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EDITORIALS

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The Transmission of Leprosy in Man[1]

Leprosy is estimated to have a prevalence in the world of between 11 and 12 million, and a consideration of its mode of transmission is of importance. Strong prejudices against it, the long duration of the disease process, and the frequency of disabilities create special problems often absent in other diseases. Although early detection and treatment of established cases is important to individual patients, ultimate eradication must also involve prevention of illness in those hitherto unaffected. No short, intensive chemotherapy for leprosy exists, and the increasing incidence of dapsone resistance[2] makes it necessary to resort to expensive alternatives. It is possible that existing immunological knowledge may make immunoprophylaxis possible in the not too distant future, but its full development, production, and administration are problems as yet unsolved. Finally, it is uncertain whether socioeconomic progress in leprosy-endemic areas will by itself make an impact on its incidence within a reasonable period of time.

The present review will assume *Mycobacterium leprae* as the sole causative organism of leprosy[3]. Certainly it is identifiable in virtually every case of leprosy. It can be cultured in mouse foot pads, causing experimental disease[4]. Recent reports of the *in vitro* culture of the organism in the presence of hyaluronic acid[5] give hope that the organism may eventually satisfy Koch's postulates. Studies bearing on leprosy transmission may be thought of as falling into three categores. There are the clinical observations on patients with the condition,

[1] This review was originally written as an essay by Christopher Huang, M.B., in 1976, while he was a medical student at Oxford. It was written in response to the annual competition set up by the British Leprosy Relief Association (LEPRA) for essays on various aspects of the leprosy problem (see Int. J. Lepr. **48** [1980] 216–217) and was the prize-winning essay in the 1976 competition. We take pleasure in publishing this timely review. Dr. Huang's present address is The Physiological Laboratory, Cambridge CB2 3EG, United Kingdon.—RCH

[2] Waters, M. F. R., Pearson, J. M. H. and Rees, R. J. W. Sulphone resistance in leprosy: A review of 100 proven cases. Leprologia **19** (1974) 243–248.

[3] Delville, J. and Pichel, A. M. Microbiology of leprosy. Does an *in vitro* cultivable phase of the leprosy bacillus exist? Ann. Soc. Belg. Méd. Trop. **55** (1975) 109–118.

[4] Shepard, C. C. The experimental disease that follows the injection of human leprosy bacilli into footpads of mice. J. Exp. Med. **112** (1960) 445–454.

[5] Skinsnes, O. K., Matsuo, E., Chang, P. H. C. and Anderson, B. *In vitro* cultivation of leprosy bacilli on hyaluronic acid based medium. I. Preliminary report. Int. J. Lepr. **43** (1975) 193–203.

which form the bulk of the work as they are the easiest to do in the field. Studies have also been made of experimental systems, and, finally, there are epidemiological studies to which a separate section is devoted in this account. The results of such work can be brought to bear on one or more of the following steps, here assumed component stages in the transmission process:

a. The release of viable organisms from the host into the environment.
b. The presence of viable organisms so released in the environment.
c. Entry into the new human host and distribution within the body.
d. Production of clinical illness.

Any one of these factors could determine the apparent rate of transmission. Thus in the presence of very large numbers of organisms in the environment, the overall incidence could well become a function of the last step, making "constitutional" factors the main determinant of the appearance of clinical illness.

1) THE RELEASE OF VIABLE ORGANISMS FROM THE HOST INTO THE ENVIRONMENT

a. Skin. It has been assumed until relatively recently that leprosy transmission is by prolonged skin-to-skin contact. This notion probably derived from the cutaneous clinical signs. Periaswami[6] found considerable numbers of acid-fast bacilli in intact skin of lepromatous patients. In 1976, Ridley, *et al.*[7] found the fingers to be the skin site bearing the highest bacterial load. However, convincing evidence was not presented that *M. leprae* could cross intact epidermis. Such organisms as were found could well have come from portals of exit elsewhere. This assertion would predict the presence of bacilli on skin as an inconstant finding, and, indeed, Pedley[8] found very few leprosy bacilli on lepromatous patches of skin, using a composite skin contact smear technique. However, where skin is breached, it may not be unreasonable to assume that a heavily infected underlying dermis might enable leprosy bacilli to escape onto the surface and thus into the environment. One publication[9] has indicated that more than 20 million bacilli per day could have been shed into the environment from a patient with ulcerating lepromatous leprosy.

