group of clinicians, using standard methods, would reach very similar conclusions as to whether or not a patient had leprosy in the obvious and developed forms of lepromatous, tuberculoid and indeterminate leprosy, and also in some of the subclassifications. On the other hand, they might disagree upon the classification of the form of leprosy that was present, even when using the lepromin test and the recommended international definitions, as the dividing lines are not clearly marked, and the criteria are mainly subjective. In the minimal lesions, which frequently do not progress, not only is disagreement often probable if the patient is seen in isolation and without a clear contact history, but there appears to be real doubt as to whether many of the lesions are indeed those of leprosy. Partly because of these doubts, and partly because these sorts of lesions are thought neither to be infective nor to require treatment, the advice sometimes given in the literature is to withhold the possible diagnosis from the patient pending re-examination, so as to save him (or her) the mental anguish that could result from fear and uncertainty.

In persons exposed and thought to be infected but without clinical signs of leprosy, no generally accepted method of identification of leprous infection is known. Some possibilities based upon the demonstration of acid-fast bacilli in either the nose or the skin have been put forward, but they await confirmation.

For these reasons of definition, it is to be expected that different observers using the same criteria, or only some of them, both in normal clinical work and in community surveys, would report different persons as having leprosy and different proportions of the various leprosy types, especially of the marginal forms. Geographical comparisons between published studies of different research groups, other than those of gross and obvious cases, therefore appear to be dangerous and likely to result in inaccuracy or error. In addition, there are reports that some types of leprosy are more difficult to diagnose with certainty in some racial or regional groups, such as Africans. This uncertainty must add to the difficulties of comparison.

Various surveys and reports are inconsistent in the division and definition of what is a healed, arrested, or a cured leprosy case. Some surveys include all known cases; others exclude all known bacteriologically negative persons who have shown no clinical evidence of activity for various periods of time. Some observers state that almost lifelong supervision is necessary for a known case, while others produce convincing evidence that as many as 75% of minimal childhood lesions heal spontaneously without stigmata and are not subsequently ascertainable without constant and detailed case-finding. It is exceptional, rather than normal, for the criteria for inclusion or exclusion to be stated in leprosy publications. This fact casts doubt upon many of the painstaking and time-consuming community studies which have been done and makes accurate comparisons impossible; it also could help to explain some of the conflicting results published by different groups.

Clinical types

The methods of clinical recognition of leprous lesions are fully described in a number of text-books and are not repeated here. Important points include the colour, site, edges, raising from the surface, and pain, temperature and touch discrimination in the skin lesions; the feel of underlying tissues; palpable changes in nerves, with especial emphasis upon certain ones in accessible sites; specific changes in

the eye and terminal bones; and other recognizable phenomena.

Changes in these respects and gross differences (in conjunction with histology, the demonstration of acid-fast bacilli, and the lepromin test) divide the broad category of leprous lesions into three major divisions: lepromatous, tuberculoid and indeterminate. Lepromatous leprosy is the most rapidly progressive and has the worst prognosis. In this form of the disease there is a relatively distinct tissue reaction, as shown histologically, and large numbers of acid-fast bacilli can be shown in and under the skin. It is thought to be more highly infectious than either of the other two forms and is invariably Mitsuda-negative.

Tuberculoid leprosy can have an uncertain course, with periods of exacerbation and remission, but in a proportion of patients it is self-limiting and can disappear spontaneously. Major reactions of the host occur, and severe deformity can result. Acid-fast bacilli may not be seen or may only be present in small numbers in some structures such as nerves. Tuberculoid leprosy is not thought to be so highly infectious as lepromatous leprosy. The Mitsuda reaction can be negative (this is denied by some people), questionable, or positive; it is positive more frequently and to a greater degree than in people of similar age but with no clinical signs of leprosy.

The indeterminate form shares some characteristics such as distribution of skin lesions with both the lepromatous and the tuberculoid types. A patient's condition may be indeterminate for a short time or for the total period of his illness. However, in many cases, it may change to either the lepromatous or the tuberculoid form or recover without change in classification.

There are other recognizable subdivisions, and there are some local or regional forms that appear to be specific and unrecognizable elsewhere. Their significance is not clear.

Histology

The histological appearance of biopsy material may be of importance in diagnosis. Although there are lesions that are non-specific and questionable histologically, the reports of the biopsies of many of them may be so clear that most other possibilities can be excluded. A report may emphasize the presence of acid-fast bacilli in certain sites, both within and outside cells, the peculiar type of clumping of bacilli found only in leprosy, the appearance of a granuloma, and the type of tissue response. Some

lesions may be less specific. The point of origin of the skin biopsied may be relevant; for example, biopsy material from the centre of a lesion may have a different appearance from material taken from an edge. The use of histological techniques to assist definition appears useful, if they are used in conjunction with clinical observation and the demonstration of acid-fast bacilli.

Bacteriology

Although *M. leprae* has never been grown on artificial media, and although it is not invariably found in all forms of leprosy, the demonstration of acid- and alcohol-fast bacilli that cannot be cultured and show typical staining reactions and gross morphology can be helpful to diagnosis, classification of clinical type, and possible prognosis.

In practice, a cut-and-scrape specimen from a skin lesion, a swab or a scraping from the nasal mucosa, or both, are the usual specimens needed for examination. They are stained and examined directly, and bacterial counts may be made.

When these methods are described, great emphasis is put upon the precautions that should be taken to avoid contamination of the specimen with saprophytic mycobacteria from the environment. Some studies have been criticized (Cochrane, 1959) because these precautions were inadequate or because of doubts as to the techniques used. The description of the pitfalls of recognition, and the comments of some leprologists on the studies of others lead an outside observer to wonder whether the recognition of *M. leprae*, partly by exclusion and partly on morphological grounds, may not be doubtful. If saprophytic mycobacteria can be so similar and so troublesome, how can one be certain that they are saprophytic and not *M. leprae* also? Suggestions have also been made that some non-acid-fast mycobacteria found in some leprous lesions may be variants of *M. leprae*.

All of these doubts are unlikely to be resolved until specific methods are developed for the culture or animal passage of *M. leprae* and for its possible antigenic recognition. Although work in these directions is in progress, these new methods are not considered in this review.

There are differences of opinion as to where *M. leprae* may be found in infected persons. While it is agreed that large numbers of *M. leprae* can be seen in the liver, spleen, lymph-nodes and other internal sites in many lepromatous cases seen at post-mortem, it is unknown when this dissemination to sites other than the skin occurs. Does it occur

before the first known skin lesion, simultaneously, or afterwards? This question is unlikely to be answered until the mycobacteria can be grown *in vitro* or in laboratory animals. The direct recognition of these organisms in small numbers in the tissues could be as difficult as that of the typhoid bacillus or any other known bacterial pathogen. However, the frequent demonstration of *M. leprae* in the nasal mucosa, the isolated and unsupported suggestion (Nègre & Fontan, 1956) that radiologically detectable changes in the lung may possibly be present in some infected persons, and the virtual omission from the literature of reports of searches for *M. leprae* elsewhere in the body lead one to question the inferred view (Cochrane, 1959) that leprosy is primarily a disease of the skin and peripheral nerves. It is possible that *M. leprae* is distributed widely within infected persons but has certain areas of concentration, such as in some subcutaneous sites. The answer to this question could be relevant to the methods of transmission of the disease and to diagnosis, yet this possibility has been largely ignored or considered in a most cursory manner.

Cochrane (1959) does not believe that initial nasal lesions exist, and he thinks that in reports of patients with early nasal lesions, either a lesion of the skin or elsewhere was already present, or saprophytes rather than *M. leprae* were seen. In contrast, he quotes Stanley Browne as stating that the nasal mucosa remains positive as long as the cutaneous lesions do. Few observations appear to have been made as to the order of possible infected sites, and the arguments for and against an early or initial nasal lesion appear to be more philosophical than scientific.

Desai (1955) has stated that, by a concentration method, he can demonstrate acid-fast bacilli in the normal skin of 80% of the family contacts of leprosy patients. Other investigators have been unable to confirm this finding in the same proportions, although Dharmendra (1955) believes that skin-positive family contacts were sometimes present. No published work on a follow-up of this observation is available, nor is it known whether acid-fast bacilli can be present in normal skins in other areas or in people not so highly exposed.

As no method exists for positively identifying *M. leprae* or for cultivating it on an artificial medium, Koch's postulates cannot be fulfilled, and the belief that this organism is the causative agent in leprosy is based upon indirect evidence and upon analogy with tuberculosis. However, it is most probably correct.

Little is known of the properties of the organism, and what is suspected is frequently based upon the observed behaviour of *M. lepraemurium*, which is thought to be similar to it in many respects.

For example, *M. lepraemurium*, when quick-frozen, can survive for long periods of time (Cochrane, 1959); recent work indicates that this is also true of *M. leprae*. Survival time at room temperature or when free from tissue is unknown.

Experimental transmission of *M. lepraemurium* in rats has been accomplished by many different routes of inoculation, including subcutaneous, intraperitoneal, epidermal, intracardial, intraocular, intravenous, intracerebral, intradermal and intratesticular (Cochrane, 1959). It is said that the natural transmission of the infection in rats appears most likely to occur through the skin as a consequence of abrasions, lacerations, bites and other wounds. Different strains of laboratory rats differ in their susceptibility to experimental infection, and it has been noted that different strains of *M. lepraemurium* vary in apparent virulence.

Serology and skin reactions

Hanks (1961) states that no significant levels of antibody have been demonstrated in those forms of the disease (tuberculoid) that are characterized by very small numbers of bacilli, strong Mitsuda reactions and frank tendency towards self-healing. In lepromatous leprosy, Mitsuda-negative persons appear to possess abundant antibody. This apparent inversion of what would be expected has not been explained.

Serological methods are not used for diagnosis, and no community studies have been reported.

The lepromin test and the Mitsuda reaction are referred to in a later separate section.

Incubation period

There are difficulties in accurately defining the incubation period, as many known leprosy patients have no clear history of exposure to the disease. Also, minimal early lesions may not have been detected, or an ill person may not have sought medical attention or have been diagnosed until several years after the first abnormal occurrence.

The widely accepted view is that the period of time between infection and the appearance of the first symptoms can be long and varied, often a period of years (Cochrane, 1959; Muir, 1948, Rodriguez, 1958; Rogers & Muir, 1946; Doull, 1961). In persons thought to have been exposed only during war

service, latent periods of 40 years have been reported. It is thought, however, that the usual interval is about three to five years. In some series of children known to have been exposed since birth, as high a proportion as 50% of known secondary infections occurred before the fifth year of life. In certain other series of children, 66% of the infections were said to occur before the second year.[1]

In mice, Shepard (1961) reported that the incubation period was a function of the infecting dose of organisms.

The interval between infection or exposure and the appearance of demonstrable skin or nasal acid-fast bacilli is unknown.

Distribution of leprous lesions

The distribution of initial lesions varies with the type of leprosy. Cochrane (1959) described tuberculoid leprosy as being most frequent on the face, lateral aspects of the extremities, buttocks and over the scapulae, while macular lepromatous leprosy was most often scattered over the body in a symmetrical manner.

In the community studies in Cebu (Doull, Guinto & Plantilla, 1936) the different proportions of first lesions by site were those listed below:

Site	Percentage
Arm	26.3
Leg	23.7
Thigh (including hip and buttock)	42.1
Back	1.3
Pectoral region	1.3
Epigastric region	1.3
Face	4.0
All sites	100

It is probable that the site of first lesion varies partly with age and with regional and ethnic grouping. This variation has been suggested in a number of papers, but it is rarely dealt with in sufficient detail for firm conclusions to be drawn. The differences have been explained by either variations in the possibilities of direct skin-to-skin contact or variations in the risks of skin injury, trauma, or inflammation.

Portal of entry and means of spread

The prevailing view is that the bacilli usually enter the body through wounds in the skin (Doull, 1961).

There are well-documented examples of leprosy lesions at the site of recorded trauma due to needle pricks (Marchoux, 1934), tattooing (Porritt & Olsen, 1947) or cuts (Hamilton, 1926). Rogers & Muir (1946) state that, in India, the earliest lesions are more frequently found in the feet in patients from hilly and stony districts than in those from districts where the soil is alluvial. Khanolkar (1955) believes that *M. leprae* can pass through the intact healthy skin and find its way under the epidermis through the superficial lymphatic network.

Binford (1961), quoting the observations of Nolasco & Lara (1940) on children who had remained in the first year of life or longer with an infected mother, stated that the presence of several skin lesions in some of the children represented different primary foci rather than dissemination from a single one. In a histopathological study of an early case of leprosy in a young child of leprous parents who died of pneumonia, bacilli were found in the homolateral inguinal lymph-node, but none were found elsewhere, although an exhaustive search was made.

In any infectious disease, it is often difficult to decide the portal of entry of the pathogen. The evidence must often be indirect. The site of lesions is not necessarily directly related to point of entry, especially in those infections where it can be shown or suspected that systemic spread does, or can, occur.

In leprosy, surface and subcutaneous lesions are obvious expressions of the disease. They occur in infected persons who can be shown at necropsy to have bacilli widely disseminated through the internal organs and most of the body, even though during the illness these bacilli had interfered with internal functions in only minor ways. It is difficult to diagnose leprosy unless a skin lesion is present, but we cannot assume that a skin lesion is present in every infected person. The existence of the symptomless infected person is frequently suspected and is the most reasonable explanation of the connecting link in the spread of infection to some otherwise unexplained sporadic cases. It is possible that some of these symptomless persons have skin lesions that have not been diagnosed. It is equally possible that these cases have a form of the disease that is not primarily of the skin and is therefore undiagnosable using the present methods.

The symmetrical distribution of lesions in macular lepromatous leprosy is unlikely to be the result of symmetrical contact opportunities. However, although it is probable that these expressions of infection are due to dissemination *via* the blood-

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[1] Lara, C. B. (1961) Unpublished document WPR/Lep/24, presented at the WHO First Inter-Regional Postgraduate Leprosy Training Course, Manila.

stream, the possibility that the organism first entered the body through the skin cannot be excluded.

Some conclusions are possible. The organism is found in large numbers on the skin and superficial lesions and in the nasal mucosa of infected persons and could pass to uninfected persons directly or by means of fomites, through the air in droplets or dust, or by means of insects. It could enter the victim through the intact or injured skin, through the nose or pharynx, or through inhalation or ingestion.

