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## EDITORIAL

*Editorial opinions expressed are those of the writers.*

### Leprosy Research and Patient Care Over the Past Century\*

It is a great pleasure to address this distinguished audience on the topic of leprosy research and its relation to care of patients over the last century. I thank all who have participated in the preparations for this centennial celebration of the First International Leprosy Congress, especially the staffs of the German Leprosy Relief Organization and the Sasakawa Memorial Health Foundation.

The title of this talk poses a daunting task—to cover 100 years of dedicated effort by thousands of health workers and laboratory scientists in a brief span of time. The assigned title was accepted with much trepidation, so I ask your indulgence where I may omit important developments and the people responsible, and likewise for any perceived bias in selection of topics discussed.

From ancient times, leprosy has been uniquely steeped in folklore, and the patients more often than not have been subjects of fear, derision, ostracism and ne-

glect. The disease and its stigma have long been inseparable in most societies throughout the world. In Frankfurt-am-Main, for example, just outside the site of the former city wall, there is a street called "Gütteleutstrasse." The name goes back to the Middle Ages when there was a leprosarium at this site that housed the "good people" with leprosy, who were not criminals but were required to be segregated and confined outside of the city.

To provide background for a discussion of leprosy research and patient care during the 20th century, we will step back briefly to a slightly earlier time.

Undoubtedly, early attempts to apply scientific methods to the understanding of leprosy took place in many locations in other countries, but there is no question of the significance of events that began in Norway in the early 19th century.<sup>1</sup> There, studies by Hjort on the epidemiologic and social aspects of leprosy beginning in 1832, aroused the interest of health authorities and captured the attention of Danielssen in Bergen. Based on scientific criteria, Danielssen and

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<sup>1</sup> Irgens L. M. Hansen, 150 years after his birth, the context of a medical discovery. *Int. J. Lepr.* **60** (1992) 466–469.

Boeck in 1849 established leprosy as a clinical entity. This resulted in the founding of a 90-bed leprosy research hospital and three other facilities for more than 1000 patients. The Norwegian government then created a Leprosy Registry, providing information which, in 1858, convinced Hoegh, the first Chief Medical Officer for Leprosy in Norway, that leprosy was an infectious disease: a salient advance toward the era of enlightenment for leprosy about to dawn.

G. Armauer Hansen, as a newly graduated physician, came into this atmosphere of progressive medical inquiry in 1866. There were at that moment three prevailing schools of thought on the cause of leprosy: Danielssen (Hansen's father-in-law) viewed the disease as "an hereditary dyscrasia sanguinis," others believed it was a host response to nonspecific unfavorable environmental factors, and the last school, Hansen's group, was convinced that leprosy was infectious. Hansen pursued his conviction and on 8 February 1873, after numerous meticulous microscopic observations of unstained tissue fluid from leprosy patients, recorded his belief that the brownish rods or "sticks" he saw were the cause of leprosy, and depicted these bodies in drawings.<sup>2</sup> This landmark event in the annals of microbiology, then in its infancy, launched the quest for a scientific understanding of leprosy as a disease. Not only was the leprosy bacillus the first mycobacterium discovered, it was the first etiologic agent of a chronic disease of humans. Perhaps this finding stimulated and hastened the search for other pathogens of humans.

Halfway around the world in the same year, 1873, a Belgian priest known as Father Damien went to the island of Molokai in Hawaii, and took up residence among the large group of leprosy patients who suffered not only the ravages of the disease, but forcible separation from their families on an isolated spit of land called Kalaupapa. The Pacific Ocean surrounded this veritable prison on three sides and on the remaining border there was a pali, or high cliff. Father Damien brought hope and dignity to these

isolated, hopeless and downtrodden patients. By his life devoted to compassionate care, punctuated by acts of political activism published around the world,<sup>3</sup> Damien raised the social conscience of humanity toward the stigma of leprosy and the need for its mitigation. Damien's death in 1889 of complications of lepromatous leprosy secured his name for all time in the chronicles of the struggle against not only the stigma of leprosy but all human injustice.

There is a long history of religious groups providing charity and comfort for those with leprosy, but The Mission to Lepers (The Leprosy Mission, London), founded in 1874, was one of the earliest internationally coordinated efforts established uniquely for the care of leprosy patients.