b) Urogenital tract. Present evidence available attaches little importance to this route. Testes of mice, whether normal or immunologically deficient[10], and the testes of males with lepromatous leprosy contain large numbers of organisms, but it has not been shown that they are present in significant numbers in semen. Bacilli are rarely found in glomeruli or renal tubular cells. Their occurrence in urine has not been convincingly demonstrated.

c) Mammary glands. The milk of lactating mothers contains large numbers of *M. leprae*, Pedley[11] having found 118 bacilli in one drop spread over a slide. Although neither this nor other publications have counted bacilli in a series of such patients, the above observation, taken with the finding of large numbers of bacilli in the lumen of the lactiferous duct[12], suggests that a child drinking one pint of breast milk daily might well ingest—often over a period of years—significant numbers of bacilli. The importance of this route in the spread of leprosy is, however, far from clear; pharyngeal or intestinal lesions analogous to those in tuberculosis are not known to occur in leprosy, and index cases in families are very frequently not the mother.

d) Upper respiratory tract. In the developed case, ulcerating lepromatous granulation tissue may occur in the soft palate, uvula, and nasopharynx. Conceivably,

[6] Periaswami, P. The distribution of *Mycobacterium leprae* in different structures of the skin. Lepr. India **40** (1968) 178–189.

[7] Ridley, M., Jopling, W. H. and Ridley, D. S. Acid fast bacilli in the fingers of long-treated lepromatous patients. Lepr. Rev. **47** (1976) 93–96.

[8] Pedley, J. C. Summary of results of a search of the skin surface for *Mycobacterium leprae*. Lepr. Rev. **41** (1970) 167–168.

[9] McDougall, A. C. and Rees, R. J. W. Ulcerating lepromatous leprosy in a patient with dapsone-resistant *Mycobacterium leprae*. Lepr. Rev. **44** (1973) 59–64.

[10] Rees, R. J. W., McDougall, A. C. and Weddell, A. G. M. The testis in mice infected with *Mycobacterium leprae*. J. Pathol. **115** (1975) 73–79.

[11] Pedley, J. C. The presence of *M. leprae* in human milk. Lepr. Rev. **38** (1967) 239–242.

[12] Pedley, J. C. The presence of *M. leprae* in the lumina of the female mammary gland. Lepr. Rev. **39** (1968) 201–202.

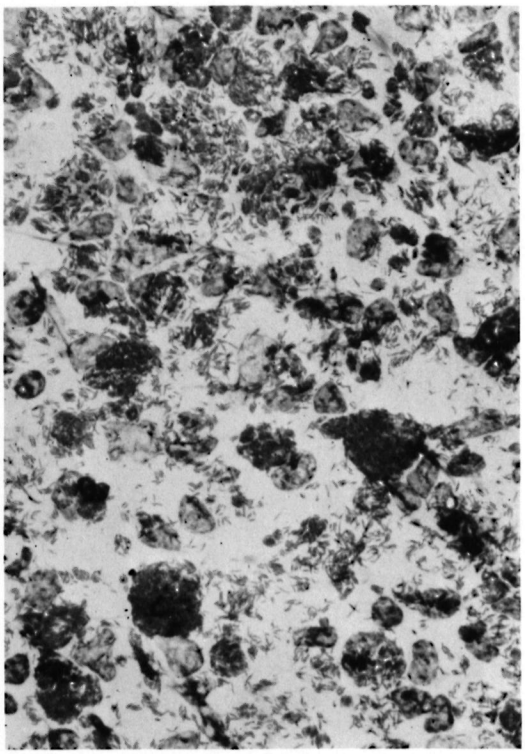

FIG. 1. At an original magnification of ×1000 and in an area occupying approximately one-third of an oil immersion field, leprosy bacilli are seen: a) singly, b) in groups of various sizes, and c) in large globi. Nasal smear from a patient with untreated lepromatous leprosy in Nepal (Dr. J. C. Pedley, Tansen, Nepal), Ziehl-Neelsen stain. Leitz Orthomat microscope. Kodak 2483 photomicrography film.

these might release bacilli, but more remarkable is the early nasal involvement in lepromatous leprosy, first noticed in the 1890s. Rogers and Muir[13] suggested that viable bacilli could occur in clinically important numbers in nasal discharge, even in the absence of florid clinical features, especially during coughing or sneezing (Fig. 1). Recent work confirms this theory for lepromatous and near-lepromatous leprosy. Thus:

1) Nasal involvement is clinically apparent at an early stage in lepromatous leprosy[14].