The epidemiological picture of the disease makes some of these possibilities more probable and virtually excludes others.

(1) No evidence exists as to whether insect-borne transmission is possible. However, it appears unlikely. The variations in the incidence of the disease by area do not conform to the distribution of any known vector. In a given area, the local segregation of the clinically ill apparently decreases the risks of infection to the community, although it is still exposed to the same vectors. *M. leprae* cannot apparently pass over walls.

(2) The long incubation or latent period might effectively mask outbreaks due to the ingestion of infected foods. However, the distribution of the disease within communities, while frequently occurring in family feeding groups, is not at all similar to other gastrointestinal diseases. This method of spread is possible, but unlikely.

(3) Direct person-to-person contact was for a long time the most-supported explanation, although the evidence for it was slim and circumstantial. It was apparently based upon the observation that skin lesions were the expression of disease in both the donor and the victim, that the risk of illness increased for those who lived in infected households and possibly was at a maximum in the child of an infected parent, and that variations in the site of the initial lesion varied by area and could be interpreted as being due to different possible types of skin-to-skin contact determined by different cultural patterns.

These observations could be equally well explained by spread from person to person without direct skin-to-skin contact if either the organism was one with a short survival time or if multiple exposures or challenge by a large number of organisms were required for infection. The predominance of lesions in peripheral sites and the variations in site distribution in different societies could be due to trauma acting as a localizing factor.

The likelihood of direct skin-to-skin contact being essential for person-to-person transmission appears to be small. The order of frequency of sites is not that of the parts of the body most likely to be touched in any society. It also seems theoretically unlikely that direct contact would be required for any infectious disease when all that must be demonstrated is the passage of an agent from person to person. It is known that many organisms on the skin surface or in the nasal mucosa can easily be transferred to another individual without the skins being in contact. There is no reason to suspect that this does not also happen in leprosy and that droplets, dust and fomites do not play a significant part.

Some doubts on this point might be resolved if it could be demonstrated that a relationship exists between the site of the lesion on the infected donor and both the risks of infection and the sites of infection of the exposed secondary case; for example, a facial lesion of an infected mother could result in more facial lesions in her family than in another family whose mother's lesion was on a foot; or a family with an infected father with lesions on the hands could have a higher secondary attack rate than a father with only infected buttocks. If direct skin contact was common, the distribution of lesions would be expected also to differ by age and sex and in persons infected in a family situation when compared with patients who apparently were sporadic cases and whose source of infection was unknown. This type of study would require detailed observation of large numbers and would hardly be justifiable other than as an incidental bonus from a study planned for other reasons.

The possibility that the agent passes through the intact or traumatized skin is harder to support or refute. There are few, if any, infectious bacterial agents that are known to be able to pass through healthy skin. This does not mean that they do not exist, nor that *M. leprae* does not have this ability. However, if this is postulated, some special quality in the agent must be proposed that would give it this ability, which is not possessed by other mycobacteria. Few specific qualities are attributed to *M. leprae* other than its apparent hardihood in tissue and its possible inability to propagate outside of the human body; neither of these appears likely to be associated with an increased penetrative power. If minor trauma is needed to assist penetration, the distribution of lesions by age, sex and site would be expected to be similar to those seen in other diseases where trauma or a skin lesion is initially necessary, such as in tetanus or in cutaneous diphtheria. If this is a reasonable analogy, leprosy in children would be more common in those aged 3-6 years than in young toddlers and most common in the age-group 7-11 years. The sex ratio would be nearly 1/1 up to

the age of 5-6 years and then show a marked pre-ponderance of boys. The sites of election would be the extremities, especially the feet and fingers, followed by hands and wrists. Lesions of the buttocks, thighs and trunk would be uncommon, and lesions of the face would be largely on the front of the face, especially on the lips, nose and forehead rather than on the ears. This is not the common distribution of leprous lesions.

If the spread of leprosy were by the respiratory or pharyngeal route, and the place of infection was the nasopharyngeal mucosa, none of the known leprosy findings would be impossible or unexplainable. A unilateral initial lesion with systemic spread is possible, the similar sex distribution is consistent with the findings, and the variation in site by society could be analogous to the variations found to be attributable to secondary factors, as has been described in poliomyelitis (Greenberg & Abramson, 1952). There is little direct evidence to support this view, but it is the theoretical choice of possibilities if it is coupled with the assumptions that challenge by a large number of organisms must usually occur to cause an infection, or that frequent exposure is necessary.

THE EPIDEMIOLOGY OF LEPROSY

Changes in time and place

Leprosy, as then described, is said to have been at its height in Europe at A.D. 1000-1400. Since that time it has gradually declined but in an uneven manner. The last indigenous case in Great Britain was said to have been that of a patient who died in 1798. Norway showed an increased prevalence in the eighteenth and nineteenth centuries but only 11 cases in 1950. The disease persists in Spain, Portugal, the Balkan states, the European areas of the USSR, Turkey and in France in the Maritime Alps (Cochrane, 1959).

In North America there has been a decline, but leprosy still occurs regularly in Texas, Louisiana, Florida and California.

There are appreciable numbers of cases in Argentina, Brazil, Colombia, Paraguay and Mexico.

The majority of present endemic areas are in tropical Africa, Asia and the Pacific. In some of these areas, the number of cases may well be stationary or increasing.

There have been recorded " epidemic " periods in a number of clearly defined areas. These include the Hawaiian Islands in the nineteenth century (Cochrane, 1959) and on Nauru Island since 1912 (Wade & Ledowsky, 1952). In many places, however, the prevalence of the disease has remained fairly stable for long periods.

Even when allowance is made for the long latent period, the remissions and exacerbations of many of those ill, the possibilities of minor unrecognized lesions in many persons thought to be infected, and the suspected relatively low mortality rate associated with this disease, two observations stand out as being remarkable.

The first is the apparently minor nature of changes in segregation or social and medical policies that have been connected with a decreasing incidence of leprosy. The European policy towards those known to be infected was that of concentration rather than of segregation or isolation. It is hard to believe that methods of ascertainment of infection were highly efficient, and either the factors influencing the continuation of the disease must have been most precarious or other more important factors must have been involved in the decline. It has been suggested that an improvement in general health and better diet could have been influences, but considering that this was the early period of the Industrial Revolution, with the urbanization, overcrowding, and environmental abuses that quickly raised other communicable diseases to epidemic proportions, this explanation is improbable. Doull (1961) speculates as to whether there could have been a loss of pathogenicity of *M. leprae*, or whether there may have been a slight increase in resistance of the population. Any loss of pathogenicity must have been only local.

The second point of interest has been the almost complete absence of cases for long periods (many generations) in those areas where leprosy decreased and disappeared. Either the form of the disease became atypical and unrecognizable, or it no longer existed. It is more probable that it disappeared, and that *M. leprae* was eradicated from a local area. If true, it would support the conclusion that man may be the only host, at least in temperate regions, and that the number of symptomless infected persons suspected to exist must be either few in number or only infectious to a relatively minor degree. Although in the British Isles there has been a constant influx of people found later to have leprosy, probably contracted outside of the country, and the entrance of undiagnosed minor cases is probably frequent, there are few reports of secondary cases and none of new foci of infection. In comparison,

the entrance into Nauru Island of one known leprosy case (or possibly two) is believed to have resulted in an outbreak thought at one time to have involved with symptoms 30% of the population. One must conclude from these dissimilar experiences that the presence of *M. leprae*, although probably essential for the development of leprosy, must be placed in conjunction with other factors that may be of dominating importance in influencing the occurrence of the disease in a population. Variations in the pathogenicity of the agent may be one such factor, and susceptibility or resistance may be another; these are discussed in another section. By exclusion, one is left with the conclusion that the method of spread and environmental factors must be dominant.

This is supported by some of the concentrations of cases noted by Badger (Cochrane, 1959) in the southern part of the USA. In Florida, 80% of the leprosy cases came from the city of Key West; in Key West 87% of the leprous individuals resided in one area of the city; 60% of these persons lived in an area of five by five blocks. Cochrane (1959) described an area in India where in one village the " incidence " of leprosy was 5%, while in the adjacent village, only 20 yards away, there was no leprosy at all. There have been descriptions of concentrations of cases in families of known relationship and historical connexions but widely separated in place and time.

The general impression given is that *M. leprae* is not distributed at random throughout the world, that it is inefficient in its methods of survival, and that transmission may be difficult and be associated with a massive infecting dose, an intimate method of transfer and/or an environmental factor about which there is insufficient information at present even to permit a guess as to its nature.

Age

Consideration of age-specific incidence and prevalence rates for leprosy are complicated by differences between different clinical forms of the disease, differences by areas, lack of agreement as to definitions of terms, and the long interval that may occur between first symptoms and diagnosis.

It has often been stated that children are more susceptible to leprosy than are adults (Cochrane, 1947; Cochrane, 1959; Doull, 1957; Muir, 1948; Rogers & Muir, 1946). Some investigators have gone so far as to state that the great majority of patients become infected in early childhood, and that it is

rare for adults to become infected. However, there are marked regional variations, and a distinction must be made between opportunities for exposure and susceptibility. In both Hawaii and Madras (Cochrane, 1959), the mean age of onset is less than in the four States of the USA with endemic leprosy, where the estimated age at time of infection (assuming an incubation period of 10 years) of 53.9% of the known cases was greater than 20 years.

Lara (1961, *op. cit.*), reporting results from the Culion Colony in the Philippines, where children were kept with their infected parents, stated that of the 200 secondary cases observed, 99% had their onset at the age of 6 years or less, 95% at 3 years or less, and 66% at 2 years or less. The youngest cases observed were in children aged 9-11 months, but the incidence at less than 1 year was less than 0.5% (one case among 200). This group of children could be considered as living in exceptional conditions and being observed with great frequency. The leprosy rate in continuously exposed children aged 3-6 years, observed for differing periods of time, was 36.2 %. The lesions included self-limiting ones that could undergo spontaneous disappearance. In another paper, Lara & Nolasco (1956) wrote that 77% of these early childhood cases had lost all leprous lesions before adult life.

Under survey circumstances some of this minimal type of leprosy might not be ascertainable. In some children, the lesion could have already disappeared, and the child would not be included in those thought to have been infected.

Doull (1961) described the peak incidence in the Philippine island of Cebu, in household associates of leprous persons, to be from 10 to 14 years, and the median age of onset of those not so exposed to be older. Bechelli & Martínez Domínguez (1963) in Brazil showed that new immigrants had a higher mean age of onset than did native Brazilians.

Doull (1961) relates the Philippine findings to the age of opportunity for exposure. He follows this by stating that, in areas where the disease is common, the controlling factor is the acquisition of resistance due to unknown causes.

McCoy & Goodhue (1913) report that the infection rate in husbands and wives of infected spouses is of the order of 5%. This rate is similar to that seen in spouses of hospitalized patients in the USA at Carville, La. (Cochrane, 1959). Using data from the hospitalized group, Badger (Cochrane, 1959) wrote that there appeared to be little difference between the incidence among the adults and among

the children in families into which the disease had been introduced. (Rates varied from 4.4% to 5.5%.)

None of these rates takes into account years of exposure or what conditions could be included or excluded as leprosy, and they are therefore not in any way comparable. In general, it appears that a high proportion of exposed children get minimal lesions before the fourteenth year of life, and a small proportion of these lesions continue and are ascertainable after adolescence. There is some doubt as to whether an adult is as liable to contract these minimal infections and whether adults similarly exposed would have similar annual incidence rates.

Different surveys, some of them using sampling methods, in a number of different endemic areas, showed that prevalence rates by age increased progressively in lepromatous leprosy, but that in tuberculoid leprosy the prevalence rate was low in the age-group 1-4 years, increased at 5-14 years and then remained without major change in the age-groups 15-44 and 45 and over. In the Philippines (Doull, 1961), the median age of onset was lower in non-lepromatous than in lepromatous leprosy, and the prevalence rates for both forms rapidly declined after adolescence. The relative concentration of tuberculoid cases in children has been partly explained by the longer interval required from infection and onset of symptoms to a fully definable case in lepromatous leprosy; i.e., the higher proportion of tuberculoid cases in childhood could be attributable to a deficiency in or postponement of lepromatous cases. However, the regular increase by age in prevalence rates of lepromatous leprosy, when compared with tuberculoid leprosy, indicates different epidemiological pictures, unless it can be assumed that some tuberculoid leprosy patients recover and are lost to survey, while many lepromatous cases are permanently ascertainable.

Sex

Badger, quoting Doull (Cochrane, 1959), states that lepromatous leprosy is much more frequent in males than in females, with a ratio of 2:1 in most studies. The reason is not known, but, because higher rates are observed in male children and adolescents, it is attributed to greater susceptibility rather than to environmental differences. No sex difference has been found in the tuberculoid type of leprosy.

Most investigators partially agree with this statement. Tuberculoid leprosy, or non-lepromatous leprosy generally, has been recorded equally in the two sexes. However, there are exceptional areas, such as in some parts of Nigeria (Bechelli & Martínez Domínguez, 1963) where one sex or the other predominates. This situation is most unusual and may well be related to special community influences. Lepromatous leprosy has consistently appeared to have a male predominance in persons over 14 years of age (Bechelli & Martínez Domínguez, 1963; Doull, 1957; Doull et al. 1936; Guinto & Rodriguez, 1941; Innes, 1938; Lowe, 1938). Not only has this been a consistent finding, but the ratio has varied within only a very minor range. In general, this variation is from 1.6 to 2.0 males to each female. Below 14 years of age, where the proportion of lepromatous cases is small, there is some doubt. Doull et al. (1936), in some of the studies in the Philippines at Culion, could not demonstrate significant sex differences in total leprosy rates or in either of the clinical groups in children, although there were marked differences in adults. In Brazil and in the African and Thailand sampling surveys (Bechelli & Martínez Domínguez, 1963) no differences could be shown in children. In examining some of the studies that have been said to indicate no sex differences in leprosy, such as on Nauru (Wade & Ledowsky, 1952), and returning to the original quoted figures, it can be seen that these were areas or outbreaks where the non-lepromatous proportion of all leprosy cases was high. If the quoted cases are broken down into groups that contain a high or low proportion of lepromatous cases, using such criteria as segregation or the clinical description of nodular and maculo-anaesthetic, a marked excess of males can be seen in the segregated or more severe cases and no real differences in sex in the remainder.

