

EDITORIAL

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Leprosy Research Declines, but Most of the Basic Questions Remain Unanswered

A century ago, most of those who worked on leprosy did so in near isolation, scientifically and geographically. Their situation was chaotic, intellectually and otherwise: leprosy had a confusing diversity of clinical manifestations, classifications, and complications. It was incurable, and caused enormous upheaval in the families and communities where it occurred. Most workers were missionaries, and there was little financial support for research. The overall situation improved after dapsone became available to cure the infection, but leprosy still did not attract many medical scientists.

This situation changed dramatically in the 1960s, with an extraordinary coincidence of scientific thinking and discovery that led to a "golden age" of leprosy research. In a chapter on "The Immunopathologic Spectrum of Leprosy" (1964), Olaf Skinsnes presented the first full formulation of the concept we now consider basic to the understanding of leprosy, i.e., that the diversity of clinical, pathological, and microbiological findings in leprosy are a result of varying degrees of cellular immunity to *Mycobacterium leprae* in different patients (6). Scarcely two years later, Drs. Ridley and Jopling published their practical classification system that was congruent with this theoretical foundation (5). Based on clinical and histopathologic findings, this classification system enabled physician investigators around the world to classify patients according to a common standard. The combination of a well-grounded theory and a practical method of universal classification gave new impetus to research.

Meanwhile, during the 1960s immunologists identified the distinction between T cells and B cells, and recognized their re-

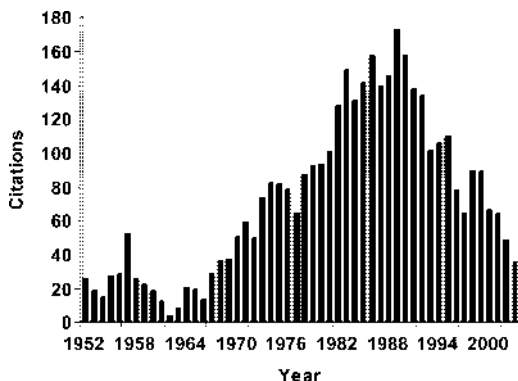
spective roles in cellular and humoral immunity (e.g., references 3 and 4). Scientists rapidly developed an entirely new set of tools, and simultaneously discovered leprosy as a challenging human disease that appeared to be an ideal model in which to examine theories and methods related to cellular immunity in man.

The convergence of these developments prompted an extraordinary burst of research effort and publications that increased in a linear fashion from a nadir of 3 papers in 1962 to a maximum of 172 papers in 1989 (The Figure). This approach to assess the extent of scientific effort expended per year is crude, and may miss some publications. It does, nevertheless, offer a reasonable estimate of the trend with respect to the level of research activity as reflected by publication in the scientific literature. A total of over 2000 medical and scientific publications indexed on "leprosy AND immunology" appeared during this period of time.

And then, around 1989–90, the bottom appeared to fall out of this effort. The number of papers published annually on the immunology of leprosy began a decline that is as precipitous as its rise had been only a decade before (The Figure). At the current rate, we can expect that around 2010–11 there will once again be only 3 papers published on the immunology of leprosy.

What happened? Did the ability to cure infection with *M. leprae* bring an end to the inquiry? Were the compelling questions concerning human immunity answered? The answer to these questions is "no."

Even after effective monotherapy with dapsone was available, and additional effective agents were added to the treatment regimen, medical scientists were emphatic-



THE FIGURE. PubMed citations on the immunology of leprosy, 1952–2003. The annual number of citations retrieved from the National Library of Medicine’s PubMed database, using the search expression “leprosy AND immunology,” is shown from 1952 (the earliest year for which such information is available in this database), through 2003.

cally agreed that it was imperative to *understand* the underlying mechanisms of this disease. The earnest introductions to hundreds of papers published from the 1960s through the 1980s brim with the conviction that leprosy was not only a major problem in the world, but that an understanding of its immunological characteristics would unlock profoundly important insights into this and other diseases. An unsuspecting observer might think that around 1990 the important, basic questions about leprosy had suddenly and decisively been answered; the mechanisms underlying the remarkable spectrum of leprosy must have been discovered, and immunotherapies and vaccines developed, and this scourge had been eliminated.

Among the developments during this period of time were new global health problems, especially HIV/AIDS, and a renewed concern about tuberculosis. These competing imperatives, however, do not obviate the oft-repeated assessment that leprosy really does present an extraordinary scientific challenge that will yield important lessons for other diseases, as well. Another important factor was the inauguration in 1991 of the World Health Organization campaign to eliminate leprosy as a public health problem by the year 2000. The elimination has not happened, however, and sound, scientific epidemiological evidence and models clearly indicate that it will not happen anytime soon with only the methods of diagno-

sis and treatment now available (^{1,2}). Research into the underlying immunological mechanisms of this infection, however, has nearly been eliminated, as evidenced by the decline in publications.

What were the basic questions in leprosy that scientists of the 1960s, 70s, and 80s found so compelling? The proceedings of several ILA Congresses and workshops from the 1960s to the present, and the reports of WHO committees and advisory groups in the same half century, repeatedly asserted the high priority of the following basic research questions:

1. What is the mechanism of transmission of *M. leprae*?

2. Why is *M. leprae* an obligate intracellular parasite? What is this organism lacking that it cannot be cultivated?

3. What is the mechanism underlying the unique spectrum of cellular immune responses in leprosy, and the selective non-responsiveness of polar lepromatous patients?

4. What is the mechanism of Type 1 reactions?

5. What is the mechanism of Type 2 reactions?

6. What is the mechanism of nerve injury?

All of these questions remain unanswered today, and the last 4 of 6 in this list are closely related to the immune response to *M. leprae*. However, the perception that the elimination of leprosy is imminent has undoubtedly discouraged many scientists and funding sources from pursuing it further. The unfortunate experience of premature de-emphasis on research in such infectious diseases as tuberculosis and malaria, however, suggest that with a disease as slow but persistent as leprosy, continued effort to understand the underlying mechanisms of disease is essential to the quest for genuine success in conquering it.

—DMS

REFERENCES

1. MEIMA, A., GUPTA, M. D., VAN OORTMARSEN, G. J., and HABBEMA, J. D. SIMLEP: a simulation model for leprosy transmission and control. *Int. J. Lepr. Other Mycobact. Dis.* **67** (1999) 215–236.
2. MEIMA, A., SMITH, W. C., VAN OORTMARSEN, G. J., RICHARDUS, J. H., and HABBEMA, J. D. The future incidence of leprosy: a scenario analysis. *Bull. World Health Organ.* **82** (2004) 373–380.

3. MILLER, J. F. A. P. Immunological function of the thymus. *Lancet* **10(Sept)** (1961) 748–749.
4. MITCHELL, G. F., and MILLER, J. F. A. P. 1968, Cell-to-cell interaction in the immune response. II. The source of hemolysin-forming cells in irradiated mice given bone marrow and thymus or thoracic duct lymphocytes. *J. Exp. Med.* **128** (1968) 821–838.
5. RIDLEY, D. S., and JOPLING, W. H. Classification of leprosy according to immunity, A five-group system. *Int. J. Lepr. Other Mycobact. Dis.* **34** (1966) 255–273.
6. SKINSNES, O. K. The immunological spectrum of leprosy. In: *Leprosy in Theory and Practice*. Baltimore: Williams and Wilkins, 1964. pp. 156–162.