2) Nasal infection is bacteriologically demonstrable especially in the middle and inferior turbinates and more marked than in skin in early lepromatous leprosy[15].

3) Highly bacilliferous nasal discharges occur in cases of untreated lepromatous leprosy. This was clear from nasal mucous smears from such cases, which showed high bacterial and morphological indices clearly exceeding those obtained from skin. Similar results have been obtained from studies of nasal discharges (Fig. 1). Mouse foot pad studies confirmed that the organisms were *M. leprae*[16].

4) Large numbers of leprosy bacilli are projected from the upper respiratory tract for distances of up to 30 to 50 cm during sneezing and coughing[17]. This is consistent with the aerosol effect of a sneeze (Fig. 2), which would clearly provide an efficient route of exit for bacilli. It is possible that

FIG. 2. Droplet dispersal following a violent sneeze. (From Jennison, M. W. Atomizing of mouth and nose secretions into the air by high-speed photography. In: *Aerobiology*. Foust, R. M., ed. Washington: American Association for the Advancement of Science, No. 17, 1942, p. 102. Up to 20,000 droplets are produced in a stream, mostly from the mouth, but larger masses of material ("streamers") as well as droplets are expelled from the nose when there is excess nasal excretion. Reproduced with permission from Mims, C. A. *The Pathogenesis of Infectious Disease*. London: Academic Press, 1977, p. 29.

[13] Rogers, L. and Muir, E. *Leprosy*. 3rd ed. Bristol: John Wright & Sons Ltd., 1946, p. 152.

[14] Barton, R. P. E. A clinical study of the nose in lepromatous leprosy. Lepr. Rev. **45** (1974) 135–144.

[15] Davey, T. F. and Barton, R. P. E. Multiple nasal smears in early lepromatous leprosy. Lepr. Rev. **45** (1974) 158–165.

[16] Davey, T. F. and Rees, R. J. W. The nasal discharge in leprosy: Clinical and bacteriological aspects. Lepr. Rev. **45** (1974) 121–134.

[17] Pedley, J. C. and Geater, J. G. Does droplet infection play a role in the transmission of leprosy? Lepr. Rev. **47** (1976) 97–102.

some organisms may even be released during normal breathing[18].

5) Leprosy bacilli may persist in the nose, as evidenced from scrapings and biopsies of nasal mucosa, even after clinical improvement following prolonged dapsone therapy[19]. However, in these cases the histological integrity of the overlying epithelium was restored. Most organisms seen were fragmented[20]. Furthermore, Pedley[21] found that morphologically normal bacilli were absent from noseblows after six months of dapsone treatment. Therefore, nasal release of bacilli is probably of importance primarily in active untreated lepromatous leprosy.

Experimental results concur with the clinical findings. Normal and immunologically deficient mice were inoculated with *M. leprae* locally in the foot pad and ear and intravenously and intraperitoneally. Subsequent quantitative bacteriological assessments revealed a large percentage of animals with more than 5×10^4 bacilli in the uninoculated ear, foot pads, or nose; the nose was the most frequently and heavily infected. Here bacilli were histologically demonstrable in nasal ciliated epithelial cells from which they might conceivably be released. In contrast, bacilli were rare in the squamous epithelium of the skin, even when the underlying dermis was heavily infected[22]. Similar results have been obtained from studies of the armadillo.

Discussion. If *M. leprae* and *M. tuberculosis* are phylogenetically related organisms, then it is not entirely unreasonable to conceive of their having parallel routes of exit from their human hosts. Evidence at hand makes this possibility increasingly attractive. The importance of a discharge of millions of leprosy bacilli from the nasal tract, indicated by the evidence cited above, cannot be discounted easily. The analogy persists also in quantitative terms. Comparison between outputs of leprosy bacilli from 24 hr noseblow collections and tuberculosis bacilli from 24 hr sputum collections gave pathogen yields of the same high order of magnitude (10^6) with respective standard deviations of only one order of magnitude[23].

