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EDITORIAL

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Factors Influencing the Development of Leprosy: An Overview

Leprosy is an infectious disease caused by an intracellular acid-fast bacterium: *Mycobacterium leprae*. In 1874, Armauer Hansen was the first to describe the bacterium as the cause of leprosy.[33] However, the triad of Koch is still not fulfilled. It has not been possible to infect someone willfully with *M. leprae*,[57] although anecdotal reports indicated infection after tattooing,[71] dog bites, accidental inoculation[68, 76, 78] and following the skinning and cleaning of infected armadillos for cooking.[55]

CLINICAL SPECTRUM

There are various clinical manifestations of leprosy. However it is possible to classify the patients along a clinical spectrum. This was done elegantly coincidentally and independently by Ridley and Jopling[75] in the U.K. and by Leiker[48] in The Netherlands in 1966. The classification is based on the cell-mediated immune (CMI) response of the patients against *M. leprae*. At one end of the spectrum, the tuberculoid (TT) leprosy patients present with a relatively high CMI toward *M. leprae*, with one or a few well-defined hypopigmented or erythematous patches, usually with central healing and loss of sensation in the patch, and/or with an enlarged peripheral nerve. *M. leprae* are usually undetectable. At the other end of the spectrum, the lepromatous (LL) leprosy patients present with a complete tolerance to *M. leprae* and without any detectable CMI against the microbe. These patients are actually teeming with bacteria; they are the "perfect culture medium." The bacteria may be present anywhere in the body, with the possible exception of the central nervous system. The lepromatous patients may show ill-defined, minimal hypopigmented or erythematous patches, but sensation is still present. However they may show "glove-and-stocking" anesthesia with symmetrically enlarged peripheral nerves. They may also show nodules and plaques, skin colored or hyperpigmented, or show only a diffuse infiltration. There may be loss of eyebrows (madarosis) and a more-or-less generalized diminished sweating. Between these two ends of the spectrum, the borderline leprosy group is found, encompassing most of the patients. The clinical range is from borderline tuberculoid (BT)

leprosy with a few asymmetrically distributed, well-defined tuberculoid patches and a few enlarged nerves to borderline lepromatous (BL) leprosy with symmetrically distributed hypopigmented or erythematous macules and/or plaques, papules and nodules. The latter are mainly located on the cooler parts of the body. In the middle of the spectrum, mid-borderline (BB) leprosy patients have elevated lesions with an immune area (the center of the lesion is not involved) and typical dome-shaped, elevated small plaques.

In the borderline range, patients may up- or downgrade (change their classification within the spectrum). Upgrading indicates that the patient develops more tuberculoid features; downgrading, more lepromatous. In upgrading leprosy the bacterial load diminishes; in downgrading the bacterial load is increased by bacterial multiplication. In a downgraded patient, a few of the older patches may show loss of sensation; whereas the new lesions do not. In an upgrading patient, new tuberculoid-like lesions may appear or the lesions may become atrophic (heal).

Upgrading and downgrading occurs either silently or is accompanied by a reactional phenomenon called reversal reaction (RR), in which an enhanced CMI toward *M. leprae* antigenic determinants may cause irreversible nerve damage.[64]

Indeterminate leprosy comprises a special group of leprosy patients having one or two slightly hypopigmented or erythematous macules with or without detectable loss of sensation or loss of sweating. The biopsy may show a single bacterium or a minimal lymphocytic infiltration in a dermal nerve. The diagnosis is difficult to establish, and some leprologists consider it to be an early form of either multibacillary (MB) or paucibacillary (PB) leprosy which may either heal (over 80%) or become frank MB or PB leprosy.[66]

MODE OF INFECTION AND DEVELOPMENT OF DISEASE

The mode of infection is still a point of discussion. Most leprologists no longer consider the skin to be important as the port of entry or exit of *M. leprae*.[39] However, it was recently reported again that a marked number of *M. leprae* is present in all layers of the epidermis, including the stratum corneum in lepromatous leprosy patients.[40] It may well be that this "exit" has been neglected since the reports by Pedley on the nonemergence of *M. leprae* from intact lepromatous skin[70] and later by Rees and Meade on the possibility of airborne infections.[73] Nonetheless, some leprologists and pathologists still continue to consider it to be a real possibility.[49] As *port d'entrée*, the skin is only mentioned in anecdotal reports of infection occurring after tattooing,[71] dog bites and accidental inoculation[68, 76, 78] or after the skinning of infected armadillos.[55] There are also numerous observations of a first patch on the forehead or on the cheek of a baby carried on the back of its lepromatous mother, and the first lesions seen on the bare buttocks of toddlers sitting on contaminated soil. Horton and Povey[35] concluded that the distribution of the first lesion is not at random but confined to exposed parts of the body. This concept was recently supported by Abraham, *et al.*[2] who concluded that the first lesions occur exactly at the sites most vulnerable to trauma. Naafs[61] showed for Ethiopia that the age at onset of leprosy between 1973–1979 followed the same pattern as that of tetanus, excluding neonatal tetanus, when allowing an incubation period of between 2–5 years for leprosy. It also has been shown that contaminated thorns may infect susceptible mice.[38]