The excess of males with adult lepromatous leprosy has been observed both in household contacts and in persons not known to have been exposed within a family (Doull, 1961). It appears not to be associated with differences in duration of illness, mortality, or by population proportions, and to be the result of a higher incidence rate in males.

Until it can be shown satisfactorily that lepromatous rates are greater in males in childhood, it cannot be assumed that this sex difference is necessarily due to sex differences in susceptibility. Badger (Cochrane, 1959), presenting no direct evidence, wrote that, in the continental USA and in Hawaii, the data suggested that the main factor causing the difference in sex prevalence was opportunity for contact, and that practically no difference could be noted when the opportunity for contact by the two sexes was the

same. However, in persons living in a household with a lepromatous patient and in areas such as Nauru, where leprosy reached almost a third of the population, it is probable that everyone could have been exposed. In these exceptional groups, the sex ratio was similar to that reported in most other studies. Therefore, it is reasonable to assume tentatively that the difference is a real one, independent of risks of exposure, and that it is possibly due to a host factor connected with susceptibility. This could be genetic, it could be a physiological difference, or it could be indirect and due to environmental influences acting selectively. The last possibility appears to be the least probable, because of the widely divergent groups from which these observations have been made.

Incidence, prevalence, and the proportions of leprosy types

Most estimates of the frequency of leprosy in communities have been based upon the number of reported cases in a given period of time or on cross-sectional surveys with a clinical screening of all, or a sample of, the population. In some of the reported results, the terms " incidence " and " prevalence " have been used synonymously, and many difficulties have resulted.

Because of the difficulty of defining the minimal leprosy case or of ascertaining all of the spontaneously cured tuberculoid or indeterminate lesions, and because of the incompleteness of most leprosy reporting systems, accurate estimates of incidence and prevalence are extremely difficult. Material from small, closely observed "captive" groups such as the Culion colony in the Philippines has been collected, but even from there much of the data has been presented in a prevalence form. In practice, incidence in leprosy can only be measured by serial surveys of the same population at set intervals of time or by longitudinal surveys, using rigid criteria for inclusion of new cases. The criteria used now contain a very high subjective component, and little information is available except for small, special groups.

A number of prevalence surveys, using accepted methods of sampling and of investigation of missing or lost people, have been carried out and tabulated. The criteria for inclusion of cases have sometimes not been stated or are not clear, but some of these surveys have been carried out by the same team in different areas and could be considered to be roughly comparable.

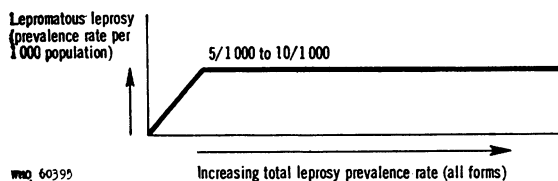In general, it can be said that the prevalence of leprosy (all forms) varies markedly from one area to another, and in very small divisions. One part of a town or a district may have a high rate and another, separated by a few miles, may have a low one. In many studies, these differences appear unrelated to climate, occupation, or ethnic grouping, although they may have some socio-economic connexions and be influenced by some possible relevant selective influence. (For example, some very inaccessible places could have an unusually high number of leprosy patients who had migrated there to avoid ascertainment or restriction.)

A high leprosy prevalence rate could be of the order of 20 per thousand total population at all ages. An exceptional group, in studies often including persons with minimal lesions and a large proportion of children and adolescents (such as on Nauru, in the Culion colony, or in populations made from aggregations of infected households), can have reported rates as great as 30%. A rate of less than 4 per thousand is still apparently high enough to allow for the perpetuation of the disease in what is thought to be an endemic area, and the minimal prevalence rate for disease survival is unknown. In Nauru (Wade & Ledowsky, 1952), the removal of all known lepromatous and infectious persons in the 1940s did not result in the elimination of the disease, although in the following years (with the addition of other control measures) its prevalence markedly declined. Leprosy-control programmes based upon segregation of infectious cases and/or treatment have resulted in an apparently decreased prevalence.

The prevalence rates of different types of leprosy (and therefore of the proportion of each type) have a very specific and recognizable pattern. This appears to have such relevance to the epidemiology and to the possible understanding of the disease that the lack of emphasis on it in the leprosy literature is inexplicable. While it has been remarked that " Contrary to what could be expected, it appears that in Cameroon, Northern Nigeria and Thailand there is no correlation between the lepromatous leprosy rate and [total] prevalence " (Bechelli & Martínez Domínguez, 1963) the constancy of the lepromatous leprosy rate and its maximum have not been stressed. From published surveys, the pattern of distribution of leprosy cases appears to be similar to that shown in the figure at the top of the opposite page.

The lepromatous leprosy prevalence rate starts from a low level in areas with few cases and rises

RELATION OF PREVALENCE RATES OF LEPROMATOUS
LEPROSY AND OF ALL FORMS OF LEPROSY

Lepromatous leprosy
(prevalence rate per
1 000 population)

5/1 000 to 10/1 000

wнo 60395   Increasing total leprosy prevalence rate (all forms)

TABLE 1
ESTIMATED PREVALENCE OF LEPROSY
PER 1 000 POPULATION IN NAURU [a]

	1924	1927	1936	1951
Population	1 300	1 300	1 600	1 600
Total leprosy cases	189	132	61	11
Estimated lepromatous cases	15	20	20	8
Total leprosy prevalence rate per 1 000	145	101	38	7
Lepromatous prevalence rate per 1 000	12	15	13	5

[a] Data from Wade & Ledowsky (1952).

rapidly until it reaches a level of 5-10 per thousand. It then remains stationary, with no apparent further increase in the total leprosy prevalence. This effect results in changing proportions of lepromatous and non-lepromatous leprosy cases, the proportion decreasing as the total rate increases. In those studies examined where this appearance was not shown, the number of indeterminate cases was high, and these indeterminate cases possessed a marked excess of males. This increase in male indeterminates fosters the suspicion that differences in classification can exist and result in interpretation errors. For example, in a comparison of three areas, using standard methods (Bechelli & Martínez Domínguez, 1963), the area with the lowest total leprosy prevalence had the highest lepromatous leprosy prevalence rate and the smallest proportion of indeterminates. If an adjustment is made in this study in all three areas, assuming that the excess of males in the indeterminates was due to the inclusion of lepromatous persons, the lepromatous rates between areas are similar, with the country with the highest rates having some excess.

If the figures of Nauru (Wade & Ledowsky, 1952), the area with the largest recorded epidemic, are rearranged according to crude divisions of possible lepromatous and non-lepromatous cases, the total and the lepromatous leprosy estimated rates are as shown in Table 1.

These are greater lepromatous rates than are recorded elsewhere, but the classification is difficult and uncertain, and quite large errors could be present. Certainly, the lepromatous rate did not decrease in parallel with the total leprosy rate. This effect could be explained by the length of illness in lepromatous leprosy and the successes of treatment in the other forms of leprosy. However, at no recorded time did the lepromatous rate reach as high as 2%.

If it is true that lepromatous leprosy behaves in this way in all societies, reaching a set maximum and then remaining constant, and if this observation is

consistent with the whole literature and with unpublished surveys, then the number of explanations is limited.

It immediately becomes improbable that lepromatous leprosy is caused by a more pathogenic strain of *M. leprae*. It is also unlikely that lepromatous leprosy is purely a more severe form of leprosy that occurs in a fixed proportion of leprosy infections. The possibility that lepromatous leprosy is partly the result of an initial or repeated massive dose of *M. leprae* must be considered to be most doubtful. If the assumption that there is a maximum prevalence rate holds true in different societies with markedly different environmental conditions, the suggestion that other influences or infections prior to infection with leprosy are related to the possibility of acquiring lepromatous leprosy when later exposed to *M. leprae* must be coupled with the assumption that these influences are world-wide and affect all societies equally. For most suggested influences, this is unlikely. Lastly, the hypothesis that the susceptibility to *M. leprae* that can result in lepromatous disease in infected persons is a host-determined characteristic that is possessed by a fixed proportion of all people everywhere is very much strengthened. The findings are what one would expect to observe as a result of such a selective influence.

Susceptibility and resistance

Susceptibility and resistance to most diseases can be judged by the variations in the number of infections in persons equally exposed to the agent, by variations in the proportions of persons infected who have symptoms, by variations in the severity of

illness in those with clinical signs, by the spontaneous cure rate and the length of illness, by the mortality due to the disease or by associated tests.

Two of these methods of measurement cannot be used with leprosy. The infection rate is unknown, as it is impossible, at present, to ascertain those infected, and the specific mortality rate is so low that it is unusable. There are, therefore, only four other possibilities.

It is clear that not all persons intimately and continuously exposed to infection, such as a child in a household with a lepromatous case, get the disease even in a minor form. The highest rates reported were those of Lara (1961, *op. cit.*) from the Culion colony, and the rate there could have been greater than 35% in children observed for varying lengths of time. Doull (1961), in a community survey, wrote that the secondary attack rate was much lower and dependent upon the type of leprosy of the primary case, as follows:

Primary case lepromatous—attack rate in household contacts, 6.2 per thousand person-years
Primary case tuberculoid—attack rate in household contacts, 1.6 per thousand person-years
Other persons in community with no known household exposure—attack rate, 0.8 per thousand person-years

Taking the figure of Lara as a maximum, it is clear that, often, two out of three exposed persons do not get a recognizable leprous illness. While it is possible that many exposed persons do not become infected, it is probable that infection can occur without recognizable illness. A large part of the variation in attack rates in Doull's study (1961) may well have been due to differences in exposure rather than in susceptibility or resistance. However, the importance of either factor is unknown.

It has been previously described that only a certain proportion of persons appear to be susceptible to lepromatous leprosy, the severest form. This is unlikely to be because there is a limit to the proportion of persons who can have a certain type or degree of exposure to the agent; it is more probably related to the limited number of susceptibles in the population who can express their infection in the lepromatous way.

Acquired resistance is said to be demonstrated by the age incidence of leprosy, with its maximum in adolescence. There are decreasing numbers of new cases in endemic areas as age increases beyond puberty, and a predominance of cases thought to have become infected in adult life in non-endemic areas, such as in parts of North America. This could

be a reasonable interpretation, if acquired resistance is thought to result specifically from an infection with *M. leprae*, and if symptomless infections can be shown to occur frequently. However, exposure opportunities also vary by age, and all or part of this variation could be due to this cause. It is very difficult to separate fully these two possibilities, although the probability is that acquired resistance must be of some importance.

The high secondary attack rate in exposed children is used as an argument for the belief that children are more susceptible than adults. However, the extremely high spontaneous cure rate (77%) reported by Lara (1961, *op. cit.*) in these children must be as high as, or higher than, the spontaneous cure rate in a comparable period of time in adults, and this cannot be described as a sign of low resistance.

Other factors

Climate is not thought to have direct relationship to the distribution of endemic leprosy areas. Although the present endemic areas are largely tropical, with high annual rainfalls, this has not been true in the past, and neighbouring areas with similar climates are not equally affected; for example, in the USA, there is high prevalence in Louisiana and Texas but low prevalence in Alabama and Mississippi.

Ethnic grouping. It has been noted that different groups within the same country may have different leprosy prevalence rates, and that there may be differences in the distribution of lesions and of the proportion of lepromatous cases in different areas. In Hawaii, the native Hawaiians and part-Hawaiians have a higher leprosy hospital admission rate than do the people of Chinese and Japanese descent (Cochrane, 1959). This author states that persons of Caucasian and Mongolian extraction have a more serious lepromatous type of leprosy than do Indians or Africans. All ethnic groupings have been reported as being subject to leprosy, but few comparisons have been made between similar groups of people faced with the same risks of exposure.

No convincing evidence exists that demonstrates variations in susceptibility or resistance by ethnic grouping. In the comparative sampling prevalence survey in Nigeria (Bechelli & Martínez Domínguez, 1963), the Hausa and Fulani, as well as being of different ethnic groupings, showed great differences in community patterns, way of life, socio-economic class, and type of person-to-person contact. However, no significant differences could be shown in

total leprosy prevalence, in the lepromatous leprosy rate or in the tuberculoid or indeterminate leprosy rates. Differences in the residual disabilities were seen, however. This is a remarkable similarity in two groups that differ in so many respects, and it could be used to argue against the existence of differences in susceptibility in these two peoples.

Precipitating or associated factors. Cochrane (1959) states that, very frequently, the first clinical evidence of the disease appears following stresses or strains such as physiological changes during puberty, pregnancy, menopause, and intercurrent and complicating disease. Reactivation of arrested cases, likewise, can occur after such episodes. This has been a frequent comment, but it is a clinical impression rather than a known, measured risk. Certainly, the peak incidence for reported leprosy occurs during puberty in many societies.

In the Philippines survey (Doull et al., 1936), there was a concentration of cases in the poorer areas. This has also been noted elsewhere, and leprosy has been said to be associated with poverty, dirt and overcrowding. This circumstance is not noticed to the same extent as in some other diseases, and whether the association is primary or secondary is unknown. In comparing leprous and non-leprous families in the Philippines (Cebu), Doull et al. (1936) found that overcrowding, as measured by a scale based upon the sleeping space per person, adjusted for age, was greater among the leprous. Age distribution and sanitary status did not differ markedly in the two groups.

Badger (Cochrane, 1959) considered that bedroom contact was important. He quoted Cochrane as reporting from India that, of the 62.7% of known patients with a family leprosy contact, 81% had " bedroom contact " and 18.9% only " house contact ". Without knowing more about the society, the proportion of houses with more than one bedroom, and the possibility of living in such a household without bedroom contact, this cannot be evaluated.

Badger (Cochrane, 1959), in his series of cases in Louisiana, thought that he demonstrated that family size was relevant, and that the larger the family, the greater the overcrowding and the more intimate the contact. He showed a progression of percentages of households who were " multicase families " according to family size. If Badger's figures are rearranged to take into account the variations in the number of persons exposed in families of different sizes (i.e., percentage of multicase families divided by family size minus the index case), this

gradient disappears, and no differences are present. This observation must be rejected.

Other diseases. As part of the Cebu (Philippines) survey of Doull et al. (1936), the occurrence of other diseases in leprous and non-leprous families was compared. These included dental caries, yaws, and skin diseases such as scabies, impetigo and tinea flava. No real differences could be demonstrated other than a possible excess of scabies in the non-leprous households.

In general, it is stated (Bechelli, 1949) that it appears that resistance is similar in all groups in all countries, and therefore predisposing causes are decisive in the spread of leprosy. If this is true, no important predisposing cause has yet been identified.

