Evidences of Aerial Route of *Mycobacterium leprae* Infection and Doubts About Transmission and Natural Protection in Leprosy

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(See the Major Article by Araujo et al on pages 1412–20.)

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The article by Araujo et al [1] raised some questions and provided some important answers about leprosy and its chain of transmission, and their results should help clarify why leprosy still persists as a public health problem in many countries. For example, a recent publication discussed some paradoxes about the current worldwide leprosy situation, with some very optimistic proposing a perspective of zero transmission of leprosy in Brazilian hypendemic areas applying just mathematical modeling [2] while other, showing in the same area, mean rates of new diagnoses ranging from 3.4% to 13.4% among towns of Pará State, Brazil, with mean detection rates of 4% among schoolchildren and 8% among household contacts (HHCs). These authors also showed the difficulties faced by authorities in notifying and treating new cases that are clinically very well established [3], probably important evidence of political influences in leprosy control.

Although some studies have demonstrated fragile evidence concerning environmental sources of *M. leprae* [4], recent studies have also shown the presence of viable strains of *M. leprae* in skin smear samples from paucibacillary and multibacillary patients, as well as in environmental samples (soil and water) obtained from around their houses [5]. Currently, we do not know the real meaning of paucibacillary patients and extrahuman sources of bacilli in the continued transmission of leprosy. Araujo et al [1] presented a longitudinal prospective study with a follow-up of 5–7 years in 113 patients with leprosy and 104 HHCs. Using quantitative polymerase chain reaction (qPCR), they found positivity rates of almost 44% and 47% in nasal swab and nasal biopsy samples, respectively, from paucibacillary patients, compared with almost 40% and 57% for samples from HHCs of these paucibacillary index case patients, data demonstrating the real risk of transmission of *M. leprae* by paucibacillary patients and the importance of their contacts examinations. Araujo et al [1] also confirmed these results, with higher percentages of positivity shown by qPCR of nasal swab and nasal biopsy samples from multibacillary index case patients and their HHCs.

Although the possible role of HHCs in the chain of leprosy transmission has been known for a long time, only now investigators identifying an emerging tool to identify it. They corroborate quantitatively the spectrum of the leprosy evolution, as proposed by Ridley and Jopling in 1966 [6], from tuberculoid to lepromatous poles, showing an increase of DNA as the spectral evolution of the disease by qPCR in nasal swab and biopsy samples and also in blood samples [1].

On the other hand, this study by Araujo et al [1] raises an important question about human protection against *M. leprae* and what this really means. Conventionally accepted is a widely held assumption that >90% of the general human population is naturally immune to infection by *M. leprae* [7]. Some have proposed that, due to host genetics, nutritional and immunological factors, only 3–5% of the population have genetic and immunologic susceptibility for leprosy [8]. Although most leprologists have accepted this teaching [7, 9, 10], few know the origins of this observation.

Concerning this point, considering the similarity of the results obtained in *M. leprae* DNA analyzing from nasal swab and nasal turbinate biopsy samples in patients with leprosy and also their HHCs (though with lower quantities of DNA in HHCs) could indicate that nasal swab samples mean more than only a single colonization from the environment, whereas the positivity of nasal biopsy samples can support the presence of a subclinical infection.

Besides the source of the HHC in the chain of leprosy transmission, Araujo et al [1] make a very important contribution with their finding about peripheral
nerve involvement in the disease resulting in sensory changes, motor disorders, and dysautonomia. This study reinforces the notion that the hematogeneous route is the only access to a normal endoneural compartment, with the presence of *M. leprae* in the peripheral blood determining high risk for the development of leprosy.

Depending on the individual genetical factors and also immune response involved in the start of peripheral nerve damage, *M. leprae* could be killed by strong cellular response in tuberculoid patients, whereas in multibacillary patients the bacilli activate a variable humoral response, which is maintained, surviving and multiplying in the host, as described recently [1]. In this way, the host develops a special mechanism involving a specific genetic factor as a stimulator of interferon genes-dependent 2′-5′ oligoadenylate synthetase–like at the bifurcation of the infection outcome, driving a fine balance between susceptibility mediated by the type I interferon response and resistance mediated by autophagy [11].

Currently, we do not have a good commercial standard lepromin test in Brazil, but Araujo et al [1] have used a standardized heat-killed *M. leprae* suspension to evaluate the cell-mediated hypersensitive response, considered the most strong resistance response against bacilli. Interestingly, the authors found 78% of Mitsuda test positivity among HHCs from paucibacillary and 62% among HHCs from multibacillary index case patients, with no mean induration difference between groups. The authors found among HHCs, individuals without any detectable signs of leprosy, lower percentual than 90%, proposed to health population with natural protection against leprosy, and much lower than paucibacillary patients with 96% of positivity. These data showed that even with high rates of Mitsuda test positivity the patient can develop a disease in a cellular immune response leprosy pole, but it does not seem to be an isolated and exclusive factor of host defense in leprosy.

As to humoral response, the antiphilinic-glycolipid-I enzyme-linked immunosorbent assay index was positive in almost 85% of multibacillary patients and it showed a good correlation with skin smear and skin biopsy samples. In addition, it was positive in 21% in HHCs, the majority HHCs of multibacillary index case patients. These data reinforce the importance of environmental factors and emphasize the capacity of *M. leprae* to survive, maintaining its infective potentiality at the environmental conditions as climate conditions as temperature and humidity climate.

For leprosy case definition, we should consider hypoesthetic or anesthetic areas in the skin, thickening of the peripheral nerve followed by abnormal sensations, or the presence of *M. leprae* in skin smears. Unfortunately, Araujo et al considered only clinical follow-up of HHCs, but nasal swab samples and/or slit skin smears from cold regions (eg, ear lobes and elbows) could help identify real incipient disease, an important way to diagnose leprosy and treat cases diagnosed early.

In conclusion, the study by Araujo et al confirms what leprologists have speculated for many years about the transmission route in leprosy. Their results in HHCs must be widely used to better control the load of infection, mainly in endemic area, despite the doubts about the natural factor of protection against leprosy still remaining unclear.

**Note**

**Potential conflict of interest.** Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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