Insect bites have long been incriminated in the transmission of leprosy.[36, 76, 87, 88] However in experimental studies it proved ineffective though possible.[5, 65, 68, 89] As a possible route of infection it cannot be fully dismissed. Moreover vomits of insects which had ingested *M. leprae* were shown to contain acid-fast material.[76] Flies were able to transport *M. leprae* on their feet.[30]

Transmission via the gastrointestinal tract received some attention because *M. leprae* was found to be present in mothers' milk.[69, 82] However, epidemiological evidence for this route of infection is lacking.[25] In an experimental set up neither in Carville[19] nor in London[46, 54, 68] could this route of infection be proven, although viable bacilli were seen in the stool of the challenged animals. Sexual transmission has often been considered,[78] but being a complex contact, the route is not clear. However the vaginal mu-

cosa of lepromatous women and the penile head of lepromatous men showed numerous acid-fast mycobacteria.[59]

Leprosy is at present considered to be an airborne disease having a transmission pattern similar to that of tuberculosis, in which infectious patients or carriers discharge bacteria from the nasal mucosa.[6] Rees and Meade elegantly showed this possibility.[73] Some authors were doubtful because the age at onset in their particular environment was significantly earlier for leprosy than for tuberculosis, although both diseases were highly endemic.[60] As *port d'entrée*, the respiratory tract has been suggested, with the nose playing a central role. Rees and McDougall[74] showed such *port d'entrée* to be possible for thymectomized mice; Chehl, *et al.*[19] for nude mice and, more recently, Vilani-Moreno, *et al.*[98] confirmed this for the immune-competent Swiss mice. The central role of the nose may be illustrated by the observation by Cerotti[16] that only 14 out of 116 mucosal biopsies showed to be normal[16] and that even in "pure neural leprosy" more than half of the patients show inflammatory changes in their nasal mucosa.[94]

It still remains unknown, however, why certain individuals develop leprosy and others do not. For a long time leprosy was considered to be an inherited disease,[11] until Armauer Hansen showed it to be an infectious one.[33] However, the observation that leprosy often affects families,[34] which cannot always be explained by a more intensive exposure, still holds. Rotberg proposed a theoretical, inherited, N-factor.[79, 80] Beiguelman showed a family association of Mitsuda positivity.[7–10] Of interest in this respect is the observation that the Nramp1 homolog seems to be associated with a granulomatous Mitsuda reaction.[3] That it could not be a simple straight forward inherited factor like, for instance, the factor that codes for epidermodysplasia verruciformis was shown in twin studies.[18]

An innate immunity has been proposed for some of the infected individuals.[90] For the majority, however, the CMI seems to be of crucial importance. For a short period of time, it was thought that the HLA-DR loci were the decisive factors,[99] but this was soon challenged.[92] Later, it was shown that both HLA-DR phenotypes 1[13, 56] and 2 had some influence on the type of leprosy that develops after infection, but had no influence on whether or not someone developed leprosy.[13, 14, 22, 23, 67, 100] Feitosa, *et al.*,[24] using complex segregation analyses of 10,886 individuals distributed among 1568 families, concluded that there might be a recessive major gene controlling susceptibility. However, they could not find evidence for unique genetic determinants for the leprosy subtypes, although they found indications of a segregating major effect between tuberculoid and lepromatous. Recently Silva, *et al.*[86] investigated the Lewis blood group phenotypes in leprosy patients and showed that nonsecretors developed significantly more leprosy than secretors. This finding suggests that the glycoprotein that is coded for, when secreted in the nasal mucous, has a protective action, possibly hindering adherence of *M. leprae* to the mucosal surface by binding to the adherence sites on the bacterium. A similar possibility can also be proposed for urinary tract infections,[83] recurrent vulvovaginal candidiasis[17] and pyloribacterium infections which lead to gastric ulcers.[41]

A polymorphism in a nucleotide relative to the transcriptional start site of tumor necrosis factor (TNF), a critical mediator of host defense and pathology, has been associated with lepromatous leprosy, as well as with severe malaria, leishmaniasis and scarring glaucoma.[44, 81] Subtle mutations in pathways leading to cytokine or chemokine production or receptor presentation also have been suggested as possible mechanisms that could play a role in susceptibility to infections such as tuberculosis and leprosy.[50] The same applies for factors involved in the milieu interior of cells. Allelic variants which seem to be related to innate immunity, at the human Nramp1 homolog, have recently been found to be associated with susceptibility to these two infections.[3, 12]