Tuberculosis. The observations that many leprosy patients at post-mortem show evidence of tuberculosis, that tuberculosis is stated to be the main cause of death in leprosy patients, that there is a partial association of the tuberculin and the lepromin tests in young persons, and the philosophical speculations (Chaussinard, 1948) that tuberculosis could be related in some way to the decline in leprosy in Europe, encouraged the belief that the two diseases could be related or antagonistic to each other. There is little direct or indirect evidence to support either view. Indeed, there appears to be no clear correlation between reported tuberculosis mortality and morbidity rates and leprosy prevalence rates in a number of countries studied, or between the tuberculin and lepromin coefficients in different districts of São Paulo, Brazil (Bechelli, 1957). No comparative study has been undertaken of the secondary attack rates in leprosy households that have or have not also a tuberculous index case. Although the causative organisms of both diseases are classified as mycobacteria, no other relationship has been demonstrated. The suggestion that tuberculosis is a frequent cause of death in leprosy patients may reflect the living conditions and the possible restrictions and institutionalization of some groups with leprosy and be, therefore, of doubtful significance, but if there were a real association between tuberculosis and leprous illnesses, it would be evidence against the antagonism hypothesis. Insufficient evidence exists to consider this question adequately.

Genetics. There is no evidence of transmission of the. disease from parent to child. However, some scattered observations are compatible with the transmission of susceptibility.

Children born of leprous parents and separated from them at birth do not appear to have a greater risk of contracting the disease than do other segments of the population.

Although children of infected parents who live in the same household have a higher leprosy rate than other children, this secondary attack rate appears to vary with the type of leprosy of the index case and could be due to greater risks of exposure to the agent.

Susceptibility, as judged by the lepromin test, has rarely been studied genetically. In one study (Beiguelman, 1962), Mitsuda negativity in families was compatible with a genetic hypothesis based upon an autosomal recessive gene.

There are numerous reports of leprous families with either continuous or interrupted histories of leprosy infection for many generations. Whether this is due to transmitted susceptibility or to risk of exposure is undetermined.

There have been few observations of infected identical or binovular twins. In two pairs of identical twins reported by Doull (1961) both members of both pairs had lepromatous leprosy, and the disease ran a similar course.

The possible variations in the proportions of lepromatous and tuberculoid illnesses in family contacts of persons of different leprosy types have not been studied fully; that is, it has not been established whether lepromatous or tuberculoid families exist. However, in a Philippine study (Doull et al., 1936) the proportion of bacteriologically positive secondary cases was similar in contacts of lepromatous and tuberculoid index cases.

Despite this virtual absence of evidence, advocates of the " anergic " hypothesis of lepromatous leprosy think that the lepromatous individual's limited tissue response to a leprosy infection is due to an inherent inability to respond. If this hypothesis is correct, it is possible that it is a genetically transmitted character as it is in laboratory animals.

THE LEPROMIN REACTION, ITS EPIDEMIOLOGY AND IMPLICATIONS

The antigen, the test, the reading and the interpretation have been given in many papers and reports and need not be further described here. They were fully described by the Committee of Immunology (1953) at the Sixth International Congress of Leprology and are further discussed in the first and second reports of the WHO Expert Committee on Leprosy (1953, 1960).

It is clear that the lepromin reaction is a complex and unstandardized skin reaction that occurs for unknown reasons. The antigens have bacillary and human tissue components and are denatured before use. Although there are methods of partially assessing the strength of the product, when prepared in certain ways, it is highly probable that it varies from batch to batch, and that this variation in strength and nature continues to occur even when pooled tissue from different sites and different individuals is used. With these known variables, it is remarkable how consistent the results have been in the hands of different observers in different areas when testing different populations. It is possible that this consistency may be due to the relatively little influence that strength and size of dose have upon this reaction.

Despite the known and expected variations, there is still no general agreement as to the method of preparation of the antigen and the reading of the test. At the Sixth International Congress of Leprology, the Committee of Immunology (1953) recommended the Mitsuda-Hayashi method of preparation of this material.

Two types of reaction are described; the early Fernandez reaction and the delayed Mitsuda reaction. The first of these, although studied in some detail by a large number of investigators, is difficult to interpret epidemiologically, and its importance is difficult to assess. It will not be dealt with further in this review.

At the Sixth International Congress of Leprology, the recommended readings of the Mitsuda reaction made by the Committee of Immunology (1953) varied from negative (−) through doubtful (±) to three-plus (+++). The distinctions between grades are made by measurement of infiltration, with or without ulceration, and appear to be definite and objective divisions that would make major observer variation or error small. These divisions and grades appear to be generally accepted. However, the time between testing and reading varies and appears to have significance. The recommended interval is between three and four weeks, but it is stated that some reactions become positive, or change in degree, only after 60 days or longer.

In many published studies, the time interval is not stated, and in the majority, only one reading is made, frequently during the third or fourth week. This must mean that accurate comparison between some studies is impossible.

Readings classified as ± (doubtful) vary markedly in the same individuals at different points of time,

and the second report of the WHO Expert Committee on Leprosy (1960) recommended that they be classified with the negatives.

Other observers describe the grade one-plus (+) as also questionable and believe that many reactors of this order behave as negatives rather than positives. Therefore, in some studies, all reactors with infiltration greater than 5 mm (++ and +++) have been classified as positive and all others as negative. It is probable that this adaptation decreases the errors due to the variations in the time of reading.

Bechelli, Rath de Souza & Quagliato (1957) attempted to correlate Mitsuda readings with the presence or absence of a granuloma, defined histologically, at the point of injection. There was a distinct relationship, but it was not completely consistent, and the addition of histology to gross readings did not appear to add to the test's accuracy.

The discovery of the Mitsuda reaction might well have remained a curiosity had it not been soon demonstrated that the reactions of certain individuals to the test was related to their clinical form of leprosy and to the prognosis. Those persons with what is now classified as the lepromatous form of leprosy rarely, if ever, were Mitsuda-positive to the ++ degree or greater and also rarely showed reactions of even ± (doubtful) or +. There have been some reports of + reactions following sulfone treatment of lepromatous disease, but it is not clear for how long or how frequently these individuals continue to react. Lowe & McNulty (1953) were never able to demonstrate this change, and other observers have reported similarly (Doull, 1961).

This distinction between clinical types of leprosy became so widely accepted that the Mitsuda reaction has frequently been incorporated in the definition of lepromatous leprosy. Bennett (1961) expressed this clearly when he stated that the answer to the question whether a lepromatous patient ever developed a positive Mitsuda reaction was that, if he did so, the patient must have been borderline or intermediate rather than lepromatous. With this idea current, discussion of the frequency of positivity of the Mitsuda reaction in lepromatous leprosy is of little value.

In the indeterminate form, the Mitsuda reaction can vary across the whole range but is often doubtful (±) or only +.

There are divided opinions as to the possibility that Mitsuda-positive persons can become negative. Changes from ± or + Mitsuda reactions to nega-

tive (−) have been described consistently in non-infected children, although this is a relatively rare event. There have also been scattered reports of a few changes from ++ to + or −. There is more doubt as to whether a tuberculoid leprosy patient with a positive Mitsuda reaction could ever become Mitsuda-negative; some consider this to be impossible (Lowe & NcNulty, 1953). If any of these " reversions " do occur, they are rare events that may well be explained by antigenic differences in the reagents used and can at present be discounted.

It is accepted that, of the various forms of the disease, lepromatous leprosy has the worst prognosis and is the most infectious, and that the tuberculoid form is more self-limiting, with a considerable tendency towards spontaneous involution, and that the intermediate form can change to either tuberculoid or lepromatous, and that therefore the Mitsuda test is a useful clinical tool. It is also accepted that the positive Mitsuda reaction can show a granuloma histology with many similarities to a tuberculoid lesion. These two points have been related and presented in the report of the Committee of Immunology (1953) of the Sixth International Congress of Leprology in the form of a general statement that " A positive lepromin reaction is regarded as an expression of a certain amount of resistance to *Mycobacterium leprae*, directly proportionate to the degree of positivity ". It appears that statements similar to this are based purely upon the prognosis of infected persons, and that " resistance " should be thought of in this way with this disease.

Mitsuda reactivity in uninfected persons

It was initially believed that a positive Mitsuda reaction resulted from an infection, with *M. leprae*, that was clinical, symptomless, abortive, or in the stage between infection and the appearance of symptoms. However, it was quickly shown that it could also be positive in individuals who had lived exclusively in areas where no recognized case of leprosy had existed for long periods of time, if ever, and therefore were unlikely to have been infected. It was also shown that it was probable that the reaction could become positive on an individual's exposure to antigens other than *M. leprae*. One explanation for this lack of specificity in provocation has been the possibility of cross-reactions with other mycobacteria such as *M. tuberculosis*, BCG, atypical mycobacteria, or to possible non-specific naturally acquired sensitization.

If a positive Mitsuda reaction indicates increased resistance of an individual to an infection with *M. leprae*, owing to acquired or inherent reasons, the demonstration of the distribution of this ability in populations is of the first importance in understanding the epidemiology of leprosy. However, it is possible that a positive Mitsuda reaction results from two unrelated factors: the ability to react and a sensitization experience. Therefore, a negative reaction, cannot be interpreted in an uninfected individual.

A number of lepromin surveys have been carried out in different countries and in different population groups. Because of the lack of standardization of the test, highly selected methods of population sampling, and the difficulty of interpreting the meaning of negative reactions, especially in the younger age-groups where they may be in the majority, the results are not strictly comparable, and comparisons should be treated with suspicion. There are however, some patterns that are consistent and interesting.

Geographical. Small studies of the lepromin test in adults have been carried out, including Negro syphilitic patients under treatment in New York (Azulay & Convit, 1947), healthy and tuberculous adults in New York (Rotberg, Bechelli & Keil, 1950), psychopathic patients in England, and other groups in Belgium, Italy, France and other places, (as quoted by Azulay & Convit, 1947), as well as in so-called endemic areas where leprosy is known to exist and has been clinically recognized. Positive Mitsuda reactions of greater than + + were demonstrated in as many as 60% of the adults tested, and more than 80% of adults were shown to give at least a + reaction in leprosy-free areas.

In endemic areas, the proportion of adult reactors shown to have readings of + + or greater was higher—São Paulo, 72%; Cebu, 90%; Spanish Guinea, 92% (Martínez Domínguez, 1953), Nigeria, 79% (Davey, Drewett & Stone, 1958)—but showed considerable variation.

No definite pattern has been demonstrated in these rates in either endemic or non-endemic areas. There is no clear indication that, in general, a high rate of reactivity in adults is related to climate, rural or urban living, ethnic grouping, occupation, or any other gross division of the population. This failure to demonstrate differences does not mean that no differences exist. No comparative studies have been undertaken.

Despite this lack of information, it is probable that most adults, in most areas, react to lepromin with the Mitsuda reaction, and it is possible that, in areas of endemic leprosy, they react more frequently than in non-endemic areas. It is also possible, but has not been convincingly shown, that the degree of reaction may be greater in endemic areas.

No major population group of any age-group, in any area, has been shown to give a + + or greater Mitsuda-reaction rate higher than 95%, although it is possible that in some areas 97% of the population may react up to + Mitsuda. The usual reaction rate is of a lower order than this.

Age and sex. There have been no meaningful longitudinal studies of Mitsuda reactions because of the probability that the lepromin test by itself, if repeated, may cause conversion. However, a series of cross-sectional studies, in endemic areas of South America, Africa, the Philippines and elsewhere, in children not known to be family contacts of leprosy cases, have given the proportion of Mitsuda positives at different ages. The Cebu studies (Guinto, Doull & Mabalay, 1955c) show that the proportion of persons giving positive Mitsuda reactions increases with age from almost complete negativity in early infancy to high levels at the adult ages.

In adults, different studies show small differences. In Cebu (Doull, 1961) with lepromin tests made upon 776 males and 1075 females in the general population, the males showed 67% of reactors and the females 70% with no substantial differences for any age-group. In a New York study of 73 adults (Azulay & Convit, 1947), the rates were 66% in males and 86% in females. In Nigeria (Davey, Drewett & Stone, 1958), the sex differences were reversed, as follows:

	Age-group (years)			
	30-39	40-49	50-59	≥ 60
Number tested	204	163	160	79
Males Mitsuda positive	77%	74%	74%	74%
Females Mitsuda positive	56%	60%	50%	67%

In general, it is stated that, in adults, no significant sex differences exist, but this has not been satisfactorily shown with sufficient accuracy to answer one important point. Patients with lepromatous leprosy include a distinct and clear preponderance of males, and this form of the disease is known to occur only in Mitsuda-negative people. If all of the " residual " Mitsuda-negative adults, who appear never likely to become positive, have equal " susceptibility " and risk of having a lepromatous lesion, it would be expected that male Mitsuda-negative adults would outnumber female Mitsuda negatives. If, on the other hand, a further selection factor exists within

the Mitsuda-negative group that occurs more often in males, or if the Mitsuda reaction prior to illness is irrelevant to the risk of having a lepromatous illness, the proportion of negatives in the two sexes would be expected to be the same.

The issue is complicated by the observation that there is apparently a maximum lepromatous leprosy prevalence rate in a population that is lower than the Mitsuda-negative rate at any age. In no survey or study published and considered here, even in " epidemic " situations, has a lepromatous leprosy prevalence rate in a population been reported that was greater than 15 per 1000 persons and only rarely as high as 10 per 1000 persons (1 %). Therefore, it is probable that not every Mitsuda-negative adult is able to have a lepromatous leprosy illness. If the subgroup of the Mitsuda negatives who can have lepromatous leprosy has a male preponderance, then it will be only a small proportion of the total population and is unlikely to have been demonstrable in the rather small numbers tested in the reported studies. The possibility of such a subgroup being shown would be greatest in an area and in an age-group where the Mitsuda-positive rate was highest and where all leprosy patients, or at least all of the lepromatous leprosy patients, were included in the population sampled. (In those studies where leprosy patients were excluded, the opposite sex ratio might be expected.)