However, the story is probably still incomplete. The evidence above implies that nasal discharge of organisms is not important in patients with tuberculoid and borderline leprosy. Yet in the presulfone era, the risk of acquiring leprosy from household contact with a case of lepromatous leprosy was eight times the risk where there was no such contact, but it was still four times the risk where the contact was with a case of tuberculoid leprosy. These risks are within one order of magnitude. Thus transmission of leprosy to household members cannot be solely dependent on the number of organisms released from cases within the household. This number of organisms is enormous in lepromatous leprosy and low or absent in tuberculoid and many borderline cases.

2) THE PRESENCE OF VIABLE ORGANISMS SO RELEASED IN THE ENVIRONMENT

Having been released from the patient in significant numbers and in viable form, the organism must be dispersed sufficiently to explain the widespread occurrence of the disease. At the same time, there must be a sufficient concentration of organisms to infect an individual. Several possible mechanisms of dispersal must be considered.

a. Dust and droplets. Transmission of tuberculosis via this route owes much to the viability of the causative organisms in desiccated sputum. Studies of the viability of desiccated leprosy bacilli using the mouse foot pad technique revealed full survival after 24 hr but only 10% survival after 1.75 days[16].

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[18] Bedi, B. M., Narayanan, E., Streevatsa, M., Kirchheimer, W. F. and Balasubrahmanyam, M. Dispersal of *Mycobacterium leprae* by leprosy patients while breathing. Ann. Indian Acad. Med. Sci. **12** (1976) 1–15.

[19] Barton, R. P. E. and Hogerzeil, L. M. Lepromatous leprosy in the nose after one year of dapsone treatment. Clinical and bacteriological findings. Lepr. Rev. **46** (1975) 257–265.

[20] McDougall, A. C., Rees, R. J. W., Weddell, A. G. M. and Kanan, M. W. The histopathology of lepromatous leprosy in the nose. J. Pathol. **115** (1975) 215–226.

[21] Pedley, J. C. The nasal mucous in leprosy. Lepr. Rev. **44** (1973) 33–35.

[22] Rees, R. J. W., McDougall, A. C. and Weddell, A. G. M. The nose in mice with experimental human leprosy. Lepr. Rev. **45** (1974) 112–120.

[23] Meade, T. W. Growing points in leprosy research. 2. Epidemiology. Lepr. Rev. **45** (1974) 15–21.

b. Arthropods that feed on blood. Untreated borderline or lepromatous leprosy patients have an acid-fast bacillemia of 5000 to 500,000 viable bacilli per ml[24]. Nevertheless, the possible resulting transfer of pathogens via the blood feed of an arthropod remains quantitatively small compared to the number of organisms released by the nasal route. Homogenates of laboratory bred mosquitoes (*Culex fatigans*) and bedbugs (*Cimex hemipterus*) previously allowed to feed freely on lepromatous leprosy patients often contained leprosy bacilli, as confirmed by mouse foot pad studies. Some remained viable up to 48 hr after the blood meal. But the number of bacilli in both instances was small[25]. Furthermore, the frequency with which acid-fast bacilli occurred in homogenates of such arthropods from homes with an open lepromatous case did not differ from those of random collections. In both, the frequency was small[25].

c. Diptera. Studies have been made on the housefly (*Musca*), the bluebottle (*Calliphora*), and the biting stable fly (*Stomoxys*). These were allowed to feed on lepromatous nasal secretions or ulcerated skin lesions. Pooled homogenates of legs, mouthpieces, abdominal wall, and stomach were all heavily infected one hr after feeding. A small proportion had diminishing numbers of bacilli up to three days later. The flies showed a predilection for nasal secretions and were demonstrated to be capable of infecting surfaces upon which they subsequently fed[26]. Further work will be necessary to assess the extent to which flies may thus contribute to the level of environmental infection. In some parts of the world (Fig. 3) they might play a significant role in at least the mechanical transport of pathogenic organisms, including *M. leprae*.