Mucosal, secretory IgA, immunity is another factor that could influence the protection against, or the maintenance of, intranasal infection.[1, 21, 72] It was found that workers at a leprosy hospital had a high level of secretory IgA against *M. leprae*; whereas lepromatous leprosy patients did not.[20] An interesting finding is that secretory IgA secretion is enhanced by stimulation of both sympathetic and parasympathetic nerves.[15] Nerves are noted to be damaged

throughout the leprosy spectrum, but most of all in lepromatous leprosy patients.[29]

It has been suggested that the port of entry of *M. leprae* antigenic determinants may be important for the immune system,[25, 45, 61, 62, 68, 84, 93] as supported by a concept assuming a peripheral and a central lymphocyte compartment.[93] An encounter via the skin and the draining lymph nodes (peripheral compartment) stimulates CMI. A stimulus via the nerve directly into the peripheral blood/spleen (central compartment) leads to an immunosuppression, and may induce tolerance.[93] More recently, it has been shown that exposure to antigens in the nasal mucosa also can lead to an immune tolerance.[32, 85, 95, 96] This is even more interesting when one realizes that in an endemic community 5% or even up to 27% of the population may harbor *M. leprae* in their nose, as shown in a polymerase chain reaction (PCR) for *M. leprae* DNA.[37, 43] Even some visitors from nonendemic countries who worked for a period of time in a leprosy hospital have been shown to have transient positive nose swabs for *M. leprae* DNA.[63] A factor in this may be the Lewis phenotype[86] hindering or facilitating adherence to the nasal mucosa and the presence or absence of anti-*M. leprae* secretory IgA.[21]

It has been established that *M. leprae* are able to survive for several weeks (2–4) in the environment, especially under moist conditions.[42] Such conditions exist in and around living quarters in many of the endemic countries.[76] In most of these countries, blowing one nostril while closing the other cleans noses. The mucus will partly disperse, but most of it together with *M. leprae* reaches the ground. Contaminated epidermal corneal scales may also accumulate here. Kazda, *et al.*,[42] using the mouse foot pad culture, showed the presence of *M. leprae* in soil. Matsuoka, *et al.*[53] found *M. leprae* DNA in nearly half of the water samples tested in a leprosy-endemic area. There was a higher prevalence of leprosy among the people that used this water for bathing and washing. Toddlers sit, crawl and play on and in these contaminated environments, sustaining small injuries.

Children are prone to itch because they are in the process of immunological adaptation to their physical environment. They easily scratch themselves after contact with insects and other parasites, thereby introducing *M. leprae* from the soil or other sources with their nails into their skin. This inoculation into a part of the peripheral lymphocyte compartment may stimulate CMI. Acid-fast material (possibly bacteria) was found under the nails of children,[59] whether it was *M. leprae* could not be established at the time. The contact with *M. leprae*-shedding family members or visitors also may be of a more direct nature. They may discharge *M. leprae* in large amounts in an aerosol[31] as already shown by Schaeffer early in the 20th century.[97] The bacterium may then enter the nasal mucosa of a child and induce tolerance. The observation of Fokkens, *et al.*[29] that leprosy patients have a diminished number of CD8+ cytotoxic T cells in their nasal mucosa may be important. Whether this is the consequence of the infection, a facilitating factor or both could not be established. It was also noticed that the mucosa was atrophic and damaged with blood vessels very near to the surface,[29] thus providing easy access for the bacterium to the central lymphocyte compartment. It should be realized that not only the route of the infection but also the size, the viability, the interval and the frequency of the inoculum are important.[45] Little is known on this subject to date.

Not only *M. leprae* but also environmental mycobacteria may have an influence on the immune system.[4, 47, 52, 58] Auto-antigens, too, may modify the immune response. The influence of BCG vaccination is well known,[26–28, 51, 77] its effectiveness probably depending on the environmental microorganisms.[27, 28, 91]

CONCLUSION

It may be theorized that the balance between responses elicited by different routes of infection and inoculum, skin versus nasal mucosa and possibly nerve,[93] is responsible for the outcome of the infection. However, data to date suggest that the response is modulated by genetic factors, among which is HLA-DR. Even more important are previous encounters with other microorganisms and auto-antigens with antigenic determinants similar to those of *M. leprae*. The final result, resistance, delayed-type hypersensitivity, tolerance, disease or no disease, tuberculoid, borderline or leproma-

tous leprosy with or without reactions, is most likely mediated by the orchestration of the induced cyto- and chemokines.[64]

SUMMARY

The clinical manifestations of leprosy vary, seemingly depending on the host's immune response. Mode and route of infection, such as skin versus nasal mucosa, insect bites, sexual and gastroenteral transmission, together with genetic factors that may contribute to the outcome of the infection, including HLA, Lewis factor, Nramp1 and more subtle inherited alterations, are discussed. It is theorized that a balance between host responses elicited by different routes of infection and size and spacing of inocula is responsible for the clinical and immunological manifestations of the disease. Genetic factors and contact with environmental microorganisms may modulate these responses. The final result, resistance, delayed-type hypersensitivity, tolerance, disease or no disease, spectrum and reactions, is most likely reached via the orchestration of the induced cyto- and chemokines.

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