Changes in the Mitsuda reaction

Spontaneous changes. Very few factors have been measured in relation to changes in Mitsuda reactivity. Those most frequently studied are mentioned in this section. Changes occurring independently of these are described as spontaneous. The possibility that some of these changes are not the result of sensitization to a specific substance or agent but are expressions of age or to some endogenous development in the host cannot be excluded. If, however, the conversion from Mitsuda negativity to Mitsuda positivity is partly an independent and inherent expression of development of the host, it would be expected that the regional variations in different groups would be less than have been observed. The known local variations could be due to ethnic grouping or they could be attributable to variations in sampling, reagents used, method of reading or other differences. However, it is probable that none of these explanations is adequate to explain the variability observed, and it is more reasonable to postulate that some unrecognized agents, sub-

stances, or factors in the environment, with different degrees of contact with young children, are related to conversion.

A number of accurate and interesting studies have attempted to measure the " spontaneous " conversion independently of changes that could have been due to the lepromin test itself or to immunizing agents. One important one (Doull, Guinto & Mabalay, 1957) in the Philippines was upon young children from endemic areas but with no known family exposure to leprosy. In the Philippines, 11.5 % of the children studied were calculated to have changed from Mitsuda-negative to Mitsuda-positive spontaneously in approximately 100 days. Even though the age-groups studied were those with the highest known conversion rates, this would assume, if all children behaved alike, that 80 % of the child population would become Mitsuda-positive spontaneously in about three years. It is known from other studies in the same area, however, that this is not the case. Nevertheless, it is clear from the control populations in these experiments that conversion of the reaction occurs that cannot be explained by exposure to *M. leprae*, *M. tuberculosis*, the lepromin reagents or tuberculin. It is speculated that this could be due to infections with other mycobacteria, but no evidence is presented.

The substances, agents, or influences responsible (if such factors exist) are ones that must have world-wide distribution, a high attack rate in all populations and act upon babies and children in the first few years after birth. They apparently can be prevalent both in the cities and in the rural areas. They possibly can show considerable variations in their influences in different local areas within the same region. It is probable that they are as prevalent, if not more prevalent, in what are known to be endemic leprosy areas, as nearly every endemic area tested and reported (mostly using unstandardized study techniques) has a high Mitsuda-positivity rate, although few, if any, childhood surveys have been done in non-endemic areas and therefore only adult comparisons are possible. There is no evidence to show that, in areas where the conversion rate is lower at a given age, the leprosy rate (prevalence or incidence) is higher or that the incidence or prevalence of lepromatous leprosy is greater. Indeed, the fragmentary evidence that exists is opposed to this.

Changes due to M. leprae *infections.* When the Mitsuda reaction was recognized, it was thought that a positive test indicated a previous *M. leprae* infection. When this idea was discarded, it was

replaced by the hypothesis that agents other than *M. leprae* could cause or precipitate conversion.

As leprous infections cannot at present be consistently recognized by clinical or any other methods, as the incubation period of known leprosy patients is rarely known or estimable, and as the Mitsuda reaction may change during a leprous illness, there is no direct method of demonstrating the effects of *M. leprae* upon the Mitsuda reaction. Any evidence that is available is indirect and must be related to the experience of individuals who have different degrees and intervals of exposure to infected persons and therefore different chances of clinical and subclinical infections. That differences of exposure lead to different secondary attack rates of illness is well documented.

For example, in some studies conducted in the Philippines (Doull, 1961) the leprosy secondary attack rate per 1000 exposure-years in households with a lepromatous index case was 6.2, in households with a tuberculoid case it was 1.6, and in the community not known to have household exposure the rate was 0.8.

In this study, it would be expected that the children exposed in these different ways would show a similar trend of Mitsuda-positive proportions by age, with the highest rates in the families of lepromatous patients. However, the evidence published relating to this is mixed and unsatisfactory. In 1938, De Souza Campos (quoted in Lara, 1940) stated that all children isolated at birth from their leprous parents reacted to lepromin negatively, while the more strongly positive reactions were in relation to longer periods of life with their infected parents. This finding is not in accordance with other studies, as it is known that Mitsuda-negative children can be found in lepromatous households and positive children in non-infected households. The age of the children in the De Souza Campos study was not stated.

Lara (1940), in a study of 110 exposed children, believed that there was an indication that prolonged and constant exposure to leprosy and repeated testing acted as sensitizing factors. However, his groups of subjects do not appear comparable, and the figures that he quotes are of questionable significance.

Guinto, Doull & Mabalay (1955b) could show little or no difference in lepromin reactivity (at the + + level). Comparable age-adjusted percentages of Mitsuda-positives for all ages in their study community were:

Subjects	*Percentages*
Contacts of lepromatous cases	73.4
Contacts of tuberculoid cases	68.3
Never lived in a household with a leprosy case of either type	68.2

In this study, which showed no difference of any statistical significance, there appeared to be a possible trend of a greater number of Mitsuda reactors in children aged 10-14 years living in lepromatous households.

It could be argued that, if this study group included mainly adults or adolescents, any differences might be cancelled out by spontaneous sensitization. The proportions of reactors at younger ages on an age-specific, rather than on an age-adjusted, basis would be the only reasonable comparison. Therefore, in general, the question is still in doubt and unresolved. Certainly, it appears unlikely that the large proportion of positive reactors in adult life are the result of *M. leprae* exposure.

Changes due to tuberculosis and the relationship of the lepromin and tuberculin tests. The relationships (described in a previous section) between tuberculosis and leprosy have been studied also in relation to the lepromin test. A large number of studies have been carried out to try to document this, but some of the results are contradictory.

In summary, it can be said that, while tuberculosis is frequently concurrent with leprosy and (by some observers) is actually the most frequent cause of death in that disease (Cochrane, 1959), in adults the proportion of persons known to be infected with tuberculosis who are Mitsuda-positive is not markedly different from that of the general population. In people with severe tuberculosis, a large proportion may be Mitsuda-negative, but this is believed to be a temporary state (Radna, quoted by Azulay & Convit, 1947).

In many different population groups that have not been given BCG, an association has been clearly shown between tuberculin-positive and Mitsuda-positive reactors. This association is closer if large doses of the antigens have been given, the higher readings have been used, or the comparisons have been made in adolescents and young children rather than in adults. This association is not a fixed one. In different areas using the same antigens in the same age-groups and in different studies in different regions, the proportions of reactors to one test who also reacted to the other have varied markedly. If those members of a community who react to the tuberculin test with purified protein derivative

(PPD) are said to include all of those persons who have been sensitized to *M. tuberculosis*, then this infection cannot be said to cause, or to be responsible for, a large proportion of Mitsuda-positive reactions. In a number of studies, the proportion of tuberculin-positive adults has been found to be similar in the Mitsuda-positive and the Mitsuda-negative fractions of the community.

From the literature, it is difficult to appreciate fully what proportion of the tuberculin reactors become positive before or after their Mitsuda reaction becomes positive. However, it appears that the age of major conversion to these two tests is not the same in most societies; the Mitsuda reaction changes first, in early childhood, and the tuberculin reaction changes around adolescence.

It is not known whether those persons who are assumed to have converted from Mitsuda- and tuberculin-negative to positive simultaneously, and possibly as a result of a tuberculous infection, would have converted spontaneously to Mitsuda-positive at some later date if they had not been so provoked. It is assumed that they would, as the adult Mitsuda-positive rate appears to be similar in different societies with different tuberculosis experience. The evidence for this is most incomplete.

Changes due to repeated lepromin testing. The suggestion that repeated lepromin testing could by itself cause an increased proportion of positive reactors in some Mitsuda-negative persons when tested subsequently was hotly contested for some years (Wade, 1955). This question was important, as it affected the validity of a number of longitudinal studies.

Later, a number of studies, controlled, and with an adequate number of observations in Brazil (Bechelli, 1959), the Philippines (Doull, Guinto & Mabalay, 1957) and elsewhere, confirmed this possibility, but showed that in children the changes were of a low order (7.2% in the Philippines) and less than the changes due to " natural causes " or to BCG. The proportion of conversions varied in different population groups and in different experiments.

Bechelli (1959) and others were also able to demonstrate that the type of Mitsuda reactions also appeared to change, and that weakly positive reactors were more infrequent in the group repeatedly tested.

The inconsistency and unpredictability of the reactions of those who convert after this experience were similar to those commented upon under tuberculosis.

Wade (1955), in an editorial, discussed the inconsistencies of reported studies and stressed that the changes due to repeated testing were denied by some workers and described by others as unusual experiences.

Despite these disagreements concerning fact and observation (which plague so much of the leprosy literature), it is probable that changes of a low order related to repeated testing do take place.

Changes following BCG. The ideas and discussion relating tuberculosis to leprosy led Fernandez (1939) to experiment with BCG and many other investigators to enlarge upon his findings later. One review (unpublished) describes 49 such studies of varied quality.

It is generally agreed that the administration of BCG can lead to Mitsuda positivity in a variable proportion of Mitsuda-negative persons. The changes in conversion rates vary in one series of studies (unpublished) from 30% to 100%. This wide variation could be attributed to a number of factors listed here in their probable order of importance.

(*a*) In many studies, no allowance was made, or no controls studied, to demonstrate the conversions that probably were induced by natural causes, lepromin testing or other factors in the same period of time. Some reported conversions should not be credited to BCG.

(*b*) Differences in age-groups. At the older ages, the conversion rate decreases to very low levels.

(*c*) Differences in the lepromin test, both in antigen used and in criteria for readings.

(*d*) Differences in both the potency, the type, and the methods of administration, of the BCG.

If all of these variables are taken into account, and greater weight is given to well-controlled studies carried out under a standard type of study plan, it could be estimated that possibly 35% to 50% of Mitsuda-negative children under the age of 3 years convert to Mitsuda-positivity probably as the result of either intradermal or oral BCG (considering as positives only ++ and +++ Mitsuda reactions).

The conversion of these same groups to positive tuberculin reactors does not occur in parallel (Doull, Guinto & Mabalay, 1957). It has generally been observed that a greater proportion convert to positive in the tuberculin test; i.e., there remain Mitsuda-negative children who are tuberculin-positive.

One explanation for this interesting relationship between BCG vaccination and lepromin reactivity has been that there may be some possible antigens

in common. This is possible. However, considering the non-specific nature of the lepromin test, the number of unknown factors that may apparently be related to Mitsuda conversion and the proportion of individuals who do not react to both tuberculin and lepromin tests although they have had a similar BCG exposure, the full explanation remains obscure.

Changes related to other mycobacteria. Guinto (1961) investigated the reaction of Mitsuda-positive children to PPD of the tuberculin type and suspensions of *M. tuberculosis* of the human, avian and Battey types. These findings were said to show clearly that infection with *M. tuberculosis, M. avium* and the Battey organism, or possibly with other antigenically related mycobacteria, might have caused some of the positivity to lepromin.

Nevertheless, more than 50% of those negative to the *M. tuberculosis* preparations (PPD and whole bacillus) and to the *M. avium* preparations were still positive to lepromin. The tentative conclusion is reached that mycobacterial infection cannot fully account for the high reactivity to lepromin shown by the children in the study.

Little further work has been done in this area, and no additional conclusions are possible.

Other influences on the Mitsuda reaction

Infections other than tuberculosis. Little systematic work has been carried out on this subject. There are no other infections or diseases that are known to be associated with the conversion of the Mitsuda reaction or to occur solely or mainly in the Mitsuda-positive or -negative groups. It is possible that, during a debilitating and toxic illness other than leprosy, the Mitsuda reaction can become less marked, but this effect appears to be temporary and is questioned by some observers.

Agammaglobinaemia and non-reactor states. As two of the observations of significance in the lepromin reaction are (a) the failure of segments of populations to react, and (b) the negativity of lepromatous cases, it is reasonable to ask whether the " anergic state " is restricted to leprosy, or whether the persistent negative group is generally non-reactive.

There is little evidence on which to base a judgement. Lepromatous patients and adults not known to have leprosy but with negative Mitsuda reactions appear to show similar proportions of tuberculin reactors when compared with tuberculoid leprosy patients and to Mitsuda-positive non-infected

persons. In children of certain ages, there is an excess of Mitsuda-positive children in the tuberculin-positive group; this excess varies in different studies.

There appear to be no published studies showing that Mitsuda-negative (or persistent Mitsuda-negative) children or adults have greater morbidity or mortality rates for other diseases, more frequent vaccinia reactions, or a greater prevalence of agammaglobulinaemia or hypogammaglobulinaemia. If such relationships do exist, they are unlikely to be marked, as lepromatous leprosy appears to be present in high-mortality areas where persons with such disabilities would have greatly diminished chances of survival.

Mortality and morbidity. Many individuals and family groups with leprosy (especially in the past) live in special communities with many close contacts for long periods of time and are under constant and regular medical observation. Others live in their normal communities but are regularly seen by medical people for a large part of their lives. In addition, many leprosy-control schemes follow up contacts and family groups not known to be ill or infected, but who have been lepromin-tested on at least one occasion.

Because of this, it is reasonable to expect that a considerable amount of data would be available on other conditions related to leprosy and the Mitsuda reaction, that accurate life-tables would be published and confirmed, and that specific mortality and morbidity rates by age and sex would be published.

No such studies are known to me. From necropsy studies, it is stated that tuberculosis is common and is the major cause of death in leprous individuals, at least in some areas. This finding could well be expected in any closed debilitated group and must be of questionable significance. No reasonable conclusions as to mortality from leprosy or of morbidity or mortality from other conditions among those infected with leprosy are possible.

Genetics. In many published papers, it is suggested that persistent Mitsuda negativity is an inherited characteristic. If the Mitsuda-negative group, which fails to react, is just one extreme end of the spectrum of reactors in a population (a positive expression of variation such as is seen in laboratory animals challenged with *M. tuberculosis* or other agents), it is reasonable to expect that inheritance could play a significant part.

Little is known on this subject. Young children may be Mitsuda-negative (a) because they have not

been sensitized, (b) because they have not yet reached an age when they could become positive, or (c) because they may be persistent negatives. It is not possible to divide them into any of these categories except in the light of their subsequent experience. Except by lepromin testing, no division of adults is possible by history or clinical examination other than the selection of those known to have had lepromatous leprosy and whose Mitsuda negativity can be assumed. These types of complications make reasonable population studies for genetic connexions difficult, complicated, or time-consuming, but not impossible. No results are available other than the fragmentary observations related to leprosy cases mentioned elsewhere and the one study already quoted (Beiguelman, 1962). There appears to be an urgent need to fill in this gap of knowledge.