d) Other possible environmental sources. Large numbers of acid-fast bacilli not culturable on standard mycobacterial media were found in skin lesions, nerve, lymph nodes, skin, and liver of seven armadillos captured from the wild (Walsh, G. P., *et al.* personal communication, 1976). This could reflect indigenous infection in such animals, suggesting a non-human source of leprosy bacilli. However, definite conclusions concerning leprosy bacilli originating from or lodging in animals are probably premature. Finally, there is anecdotal evidence that leprosy bacilli may be harbored in plants[27,28]. (See also the recent work of Kazda, *et al.* Int. J. Lepr. **48** [1980] 1–6, who report noncultivable acid-fast bacilli in sphagnum and moss vegetation from the former leprosy endemic areas of Norway and that these bacilli multiply like *M. leprae* in mouse foot pads.—RCH)

FIG. 3. "'*Musca sorbens*' is completely ignored by the Masai, but is the principal vector of certain eye disease infections." Reproduced with permission from *Insects and Other Arthropods of Medical Importance*. Smith, K. V. G., ed. London: Trustees of the British Museum (Natural History), 1973.

Discussion. There is a lack of evidence bearing on this aspect of leprosy transmission. Various mechanisms such as dust, droplets, and flies could be involved, but their relative importance is unknown. Perhaps further insight may be gained by an epidemiological approach (see below).

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[24] Shankara Manja, K. Demonstration of *Mycobacterium leprae* and its viability in the peripheral blood of leprosy patients. Lepr. Rev. **43** (1972) 181–187.

[25] Narayanan, E., Manja, K. S. and Kirchheimer, W. F. Occurrence of *Mycobacterium leprae* in arthropods. Lepr. Rev. **43** (1972) 194–198.

[26] Geater, J. G. The fly as a potential vector in the transmission of leprosy. Lepr. Rev. **46** (1975) 279–286.

[27] Barker, D. J. P., Clancey, J. K., Morrow, R. H. and Rao, S. Transmission of Buruli Disease. Brit. Med. J. **4** (1970) 558.

[28] Temine, P. and Privat, Y. A case of leprosy apparently contracted in France. Ann. Méd. Nancy **157** (1973) 444–445.

3) THE ENTRY OF PATHOGENS INTO THE NEW HUMAN HOST AND DISTRIBUTION WITHIN THE BODY

Possible sites of entry are considered first.

a. Respiratory tract. In view of results cited earlier, the upper respiratory tract would seem a likely site for entry. However, tissue allowing entry of the pathogen need not be where the pathology occurs. Furthermore, bacilliferous particles lodging in the nose must be of rather larger size than those lodging in the lower respiratory tract. It is uncertain whether such larger particles would be the infective fraction of the total inhaled bacillary load. The lower respiratory tract has been demonstrated to be an effective site of entry for *M. tuberculosis*[29,30]. Conceivably, this could apply also to the leprosy bacillus. Both have similar viabilities in dust and droplets. They have similar attack rates in family or household contacts[31]. The fact that the pathogens are often experimentally absent from the lung does not exclude its being a route of entry since the pathogens would be expected to be carried elsewhere rapidly. It would be desirable to test this idea more directly, perhaps by giving measured numbers of bacilli in a known dispersion via a tracheostomy to experimental animals and assessing for subsequent infection[32].

b. Gastrointestinal tract. Possibly (as noted above with tuberculosis), gut entry of pathogens might occur with children breast fed by infected mothers. It is not known whether food or drink, including that contaminated by flies, are likely vehicles.

c. Skin. Classically this has been regarded as the most likely entry point. However, in view of the nature of cornified epithelium, it seems unlikely in the absence of contrary evidence that leprosy bacilli penetrate intact skin. Only anecdotal evidence exists for pathogen entry via breaks in skin[33]; such findings could reflect an early manifestation of previous infection occurring at a site of skin trauma. Indeed, attempts to transmit leprosy to human volunteers via the cutaneous route have been largely unsuccessful. Finally, it is quite possible (see below) that lesions in the skin and peripheral nerve could reflect pathogens reaching such sites via the blood stream rather than by local skin entry.

Transport of organisms from their site of entry. Blood carriage of *M. leprae* certainly occurs. Thus visceral lesions are seen postmortem in all clinical forms, often in loci not explicable merely by lymphatic spread. Up to 10^5 viable leprosy bacilli per ml of blood are demonstrable in cases of untreated lepromatous leprosy[34,35]. Hence bacilli could well enter at a site remote from where they produce clinically evident pathology, provided that they have a predilection for these latter sites[36]. Indeed, if local temperature participates in directing bacilli to particular sites[37,38], the nasal and skin involvement is explicable without invoking them as sites of pathogen entry.

4) THE PRODUCTION OF CLINICAL ILLNESS

Factors bearing on whether infection actually leads to illness are relevant to interpretation of studies where the appearance of clinical disease is the index of transmission having occurred. In tuberculosis, ge-

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[29] Wells, J. On the mechanics of droplet nuclei infection; apparatus for quantitative study of droplet nuclei infection of animals. Am. J. Hyg. **47** (1948) 1–10.

[30] Lurie, M. B. Native and acquired resistance to tuberculosis. Am. J. Med. **9** (1950) 591–610.

[31] Rees, R. J. W. and Meade, T. W. Comparison of the modes of spread and the incidence of tuberculosis and leprosy. Lancet **1** (1974) 47–49.

[32] Rees, R. J. W. and McDougall, A. C. Airborne infection with *Mycobacterium leprae* in mice. J. Med. Microbiol. **10** (1977) 63–68.

[33] Nebout, F. Report of a case of nodular tuberculoid leprosy, localized, in an adult African male, on ritual scarification. Rep. Méd. Trop. **33** (1973) 523–528.

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[35] Palma, M. N. and Desikan, K. V. Bacillaemia in leprosy. Indian J. Med. Res. **63** (1975) 888–892.

[36] Weddell, A. G. M. and Palmer, E. The pathogenesis of leprosy. An experimental approach. Lepr. Rev. **34** (1963) 57–61.

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[38] Sabin, T. D., Hackett, E. R. and Brand, P. W. Temperatures along the course of certain nerves often affected in lepromatous leprosy. Int. J. Lepr. **42** (1974) 38–42.

notype[30], constitutional factors[39], and history of past exposure are important in this connection. Similar considerations might apply in leprosy. In the Netherlands, despite the significant increase in leprosy patients moving freely in a crowded community owing to immigration, only three autochthonous cases have been discovered[40]. But leprosy may be rather more "infectious" than is reflected in its clinical incidence, and indeed lymphocyte transformation studies were negative in subjects new to an endemic area but often positive in those longer resident or who were leprosy contacts[41]. Other immunological methods gave concordant results[42].

Some insight into this problem might come from immunological consideration of the tuberculoid-lepromatous polarity[43]. Lepromatous patients have several altered or suppressed indicators of immunological reactivity[44,45]. There is increasing agreement that this reflects a lack of T-cells able to initiate a response to *M. leprae* antigens[42,46]. Thus the specificity of the deficiency in the cell-mediated response to leprosy bacilli[47] places the lesion temporally after T-lymphocyte genesis. It is tempting to postulate that such a deficiency is also present in non-lepromatous leprosy, albeit to a different degree[48,49]. Hastings[50] considers several possible levels for such deficiencies:

a. The initial inoculum. It is possible that size, route, timing, or frequency of infection is important. In mice, past exposure could affect how much pathogen is needed to cause illness[51]. More than one leprosy bacillus strain with different virulences is conceivable.

b. T-lymphocyte activation mechanisms. These are antigen-specific and so could be sites for the defect. Possible mechanisms include a functional defect of specifically sensitized "helper" T-cells or excess "suppressor" T-cells in the heterogeneous population. Alternatively, there may be involvment of antigen-specific humoral factors involved in controlling cell-mediated immunity[49,52]. It is emphasized that such considerations are speculative.

c. Enzyme deficiencies. A genetic metabolic defect in B-glucuronidase has been suggested for lepromatous leprosy[45]. The resulting elevated macrophage hyaluronic acid might then be a nutritional substrate for leprosy bacilli[53,54,55,56].

[39] Palmer Carroll, E., Jablon, S. and Edwards, P. Tuberculosis morbidity of young men in relation to tuberculin sensitivity and body build. Am. Rev. Tuberc. **76** (1957) 517–539.

[40] Leiker, D. L. Leprosy in the Netherlands. Int. J. Lepr. **45** (1977) 195–196.

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[47] Job, C. K., Chacko, C. J. G., Taylor, P. M., Daniel, M. and Jesudian, G. Evaluation of cell-mediated immunity in the histopathologic spectrum of leprosy using the lymphocyte transformation test. Int. J. Lepr. **44** (1976) 256–264.

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[50] Hastings, R. C. Transfer factor as a probe of the immune defect in lepromatous leprosy. Int. J. Lepr. **45** (1977) 281–291.