Relationship of the lepromin reaction and leprosy

The relationship of Mitsuda negativity to lepromatous leprosy was one of the important associations that directed detailed attention to the lepromin reaction. As a test, it was useful clinically. However, in the past decade, the pressure from leprologists has been to extend the test's application towards the preventive and control aspects of leprosy. This is not easy to do on the basis of the existing data, as several possibilities exist as to how or why the reaction is related to one or other clinical form of the disease. For this reason, it is useful to examine the three existing hypotheses, both from what is known about the epidemiology of leprosy and from the confirmed observations and the possible epidemiology of the lepromin test itself, to consider the possible connexions and the evidence in favour of each one, and to make a reasoned judgement as to the one which appears to be the most probable.

(1) *Tolerance or desensitization hypothesis.* This has been proposed by a number of investigators and has been extended and discussed forcefully by Shepard (1961). It can be said that a person with clinical lepromatous leprosy and a negative Mitsuda reaction is showing a failure to respond immunologically to *M. leprae*. This could be due to "desensitization" or to "immunological tolerance". Tolerance can be induced in an immunologically immature animal by exposure to an antigen or, at a later stage, by the presence of large amounts of the antigen. If tolerance is permanent, living cells must generally be present to continue providing antigen and to maintain the tolerant state. The hypothesis that this is the cause of Mitsuda negativity in persons

with lepromatous leprosy is therefore one that assumes that the negative reaction can be a result of a massive infection and is related to the clinical type, and is not the cause of it. There are observations and arguments both for and against this possibility.

It is unlikely and against many observations that tolerance in this disease is invariably attributable to the infection of immunologically immature persons. There are many clear examples of persons with a first-known exposure to *M. leprae* in adult life who have been shown later to have the lepromatous form of the disease. The age distribution of lepromatous leprosy is older than in the tuberculoid form and also than in the indeterminate type. Although there may be differences in the incubation periods or in the times between infection and the onset of definite and diagnosable illness (for example, many actually lepromatous patients may have been recognizable only as indeterminate for a number of years), the variations are greater than would be expected if the infection occurred at the age of immunological immaturity. Consequently, in many persons, this tolerance would have to be of the induced variety.

In lepromatous leprosy, larger numbers of *M. leprae* are found than in any other form of the disease. A number of estimates of the bacterial load have been made, and these add up to enormous numbers and weights of bacilli. There is no evidence that, in indeterminate leprosy, a prediction can be made as to the likelihood of a later lepromatous illness by means of an estimate of probable bacterial numbers, even though at this stage the Mitsuda reaction may be doubtful or negative.

The large numbers of bacteria expected could be masked, unrecognizable or unlooked for, using the crude bacteriological and histological methods at present available. However, what evidence exists is against this possibility.

Most (some leprologists say *all*) lepromatous patients remain Mitsuda-negative after their acute illness is completed and when no further activity can be observed. This negativity is thought to continue for the remainder of their lives. Thus, persistent tolerance could be due to persistent infection with living *M. leprae*, as experimentally identifiable bacilli are recognizable for long periods after clinical recognition. However, in many treated or recovered lepromatous patients, using accepted methods, no bacilli can be demonstrated in the skin, although the may be seen incidentally in the bones or in the spleen.

TABLE 2
TYPES OF LEPROSY ILLNESS IN 680 PERSONS WHO HAD BEEN LEPROMIN-TESTED
15-20 YEARS EARLIER [a]

Groups [b]	No. of persons	Cases of leprosy		
		Lepromatous	Non-lepromatous	Total
1	524	0 (0 %)	17 (3.2 %)	17 (3.2 %)
2	47	6 (12.8 %)	1 (2.1 %)	7 (14.9 %)
3	93	1 (1.1 %)	4 (4.3 %)	5 (5.4 %)
4	16	8 (50.0 %)	2 (12.5 %)	10 (62.5 %)
Total	680	15 (2.2 %)	24 (3.5 %)	39 (5.7 %)

[a] Data from Dharmendra & Chatterjee (1956).
[b] Group 1, persons found to be Mitsuda-positive at earlier testing; Group 2, persons found to be Mitsuda-negative at earlier testing; Group 3, persons initially Mitsuda-negative who became positive after testing three times in one year; Group 4, persons initially Mitsuda-negative who remained negative after testing three times in one year.

An essential part of the tolerance hypothesis is that, before illness or the inducement of the tolerant state, potentially lepromatous persons should have the same proportions of Mitsuda-positive and -negative reactors as the remainder of the population; i.e., if Mitsuda negativity in infected persons is not due to host capability or to past experience, then there should be no reason to expect a selective bias as judged by the lepromin reaction.

In order to observe this, it would be necessary to follow up a population of known Mitsuda reactors, both positive and negative, recording their leprosy incidence rate by clinical type. To obtain meaningful figures, this would be laborious and time-consuming, as the follow-up period would have to be long and the population chosen be one with high exposure. A number of studies partly doing this have been published. All have various methodological aspects that make their interpretation difficult, appear to be so biased that they are unbelievable, or omit essential data of standardization or description without which no judgement is possible. The most convincing is that of Dharmendra & Chatterjee (1956). In this study, a group of 803 healthy persons had been lepromin-tested 15 to 20 years previously (age unstated) as part of two other investigations. Of this number, 123 had died or were unavailable, leaving 680 persons who could be re-examined. Thirty-nine of them were found to have leprosy.

Of the 680 found, records showed that they could be divided into four groups: (1) those tested once

and found to be Mitsuda positive (524); (2) those tested once and found to be Mitsuda negative (47); (3) those initially Mitsuda-negative but who became positive after testing three times in one year (93); and (4) those initially Mitsuda-negative who remained negative after testing three times in one year (16).

The leprosy rates in these four groups are shown in Table 2.

The variation in the leprosy rate in the Mitsuda positives divided according to degree of reaction showed no statistically significant differences.

Neither the proportion of Mitsuda-negatives and -positives in the unavailable group nor the age distributions of any of the groups is stated. These omissions could result in errors of interpretation, as it is quite possible that the three initial lepromin-negative groups (2, 3 and 4) contained a higher proportion of young persons. The lepromin-positive group (1) might contain more adults who had a lower exposure rate or from whom leprosy cases had already been excluded. This argument is less likely to be valid in a comparison of groups 2, 3 and 4. Here enormous differences in leprosy incidence are obvious, mainly, if not solely, in the incidence of lepromatous forms. The highest rates were in the " persistent " negatives, the next highest in the group that would probably contain a proportion of persistent negatives, and the lowest rates in the converters or the converted.

If the Dharmendra & Chatterjee (1956) study is accepted, it would be quite opposed to the tolerance

hypothesis, unless it is assumed that half of the group 4 subjects were already incubating the disease at the time of initial testing. This appears improbable, although the age of onset and the interval between testing and onset were unstated for any group.

Using the tolerance hypothesis, it would be reasonable to expect something to follow that does not seem to occur in practice. If lepromatous leprosy is a result of an overwhelming infection with M. leprae in a proportion of infected people, it would be reasonable to assume that either a constant proportion of infected persons would get this form of the disease, or that lepromatous leprosy rates would be partly dependent upon the size of the infecting dose.

Neither of these possibilities has been observed. The proportion of lepromatous cases among all known cases varies very markedly in different situations. It has previously been described how, in nearly every published observation, there appears to be a maximum lepromatous leprosy prevalence rate that has rarely been recorded as above 1%, even in epidemic situations. This is the type of finding that one would expect when there is a limited and finite number of possible susceptible hosts, but not under the tolerance hypothesis.

In family contacts of lepromatous and tuberculoid index cases, the risk of contracting leprosy shows great variations, which can best be explained by postulating different degrees of exposure to infection. However, in the limited number of published studies available, there is no convincing evidence that the proportion of lepromatous cases is different in the two groups.

If all of these arguments, not one of which is completely convincing by itself, are examined together, it could be said that the evidence is against this hypothesis being a valid one. However, it is unlikely that it could be disproved completely without a controlled and unbiased prospective study.

(2) *The resistance hypothesis.* This position has strong support from a large group of leprologists.

In this hypothesis, a positive Mitsuda reaction is thought to be a measure of induced resistance to M. leprae. While accepting that Mitsuda conversion from negative to positive can be brought about by exposure to M. leprae, M. tuberculosis, the Mitsuda reagent, and to natural or unknown causes, it is considered that all of the known provoking agents show antigenic overlap and result in an increased ability to withstand an infection of M. leprae and so make the lepromatous form of the disease less

likely to occur. It is thought probable that some persons do not ever become Mitsuda-positive and are therefore at considerable risk, but that there is no real distinction and difference, as far as risk of lepromatous leprosy is concerned, between the " persistent " Mitsuda-negative person and those individuals (young children, for the most part) who have not yet had the challenge that could lead to their Mitsuda conversion. According to this hypothesis, the Mitsuda reaction is important, as it measures the provocation experience, and therefore the induced resistance, rather than any inherent ability or resistance that may be present.

This hypothesis is difficult to support or refute. The study of Dharmendra & Chatterjee (1956), previously discussed, is almost as consistent with this hypothesis as it is with the anergic (factor N) hypothesis, which is discussed below.

It could be argued that the high attack rate in children is not due merely to increased exposure to infection but also to increased susceptibility, because the resistance is lower in children as measured by the Mitsuda reaction.

The increased age of onset of the disease in lepromatous patients who are not known to have lived in an infected family could be explained by the argument that young children in families without an index case are not exposed to M. leprae to the same extent; i.e., that this is an expression of exposure rather than resistance or susceptibility.

The apparent " maximum " community lepromatous leprosy prevalence rate on a world basis is harder to explain. It is possible that the exposure of any person to agents that provoke the Mitsuda reaction is so probable, on a set-risk basis, that there is a maximum percentage of Mitsuda-negative persons, without resistance, who are subject to lepromatous leprosy when infected.

In close, susceptible communities where infection is thought to have been introduced and followed by an epidemic, such as on Nauru Island (Wade & Ledowsky, 1952), information is scanty and classifications are obscure. However, there are no reasons to believe that the Mitsuda reaction would not show about the same proportions of positives and negatives by age on Nauru Island as in other parts of the world. If this were true, and this hypothesis were correct, the Nauru epidemic should have contained the same proportion of young people with lepromatous leprosy as elsewhere in the world, rather than the spread of cases to all age-groups, initially in adults, that has been described.

Continuing the same argument, if no control or other variables were taken into account, the lepromatous leprosy rate would vary according to the proportion of Mitsuda-negative persons in the community. However, the opposite appears to be the case. Even if the excess of Mitsuda positives in endemic communities is said to be due to an exposure to *M. leprae* and other antigens in minimal doses, it can still be argued that, in those areas with a low Mitsuda-positive rate, the age distribution of dates of onset of lepromatous cases should be higher. The published figures for this geographical comparison are so unstandardized and unreliable that it is impossible to find the answer to this question from them. However, there is an impression that there is no correlation between the distribution of age of onset of lepromatous leprosy and the proportion of Mitsuda-positive persons.

It is thought that there is an association between infections with tuberculosis and Mitsuda conversion. If this were so, and the tuberculosis infections occurred at an early enough age, there should be an inverse correlation between the proportion of leprosy cases with lepromatous leprosy and tuberculosis indices. Bechelli (1957) attempted to examine some aspects of this question, using the notoriously unreliable reported tuberculosis mortality and morbidity figures for a number of countries, but he could not demonstrate a relationship to leprosy (all forms) prevalence rates. He was also unable to demonstrate any relationship, in different parts of São Paulo, Brazil, between tuberculin-positive rates, leprosy prevalence rates and the proportion of different types of leprosy.

No studies have been published comparing the proportions of types of leprosy or the secondary attack rates of lepromatous leprosy in tuberculous and non-tuberculous families with an index leprosy case.

The paper by Chaussinard (1948), relating the decline of leprosy in western countries to the increase in tuberculosis, is not consistent in time and has no evidence to support it.

The observation that no lepromatous cases, even after spontaneous or therapeutic cure or arrest, ever develop resistance, as measured by a positive Mitsuda reaction, is remarkable. It is equally remarkable that no tuberculoid patients, even after a severe illness or series of reactions, ever lose their resistance, as indicated by becoming negative to the Mitsuda test. This must mean that either resistance or lack of resistance is absolute, or that they are unchangeable after a certain point. There are few examples of this in other diseases, and it is difficult to accept it for leprosy.

There are points and arguments for and against this hypothesis, and many aspects where insufficient data are accessible. Most of the evidence is against it, and at this time the resistance hypothesis must be considered an unlikely one.

(3) *The anergic* ("*factor N*") *hypothesis.* One of the leading advocates of this hypothesis is Rotberg (1957). In it, it is speculated that a constitutional factor exists that gives an individual the capacity to react specifically to *M. leprae* (factor N—for natural). The "anergic margin" is the one that shows epidemiological and prophylactic interest, as it is from this minority that lacks factor N that the lepromatous cases are drawn. Secondary or accessory factors (such as debilitating and unknown conditions) are needed to change an anergic and leprosy-infected individual into an active case of lepromatous leprosy. Persons who lack factor N are Mitsuda-negative, as are persons who possess factor N but who have not been exposed to a provoking agent. The "persistent" negatives are those individuals who lack this factor.

There are a number of observations that support this view.

(*a*) If the findings of Dharmendra & Chatterjee (1956) are accepted, their group 4 (persons initially Mitsuda-negative who remained negative after testing three times in one year) includes the highest proportion of persons who lack factor N, and group 2 (persons tested once and found to be Mitsuda-negative) contains some of them. These groups had the highest rates of lepromatous leprosy (see Table 2). In the light of their conversion from Mitsuda-negative to Mitsuda-positive, the persons in group 3 possessed factor N and therefore had leprosy rates similar to those of the other Mitsuda-positives.

(*b*) The hypothesis assumes that the inherent presence or absence of factor N is characteristic of all people, and that therefore the liability of a population to lepromatous leprosy would be greatest in any endemic area with high rates of exposure to *M. leprae*. This is in agreement with the actual observations.

(*c*) A gradient could exist, with some Mitsuda-negatives having subclinical or minor illnesses once they were infected with *M. leprae*. However, no Mitsuda-positive person would have a lepromatous illness.

(*d*) If it is accepted that the only persons certainly known not to have factor N are those who are Mitsuda-negative and have had a lepromatous illness, then none of these individuals would be expected to become Mitsuda-positive, whatever the provocation or subsequent experience. This is reported to be the case.

(e) The hypothesis assumes that where equal chances of infection exist, and when allowance is made for the long incubation period, the distribution of the ages of onset of lepromatous cases will be found to cover the entire population. This is consistent with known observations.