[51] Levy, L. Superinfection in mice previously infected with *Mycobacterium leprae*. Infect. Immun. **11** (1975) 1094–1099.

[52] Wasal, P. H., Goralnick, S. and Bullock, W. E. Defective leukotaxis in patients with lepromatous leprosy. Int. J. Lepr. **44** (1976) 243–249.

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[54] Matsuo, E. and Skinsnes, O. K. Acid mucopolysaccharide metabolism in leprosy. 2. Subcellular localization of hyaluronic acid and B-glucuronidase in leprous infiltrates suggestive of a host-*Mycobacterium leprae* metabolic relationship. Int. J. Lepr. **42** (1974) 399–411.

[55] Drutz, D. J. and Bodel, P. Mechanisms of endogenous pyrogen production in patients with leprosy: Why are patients with uncomplicated lepromatous leprosy afebrile? Int. J. Lepr. **42** (1974) 369.

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d. An underlying genetic involvement. Monozygotic and dizygotic twin pair studies display a definite genetic variation in susceptibility to clinical illness and the type of leprosy appearing[57]. There is familial clustering of leprosy patients and striking differences among different populations living in similar areas with respect to prevalence and type. Furthermore, the immune defect in lepromatous leprosy may exist before exposure to the pathogen[58]. Therefore it may be useful to examine the genes known to affect the immune response. In mice, such Ir genes are closely linked to those encoding the classical transplant antigens on the H2 complex of chromosome 17[59,60]. In man, the HLA complex probably also contains such an Ir area. The HLA antigens can therefore act as markers for the Ir system, provided that this genetic disequilibrium is consistently maintained[61,62,63].

Thorsby, *et al.*[64] found an increased frequency of HLA-BW1 in leprosy patients. Smith, *et al.*[65] considered a possible association of HLA-A10 with leprosy. Dasgupta, *et al.*[66] found a marginal increase in HLA-B8 and decrease in HLA-A9 frequencies. Nakajima, *et al.*[67] found no HLA differences between tuberculoid and lepromatous patients. Both groups had decreased HLA-AW24 and increased HLA-AW29, HLA-A9, and HLA-B8 frequencies. The last two are normally rare in the Japanese population studied. It therefore emerges that HLA studies in whole populations give contradictory results. However, this could reflect differences in genetic disequilibrium between Ir-type and HLA loci in different populations. Thus, de Vries, *et al.*[68] studied nonrandom segregation among sibs within families in relation to host response. Sibs with the same type of leprosy showed a significant excess of identical HLA haplotypes. This also applied in families where only tuberculoid leprosy occurred. Sibs with different types of leprosy shared a haplotype less often than expected. These results suggest dominant genes predisposing to different types of leprosy linked to the HLA system. Most simply, two such gene sets may operate. Other factors being equal, the presence of say, gene "t" would permit tuberculoid leprosy to follow infection. The presence of gene "l" might permit lepromatous leprosy and the presence of both, borderline leprosy. The absence of both might confer effective immunity without disease. Certainly this scheme is an oversimplification, but it merits testing.

Besides the HLA markers, there are the genes coding for the Ia-like B-lymphocyte markers. In mice, the genes encoding Ia antigens reside in the Ir region of the H2 complex[60,69]. In man, the analogous area

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probably resides on the HLA complex[70]. Studies of such markers might better reflect an association between Ir gene loci and disease susceptibility than the classical HLA antigens when testing the hypothesis that susceptibility to leprosy and the severity of the resulting illness reflect a failure of Ir genes to code for an effective T-lymphocyte response.

It seems likely that the appearance of clinical illness is a poor index of disease transmission since it is as much a function of host immune factors as it is of transmission factors. Therefore, separation of the host factors is important in assessing evidence bearing on transmission. Unfortunately, this must probably await further clarification of the mechanisms underlying the immune response.