(f) If reaction-provoking agents such as BCG and *M. tuberculosis* have an antigenic overlap with *M. leprae*, there would not be expected to be a complete correlation of the tuberculin test with the Mitsuda reaction; there would be some exposed persons who could not be converted to Mitsuda-positive, irrespective of dose or frequency of exposure to *M. tuberculosis*. As the proportion of Mitsuda negatives decreases in a population, the proportion of Mitsuda-negative and tuberculin-negative people able to be converted to Mitsuda-positive by an infection with *M. tuberculosis* or BCG would decrease. This has been demonstrated quite clearly.

Doull (1961) brought examples from laboratory experiments to support the anergic hypothesis. In general, it is true that recognized infectious disease tends to be incurred by but a small proportion of those exposed; in short, by those individuals who are innately less capable of being immunized.

This factor N hypothesis seems to be the one most consistent with known occurrences. However, there are large gaps in the evidence that must leave some room for doubt. It seems improbable that it is capable of being confirmed until a method is developed to identify those persons deficient in factor N, a factor that could be specific for this one disease.

BCG AND LEPROSY

The place of BCG in leprosy prevention is now one of the major points of discussion in the current literature on leprosy and at leprosy congresses. The possibility of finding some method of preventing illness in those exposed to leprous infection or of moderating the form of the illness is such a welcome one for endemic areas that much attention has been directed towards the use of BCG for these purposes. Although the literature on this aspect of leprosy is extensive, it does not include any report of a controlled trial of a standard type that is clear and acceptable. Such a trial in a disease with a relatively low attack rate, a distribution mainly confined to tropical areas, a long incubation period and with unsatisfactory definitions, is expensive, time-consuming and difficult to undertake. It is reasonable to propose a trial of this nature only

if there are good grounds, from both the theoretical and observational viewpoints, to think that BCG is likely to be effective. In this section, the grounds on which BCG has been proposed, some of the existing studies on Mitsuda conversion and on leprosy prevention, theoretical arguments for and against possible success, and some observations upon the form such a trial should take if one were proposed, are presented serially. Behind this presentation and discussion must lie the realization that some persons in the leprosy field are already so convinced that they feel it to be no longer justifiable to withhold BCG from children exposed to leprosy. Although unnecessary BCG vaccination may be considered not only harmless but advantageous to the tuberculosis futures of these people, there is a risk that this movement may accelerate, and that BCG vaccination will become a standard practice even though its usefulness in leprosy may be unknown or unassessed.

Supporters of BCG vaccination

Those who believe that BCG vaccination probably has an influence on leprous infection may be divided into two groups.

The first group states that *M. tuberculosis* or other mycobacteria may be antigenically related to *M. leprae*, and that acquired immunity in leprosy is possible. Although no clear relationship has been shown between prior tuberculosis infections and the number or type of leprosy illnesses in subsequently exposed persons, speculation that one exists is of long standing and is based upon the agent being of the same classification, rather than upon any actual observation. Also, acquired immunity in leprosy has not been clearly shown, although it would be reasonable to accept that it is probable. Serologically, some antigens appear to be shared by *M. tuberculosis* and *M. leprae*. If this antagonist or similarity hypothesis is accepted, it is possible that prior sensitization to *M. tuberculosis* could influence the total leprosy incidence rate, the occurrence of each form of leprosy illness, the length of illness and the prognosis.

If *M. tuberculosis* is thought to have this effect, BCG, with its antigenic connexions, might be expected to act in a similar manner. The supporters of this hypothesis argue that leprosy resistance or susceptibility can be measured by the Mitsuda reaction; that BCG can convert the reaction from negative to positive or make it more positive in some young

persons; also, that there is some apparent relationship between the tuberculin and lepromin tests in children.

The second group of supporters of BCG vaccination argue that there may be a relationship between the degree of positivity to the Mitsuda reaction at the time of leprosy infection and the type of leprous illness. Thus, the important section of the population requiring protection would be those who are Mitsuda-negative. This section has not had the opportunity to become sensitized and is therefore at increased risk if infected. If sensitization could be made to occur earlier in life and before infection with *M. leprae*, then the chances of a lepromatous leprosy illness would be decreased, although the incidence of tuberculoid leprosy might remain unchanged. This change in leprosy type could be of great significance, not only to the individuals concerned, but also to the community. The number of more highly infectious persons would be lowered, and therefore the risk of secondary infections and the total leprosy incidence (all forms) would decrease as a second step. BCG is believed to be able to convert many Mitsuda-negative persons to positivity, especially infants and young children, who may be the important age-groups. Although BCG vaccination may strengthen the Mitsuda readings of those persons already Mitsuda-positive, this effect may be of secondary importance, as the use of BCG could be justified solely upon the basis of its effects upon unsensitized persons.

This hypothesis is the one that is most widely held by advocates of BCG vaccination and is connected to the " resistance hypothesis " interpreters of the Mitsuda reaction. They do not accept the factor N or anergic theory, and they consider that the Mitsuda reading is important because of the resistance shown, rather than as a means of selecting sensitive persons who cannot react in this way.

The group that is against BCG vaccination includes some advocates of the anergic or factor N hypothesis. These people consider that neither BCG nor *M. tuberculosis* can change the Mitsuda reaction in persons without Mitsuda or factor N reactional ability, that these are the persons who are susceptible to lepromatous leprosy, and that therefore prior immunization with BCG cannot alter the occurrence of lepromatous leprosy to any appreciable extent.

The observational evidence for and against any one of these viewpoints is minimal, and most arguments must be based largely upon the hypothesis used to explain the Mitsuda reaction.

Experience with BCG vaccination

It is probable that BCG given by the intradermal or the oral routes can convert some Mitsuda-negative people to Mitsuda-positivity. The positive reaction is frequently of questionable significance and of only the doubtful ($\pm$) or one-plus ($+$) grade. The length of time this induced positivity lasts is unknown, but some reversions to negativity have been observed. The possibility of a change from negative to positive occurring is clearly age-dependent. In studies that included only Mitsuda-negative persons, conversion rates to Mitsuda-positivity of 90% or greater have sometimes been recorded after BCG vaccination in young infants when compared with a conversion rate of 30%-40%, which can occur spontaneously in the first year. In other groups of older (school-aged) children, conversions of 80% (Rath de Souza et al., 1956) were observed, but this was similar to the conversions observed in the controls, which were caused spontaneously and/or by the lepromin test itself.

The dose of oral BCG given does not bear any clear relationship to the conversion rate, and no difference has been shown between oral and intradermal methods of BCG administration.

As has been stated previously, no actual, set, Mitsuda conversion rate by age due to BCG can be extracted from the literature, although for working purposes the figure of 30%-50% conversions in the Mitsuda-negative children aged under 3 years appears to be a reasonable guess. This conversion proportion is likely to vary in different groups and areas. It may well be smaller in children from leprous households who have been exposed from birth to infection with *M. leprae*.

BCG vaccination in young people causes or accelerates a change that would occur anyway at a later age. The interval between induced and spontaneous Mitsuda-reactivity should vary by age. The interval may be a short one of two to three years or less in most children. In the Philippines study (Doull, Guinto & Mabalay, 1957) this interval could have been less than one year for many children, some of whom were older than three years.

Little evidence is available of the difference in leprosy experience between induced and spontaneous Mitsuda-positives. Dharmendra & Chatterjee's paper (1956) cites a group of persons who may have had partially induced reactivity due to repeated lepromin testing. This effect has been described previously. The " induced " group had an experience similar to that of the " spontaneous " group.

"Trials" of BCG are few, biased and incomplete, or they differ so widely in their terms and conclusions that they are hard to assess. Those of Convit (1956) and Yanagisawa (1958) were not truly controlled trials and must be discarded from consideration. Fernandez (1955) compared the experience in contacts of infected households given BCG with that of other persons who were tuberculin-positive or -negative. The numbers were small, and it is not clear whether the groups were comparable. No significant difference could be shown between the groups, as judged by the leprosy secondary attack rate, although there may have been less lepromatous and indeterminate leprosy in the BCG group. Chatterjee is reported, in a private communication to the author, to have shown big differences between his groups, but it is improbable that they were comparable. He reported a leprosy secondary attack rate of 52.4% in non-vaccinated household contacts in a five-year period. This is much higher than has ever been recorded elsewhere, even in exposed children.

Other trials with small numbers have given inconclusive results. All that have been reported vary in their conclusions, from no obvious change to a decrease in the proportion of lepromatous cases to dramatic falls in all forms of leprosy. No clear trend is present. It must be concluded that no acceptable observational evidence exists in either direction.

Theoretical bases for BCG vaccination

From the epidemiological standpoint, the "anergic" or factor N hypothesis describing the lepromin reactions and lepromatous leprosy appears to be the most acceptable. If this hypothesis is valid, BCG is unlikely to influence the small "persistent" Mitsuda-negative fraction of the community, and there appears to be little point in converting the potential Mitsuda-positive group artificially. A firm advocate of this hypothesis would theoretically reject BCG as unlikely to be a useful method of decreasing the lepromatous leprosy rate, although it could influence the tuberculoid leprosy rate.

For those who believe that resistance is measured by the degree of Mitsuda positivity, the potentialities of BCG are limited. For those advocating the conversion of exposed persons to Mitsuda-positivity in order to decrease the lepromatous leprosy rate, BCG would have to be used in the very young; that is, from birth to the age of 3-5 years. Its effectiveness could be expected to vary markedly even within this age-group.

For those who support the concept that there is a tuberculosis-BCG antagonism, the use of BCG would not be directed specifically towards Mitsuda-negative persons but would be equally advisable in all persons before exposure to *M. leprae*, with greater emphasis upon tuberculin-negative individuals. This entire concept of protection appears to be incompatible with the observed similarity of the proportions of tuberculin-positive persons in different leprous groups and in their communities.

If all these possibilities are rejected, the remaining theoretical bases either deny that BCG could have any effect or that it could only affect the distribution of leprosy forms. To investigate and confirm or reject the latter view would be practicable but expensive and time-consuming. A prospective study of the secondary attack rate in Mitsuda-positive and -negative exposed persons or an accurate comparison of the proportion of lepromatous and non-lepromatous persons known to have been exposed to *M. leprae* at different ages would appear to give similar results of equal usefulness.

The theoretical grounds for justification of a controlled trial at this time seem to be flimsy and insufficient.

Requisites for a controlled trial of BCG vaccination

If such a trial were to take place, all seven of the following conditions would have to be met.

(a) Not only should it be rigidly controlled, it should be "blind". Standardization of the treated and control groups would have to include rigid comparability by age, sex, likely duration and type of exposure, as well as by location, treatment and methods of ascertainment and criteria for clinical diagnosis and division.

(b) BCG vaccination might have to be given to two out of four similar groups of persons: (1) Mitsuda-positive with BCG, (2) Mitsuda-positive without BCG, (3) Mitsuda-negative with BCG, (4) Mitsuda-negative without BCG. In addition, either doubtful ($\pm$) or one plus ($+$) Mitsuda reactors would have to be equally or randomly distributed or would have to be included in separate groups.

(c) The lepromin test should be repeated after BCG on at least one occasion to all groups and possibly serially at set intervals. This would mean that all groups equally would have equal Mitsuda provocation. Without serial testing, no distinctions would be possible as to different experiences in persons whose Mitsuda reaction became positive after BCG vaccination when compared with those who did not convert.

(d) If four groups (as in (b) above) were studied, the ages of election for BCG vaccination would be from

birth to 3 years. In these age-groups, approximately equal groups could be selected. A trial restricted to the first years might result in difficulties in ascertaining Mitsuda-positive children. In a study of older age-groups (e.g., schoolchildren), the number of Mitsuda conversions that could be ascribed to BCG would be much smaller, and the risks of a preceding leprosy infection in exposed children would be greater. This would necessitate a large number of study children and difficulties in interpretation.

(e) Success or failure would have to be based upon measurement of the differing incidence of all leprosy cases in the study children, broken down by clinical type (lepromatous, tuberculoid and indeterminate) and, if possible, also by bacteriological and histological grade. As none of these divisions is based upon objective criteria, each would have to be assessed blind. As some cases can change categories, dependent partly upon time and partly upon the frequency of assessment, time from exposure or time from onset of first symptoms would have to be included in the classification. Final results would need to be presented as a comparison of total and specific incidence rates, in addition to proportional changes of different leprosy clinical types.

(f) As the onset of leprosy, and particularly of lepromatous leprosy, occurs mainly in adolescence, except in highly exposed captive communities, two choices are open, dependent upon the aims and objectives of the trial and of administrative and economic considerations. If children less than 3 years of age and of known lepromatous and tuberculoid leprosy parentage were the study population, the numbers required could be smaller, as the secondary attack rate would be expected to be high, and the age of onset would be expected to be lower. However, the secondary attack rate of lepromatous leprosy would be unlikely to reach the level of 1%-5%, and many of the lepromatous cases might not appear for 10-15 years; i.e., the period of observation would have to be long, and the losses due to other causes during this extended period could be considerable.

If a not-so-highly exposed population in an endemic area (such as schoolchildren aged 7-10 years) were chosen, the proportion of children tested and converted by BCG could be smaller, and the attack rate to leprosy would be much lower (possibly one-eighth of the household-contact rate). Therefore, the numbers screened and studied would need to be much greater, but the study period might be much shorter (5 years rather than 10-15 years).

(g) In deciding the required sample size, it would be illegitimate to base the estimate of numbers upon the total expected leprosy rate (all forms). One of the aims of a trial of BCG in leprosy would be to observe a change in the lepromatous leprosy rate. Even in a five-year period among household contacts, it is highly improbable that this rate would reach the level of 1%. Therefore, the numbers involved might need to be large.

In conclusion, it could be said that a trial using BCG is practically possible, if the total leprosy (all forms) rate was to be the criterion for judgement. However, if a change in the lepromatous leprosy rate was to be the measurement of success, then very large numbers and very many years of observation would be needed. It is such a change in the rate of lepromatous leprosy that is most frequently expected by many of the theoretical supporters of BCG. It is difficult to estimate the numbers required for either type of trial, as attack rates show such great variations. However, if a control programme were to take place in parallel with a trial, the numbers observed would need to be very large, even in exposed family contacts.

CONCLUSIONS

Leprosy appears to be an infectious disease in man resulting from an infection with *M. leprae*. Although not highly infectious in the sense that smallpox is infectious, the secondary attack rate can be considerable in household contacts of lepromatous cases. While the method of spread and portal of entry of the organism are unknown, the pathogen is probably airborne and may enter a susceptible person through either the skin or the nasopharynx, Some special factors within households appear to be related to the high secondary attack rate. These factors are probably the presence of susceptible children and challenge by either a large number of organisms at once or by smaller numbers over long periods of time.

The disease shows a clinical form with an unfavourable prognosis, greater infectivity, and different symptomatology in a proportion of persons (lepromatous leprosy) known to be infected. The number of patients of this type in a community may be a major influence upon the continuation of the disease and its prevalence in a given area. At present, potential lepromatous cases cannot be identified prior to illness, although it is probable that they are included in that part of the normal population that can be shown to be Mitsuda-negative. The proportion of a population of all ages likely to have this quality has never been shown to be greater than 2% and has rarely been greater than 0.5%-1%. The male-to-female ratio in lepromatous leprosy ranges from 1.6/1 to 2/1, but in non-lepromatous leprosy the sex ratio is 1/1.

The infected individual without symptoms cannot be identified at present, although the latent or incuba-

tion period of leprosy may be several years. Non-lepromatous lesions show a gradient from severe to the mild and spontaneously healing form often seen in children. It is probable that symptomless infections frequently occur. Minor cases appear to be the least infectious.

Immunity is said to vary because of inherent differences in susceptibility, possible previous symptomless or self-limiting *M. leprae* or other infections, or, possibly, age. The lepromin reaction may sometimes become positive because of mycobacterial infections or unknown causes.

No known other disease or infection (including tuberculosis and BCG vaccination) has been adequately demonstrated either to be related to infection with *M. leprae* or to alter the course of a leprous illness occurring subsequently. The tuberculin test shows a greater association with the lepromin test in adolescents and young adults than in young children or in older people.

Leprosy has had an almost world-wide distribution, although it is now largely restricted to the tropics and subtropics. Within endemic areas, its distribution is uneven. Its rise and fall and its present distribution are unexplained. Environmental and socio-anthropological factors, as well as variations in agent strains and pathogenicity, have been put forward as explanations, but none of them have been defined or demonstrated. No non-human reservoir of *M. leprae* is known or postulated.

The lepromin test (Mitsuda reaction) is the first objective test related to prognosis that has been devised. At present, it is unstandardized in both its nature and its interpretation. Reactivity has been demonstrated in many uninfected population groups in endemic and non-endemic areas, but few major variations have been shown. Few convincing epidemiological studies have been directed towards its distribution, other than by area and in relation to leprosy cases. Three theories are held to explain its findings. The anergic or factor N hypothesis corresponds most closely to the field observations.

Leprosy is an interesting disease. A stranger's first impression is of its similarities to other diseases. Later, the differences appear more significant. A disease that is so unusual, that apparently has such difficulty in survival, and that cannot be identified outside the human body must surely be controllable. The problems connected with its prevention appear solvable if reasonable effort and objectivity and existing scientific methods of approach are directed towards it.

If the whole subject of BCG is excluded, certain major avenues of approach seem justified. Further work upon the growth of the agent and the further development of chemotherapeutic substances must come first. They have not been dealt with in this review. In addition, effort must be directed towards a further elucidation of the lepromin reaction in a standard form. At present, this test, which has many possibilities, is under a disadvantage, because some of the unacceptable studies, while making the test more widely known, now bring it into disrepute. The doubts should be clarified and, if the conclusions and interpretations at present held can be based upon sounder evidence, genetic, epidemiological and immunological studies should be encouraged to increase its usefulness. The possibility that it could become a method of identification of susceptible individuals indicates its most obvious practical application outside of its present prognostic value in clinical practice.

RÉSUMÉ

L'auteur, se plaçant sur un plan purement épidémiologique, présente une revue critique de certaines des plus récentes publications consacrées à la lèpre. Selon lui, une grande partie de la littérature médicale qui traite de la question est de qualité variable, plus ou moins complète, et son contenu sujet à controverses.

La lèpre se présente comme une maladie infectieuse, due à *Mycobacterium leprae* auquel on ne connaît ni ne soupçonne aucun réservoir en dehors de l'homme. Le mode de propagation et la porte d'entrée du bacille sont inconnus; la transmission est probablement aérienne et une personne réceptive peut s'infecter par la peau ou le rhyno-pharynx.

Un certain nombre de personnes infectées présentent une forme clinique de mauvais pronostic et très contagieuse, la lèpre lépromateuse, dont la symptomatologie est particulière. Il n'existe actuellement aucune possibilité de prévoir dans quels cas la lèpre sera de forme lépromateuse avant que la maladie ne se manifeste, mais il est probable que les individus prédisposés appartiennent à cette partie d'une population normale chez laquelle on observe une réaction de Mitsuda négative. Dans l'ensemble d'une collectivité donnée, quel que soit l'âge, la proportion des lépromateux potentiels n'a jamais été supérieure à 2 % et a rarement dépassé 0,5 % à 1 %. Le rapport du nombre des malades hommes à celui des malades

femmes, qui est de 1,6/1 à 2/1 dans la lèpre lépromateuse est habituellement de 1/1 dans la lèpre non lépromateuse.

On admet que plusieurs facteurs peuvent modifier l'immunité: différences innées de sensibilité, infections précédentes à *M. leprae* restées asymptomatiques ou dont l'évolution s'est arrêtée spontanément, infections dues à d'autres micro-organismes, influence de l'âge. Des infections mycobactériennes, la répétition des tests, ou d'autres causes inconnues peuvent rendre positive la réaction à la lépromine. Cette réaction (réaction de Mitsuda) est le premier critère objectif permettant de formuler un pronostic de la lèpre. On n'a encore normalisé ni sa technique ni l'interprétation de ses résultats. De nombreux groupes de population non infectés ont une réaction de Mitsuda positive, et les taux de positivité sont peu variables, que les sujets examinés vivent ou non dans une région d'endémicité lépreuse. Le mode de distribution des réactions a été rarement précisé par des méthodes épidémiologiques, en dehors des enquêtes qui ont été faites dans certaines régions pour l'étude de la lèpre. Trois hypothèses divergentes sont avancées pour l'interprétation des résultats fournis par la réaction de Mitsuda. La première fait intervenir la notion de tolérance ou de désensibilisation:

chez le lépromateux à réaction négative, il n'existe aucune possibilité de réponse immunologique à l'agression par *M. leprae*. La deuxième, celle de la résistance, attribue à une réaction de Mitsuda positive une valeur d'indice témoignant d'une résistance acquise au bacille de la lèpre. Selon la troisième hypothèse, la plus satisfaisante, un facteur constitutionnel (facteur N) permettrait à un individu de réagir de façon spécifique à l'infection par *M. leprae*. C'est dans le groupe minoritaire des personnes dépourvues de ce facteur qu'apparaîtraient les cas de lèpre lépromateuse.

Chez les jeunes enfants, le BCG paraît entraîner la conversion de la réaction de Mitsuda négative en réaction positive dans au moins 30% des cas, mais le rapport existant entre ce virage et les modifications de la réceptivité est mal connu. Si l'on admet l'existence d'un facteur N, ces dernières ne jouent apparemment qu'un faible rôle dans la prévention de la lèpre.

La prévention s'attache actuellement à limiter la contagion à partir des cas connus; il est nécessaire de mieux connaître l'agent causal et l'épidémiologie de la maladie et de découvrir d'autres moyens thérapeutiques avant d'envisager de nouvelles possibilités de lutte.

REFERENCES

Azulay, R. D. & Convit, J. (1947) *Int. J. Leprosy*, **15**, 264

Bechelli, L. M. (1949) *Rev. bras. Leprol.*, **17**, 175

Bechelli, L. M. (1957) *Rev. bras. Leprol.*, **25**, 267

Bechelli, L. M. (1959) *Int. J. Leprosy*, **27**, 228

Bechelli, L. M. & Martínez Domínguez, V. (1963) *Leprosy epidemiological statistics in Nigeria, Cameroon and Thailand*. In: *VIII International Congress of Leprology (Abstracts)*, Rio de Janeiro, p. 54

Bechelli, L. M., Rath de Souza, P. & Quagliato, R. (1957) *Rev. bras. Leprol.*, **25**, 21

Beiguelman, B. (1962) *Rev. bras. Leprol.*, **30**, 153

Bennett, I. L., Jr (1961) *Summary and appraisal*. In: *Transactions of the Symposium on Research in Leprosy... Baltimore, Md., May 1961*, Washington, D.C., Leonard Wood Memorial, p. 33

Binford, C. H. (1961) *The problem of transmission of M. leprae to animals: comments on results of several experiments*. In: *Transactions of the Symposium on Research in Leprosy... Baltimore, Md., May 1961*, Washington, D.C., Leonard Wood Memorial, p. 235

Chaussinard, R. (1948) *Int. J. Leprosy*, **16**, 431

Cochrane, R. G. (1947) *A practical textbook of leprosy*, London, Oxford University Press

Cochrane, R. G., ed. (1959) *Leprosy in theory and practice*, Bristol, J. Wright

Committee of Immunology (1953) *Report*. In: *Memoria del VI Congreso internacional de Leprología*, Madrid, p. 101

Convit, J. (1956) *Int. J. Leprosy*, **24**, 269

Davey, T. F., Drewett, S. D. & Stone, C. (1958) *Leprosy Rev.*, **29**, 81

Desai, S. D. (1955) *Int. J. Leprosy*, **23**, 198

De Souza Campos, N. (1938) *Int. J. Leprosy*, **6**, 282

Dharmendra (1955) *Int. J. Leprosy*. **23**, 200

Dharmendra & Chatterjee, K. R. (1956) *Int. J. Leprosy*, **24**, 315

Doull, J. A. (1957) *Med. Bull. Veterans Adm. (Wash.)*, 15 March.

Doull, J. A. (1961) *Present status and problems*. In: *Transactions of the Symposium on Research in Leprosy... Baltimore, Md., May 1961*, Washington, D.C., Leonard Wood Memorial, p. 188

Doull, J. A., Guinto, R. S. & Mabalay, E. B. (1957) *Int. J. Leprosy*, **25**, 13

Doull, J. A., Guinto, R. S. & Mabalay, E. B. (1959) *Int. J. Leprosy*, **27**, 31

Doull, J. A., Rodríguez, J. N., Guinto, R. S. & Plantilla, F. C. (1936) *Int. J. Leprosy*, **4**, 141

Fernandez, J. M. M. (1939) *Rev. argent. Dermatosif.*, **23**, 425

Fernandez, J. M. M. (1955) *Int. J. Leprosy*, **23**, 243

Greenberg, M. & Abramson, H. (1952) *Amer. J. publ. Hlth*, **42**, 142

Guinto, R. S. (1961) *Cutaneous responses to lepromin and other mycobacterial agents*. In: *Transactions of the Symposium on Research in Leprosy... Baltimore, Md., May 1961*, Washington, D.C., Leonard Wood Memorial, p. 205

Guinto, R. S., Doull, J. A. & Mabalay, E. B. (1955a) *Int. J. Leprosy*, **23**, 32

Guinto, R. S., Doull, J. A. & Mabalay, E. B. (1955b) *Int. J. Leprosy*, **23**, 131

Guinto, R. S., Doull, J. A. & Mabalay, E. B. (1955c) *Int. J. Leprosy*, **23**, 135

Guinto, R. S. & Rodriguez, J. N. (1941) *Int. J. Leprosy*, **9**, 149

Hamilton, G. R. (1926) *Med. J. Aust.* **2**, 420

Hanks, J. H. (1961) *Immunology and serology : implications of skin and serologic reactivity.* In: *Transactions of the Symposium on Research in Leprosy... Baltimore, Md., May 1961*, Washington, D.C., Leonard Wood Memorial, p. 36

Innes, J. R. (1938) *Int. J. Leprosy*, **6**, 501

Khanolkar, V. R. (1955) *Indian J. med. Sci*, **9**, 44

Lara, C. B. (1940) *Int. J. Leprosy*, **8**, 15

Lara, C. B. & Nolasco, J. O. (1956) *Int. J. Leprosy*, **24**, 245

Lowe, J. (1938) *Leprosy in India*, **10**, 120

Lowe, J. & McNulty, F. (1953) *Leprosy Rev.*, **24**, 61

McCoy, G. W. & Goodhue, W. J. (1913) *Publ. Hlth Bull. (Wash.)*, **61**, 7

Marchoux, E. (1934) *Int. J. Leprosy*, **2**, 1

Martínez Domínguez, V. (1953) *Estudio epidemiológico y clínico de la endemia de lepra en la Guinea española.* In: *Memoria del VI Congreso internacional de Leprología*, Madrid, p. 1104

Muir, E. (1948) *Manual of leprosy*, Edinburgh, Livingstone, p. 165

Nègre, A. & Fontan, R. (1956) *Int. J. Leprosy*, **24**, 167

Nolasco, J. O. & Lara, C. B. (1940) *Philipp. J. Sci.*, **71**, 321

Porritt, R. J. & Olsen, R. S. (1947) *Amer. J. Pathol.*, **23**, 805

Rath de Souza, P., Bechelli, L. M., Ferraz, N. T. & Quagliato, R. (1956) *Rev. bras. Leprol.*, **24**, 9

Rodriguez, J. N. (1958) *Mth. Bull. Bur. Hlth Philipp.*, **19**, 323

Rogers, L. & Muir, E. (1946) *Leprosy.* 3rd ed., Bristol, J. Wright, p. 165

Rotberg, A. (1957) *Rev. bras. Leprol.*, **25**, 85

Rotberg, A., Bechelli, L. M. & Keil, H. (1950) *Int. J. Leprosy*, **18**, 209

Shepard, C. C. (1961) *Summary and prospects.* In: *Transactions of the Symposium on Research in Leprosy... Baltimore, Md., May 1961*, Washington, D.C., Leonard Wood Memorial, p. 128

Wade, H. W. (1955) *Int. J. Leprosy*, **23**, 310

Wade, H. W. & Ledowsky, V. (1952) *Int. J. Leprosy*, **20**, 1

WHO Expert Committee on Leprosy (1953) *Wld Hlth Org. techn. Rep. Ser.*, **71**

WHO Expert Committee on Leprosy (1960) *Wld Hlth Org. techn. Rep. Ser.*, **189**

Yanagisawa, K. (1958) *Int. J. Leprosy* **23**, 243