THE NEED FOR MORE EPIDEMIOLOGICAL STUDY

Most of the studies described above examine only one parameter whose importance to the overall scheme of transmission is uncertain. This is not to decry these studies, which have succeeded in outlining some of the mechanisms of leprosy transmission. But further work attempting to clarify the relative importance of the component events must rely increasingly on epidemiological methods. If such methods enable a precise listing of high risk groups in quantitative terms, it should be possible, in principle, to construct and act on mathematical models of the overall process. Unfortunately, immense difficulties confront the execution of such studies, some reflecting the lack of epidemiological and recording facilities in areas where leprosy is endemic. There is also the difficulty of early diagnosis. The appearance of clinical illness is the final stage in a process of infection and its sequelae that may have been proceeding for many years, and this process is itself almost certainly influenced by a large number of environmental factors as yet poorly defined.

A constructive epidemiological approach might include the following:

a. Case-control studies. These can be done quickly and at relatively low cost on a small study population, but the difficulty in proving that leprosy had not been contracted would make it difficult to match controls. Furthermore, such a study would be retrospective. It would entail tracing events happening to a patient in his distant past, often in areas with inadequate records.

b. Cohort studies. Prospective cohort studies look more promising. They could study incidence rather than prevalence, which might better reflect those infective events leading to clinical illness[71]. In view of the low incidence of leprosy, it would be necessary to include a large population, ideally one in which prophylactic measures have yet to be introduced. The population should be a static one to assist tracing and follow-up. Case-finding and detection should be rigorously standardized. The results outlined in earlier sections might imply that, besides age, sex, and race, immunological status, genetic markers, familial, and past medical history should be monitored. Other variables worth including might be history of contacts, sanitation, overcrowding, and ways of disposing of nasal secretions[72].

c. Controlled clinical trials. These might examine whether a given factor, differing in two randomized groups, affects disease incidence. However, with knowledge in its present state, such an approach would seem premature.

SUMMARY

Existing clinical, scientific, and epidemiological knowledge on the mode of transmission of human leprosy is reviewed under the following headings:

a. The release of viable organisms from the host into the environment.
b. The presence of viable organisms so released into the environment.
c. Entry into the new human host and distribution within the body.
d. Production of clinical illness.

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It is concluded that much of the published evidence deals with one, or rather few, parameters, whose relationship to the overall scheme of transmission is uncertain. Although it is beyond doubt that most leprosy bacilli emerge from the nose and nasal secretions, probably entering the environment in droplets, little is known of their mode of survival in the environment or their entry into the new host. Existing data certainly does not provide a full "model" of leprosy transmission, and it is suggested that further work attempting to clarify the relative importance of the component events in transmission may have to rely increasingly on epidemiological methods. It also emerges that consideration of the immunological factors bearing on whether or not infection causes clinical illness is important in elucidating the mechanism of leprosy transmission. Thus even the most "applied" and practical of problems must eventually turn to the realm of "pure" research for a definitive solution.

—Christopher L.-H. Huang

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Hanseniasis: The Polar Concept as It Stands Today

A reappraisal of the polar concept in Hanseniasis is offered based on a lifetime's experience and emphasizing the Latin-American contributions in the field. In accordance with the recommendations of International Leprosy Congresses in Havana in 1948, Madrid in 1953, Rio de Janeiro in 1963, Bergen in 1973, and taking into account the recent findings in clinical, histopathological, and immunological fields, we have recently proposed an actualization of the polar concept initially proposed by Rabello in 1938[1] and by Latapí in 1948[2].

In our view, a spectrum of immuno-clinical forms of Hanseniasis can be acknowledged only with the qualification that this spectrum is a rather limited one. According to the immune-response, this limited spectrum embodies two definitely opposed *groups*, namely immune-negative or L (V), i.e., lepromatous or Virchowian, and immune-positive or T, i.e., tuberculoid, leaving a group, I, "indeterminate" or immature with respect to the immunological response. These three *groups* are by definition unstable and changeable, constituting the dynamic aspect of the approach, the zone of instability of Orbaneja and Puchol[3]. In marked contrast with these groups, forms can be found characterized by their rigid stability and mutual incompatibility, namely the polar *types* L (V) and T (the so-called full polar LL and TT).

We disagree with the proposal advanced in Madrid in 1953 and suggest that the so-called "group" B, borderline, or D, dimorphous, should be eliminated. Most of these forms are, in fact, included in the immune-negative, L (V) *group*, representing a series of histotypes labeled B, BB, and BL, according to Ridley and Jopling[4]. These forms make up fewer than 10% of all the forms of the disease when the immune-positive and lipid negative tuberculoid reactional forms (TR) are correctly removed from this "group."

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