Although much more could be said about the early heroes of modern leprology, we move on now to Berlin and the First International Leprosy Congress. The Proceedings of this 1897 Congress reflects the policy of most endemic countries toward leprosy patients in that era—namely, forced isolation and "preferably on an island."<sup>4</sup> Relevant to the isolation policies discussed in that meeting, special attention was given to the discovery of the discharge of leprosy bacilli from the nose and skin. There is little doubt that acceptance of the contagious nature of leprosy contributed to the reinforcement of segregation. Lacking effective chemotherapy, these measures probably reduced the prevalence of leprosy in Europe, but such policies were more difficult to enact in endemic areas in the socioeconomically deprived tropics.

The Second International Leprosy Congress, held in 1909 in Bergen with Hansen as President, reaffirmed the isolation and segregation policies, and further recommended that "healthy children should be separated from their leprous parents as soon as possible."<sup>5</sup> Three significant biomedical research points considered at this meeting

<sup>2</sup> Hansen, G. H. A. *Undersøgelser angaaende Spedalskhedens Aarsager*. Norsk Mag. f. Laegev. 4 Suppl. (1874) 1–88. [English translation: Hansen, G. A. Causes of leprosy. Int. J. Lepr. 23 (1955) 307–309].

<sup>3</sup> Daws, G. Stigma. In: *Holy Man. Father Damien of Molokai*. New York: Harper and Row, 1973, pp. 215–252.

<sup>4</sup> Mittheilungen und Verhandlungen der internationalen wissenschaftlichen, Lepra-Conferenz zu Berlin 1897. Berlin: August Hirschwald.

<sup>5</sup> Proceedings II International Leprosy Conference, Bergen 1909. H. P. Lie, ed. Leipzig: Johann Ambrosius Barth, 1909.

were: 1) environmental sources of the leprosy bacillus, 2) hereditary and congenital factors in susceptibility and transmission, and 3) pathogenetic processes in leprosy, including specific bacilleemia.

During the next three to four decades, although devoted scientists sought to further the quality of patient care, the slow advances in medical science and technology hindered developments. Numerous studies on therapy, experimental transmission of leprosy to humans and animals, and attempts to cultivate the leprosy bacillus were unrewarding. Two developments, however, had lasting benefits: 1) Hayashi and Mitsuda in 1919 established the lepromin reaction.<sup>6</sup> This implicated host factors in determining the form of disease, and opened leprosy research to the then unsophisticated but burgeoning science of immunology. 2) Lara, beginning in the 1920s in a study of 2000 children in The Philippines, showed that a) contact was important in transmission, b) leprosy was often self-healing, and c) 6% of all the contacts developed active persistent leprosy. These data helped establish that only 5% to 10% of most populations are susceptible to progressive leprosy.<sup>7</sup>

In 1931 the International Leprosy Association (ILA) was founded in Manila, under the auspices of the Leonard Wood Memorial.<sup>8</sup> The purpose of the Association was to disseminate scientific information on leprosy through its publication, the *International Journal of Leprosy*, and the organization of periodic international leprosy congresses. Over the last six decades these activities have promoted the cohesiveness of the scientific and medical communities in leprosy research and control. The ILA Congress in Havana in 1948 was the first one held under the sponsorship of the ILA.<sup>9</sup> An

important outcome of the Havana Congress that had a direct and profound impact on the patient was the following resolution:

"That the use of the term 'leper' in designation of the patient with leprosy be abandoned, and the person suffering from the disease be designated 'leprosy patient'."

The 1940s ushered in a new and exciting era in patient care. In 1943 Guy Faget published results of the treatment of patients at Carville, Louisiana, U.S.A., with the soluble sulfone, Promin.<sup>10</sup> His success, as expected, was met with both jubilation and skepticism. The sulfones, however, proved regularly curative, and the most useful form, dapsone (DDS), was introduced for treatment of patients by Robert Cochrane in 1947 in Chingleput, India.<sup>11</sup> However, nearly a decade passed before DDS was used widely. The remarkable efficacy of orally administered dapsone began the liberation of patients from both the physical damage and stigmatizing sequelae of leprosy.

Model ambulatory treatment programs were instituted in the 1950s by a few leprosy specialists, perhaps most notably by Hemerijckx.<sup>12</sup> Leprosaria gradually became reference centers or were closed, with most patients attending satellite clinics, often under the trees along remote roads or paths. The stigma of the disease and social dislocation began to diminish dramatically. The terrain of many leprosaria assumed other uses—for example, one I worked in for some time in the Congo (and at one time had had over 4000 resident patients) became an airplane landing strip and another in the same country, a school for public health workers.

Based largely on the observations of Khanolkar in India, during the 1950s and into the early 1960s, leprosy became recognized as primarily an affliction of peripheral

<sup>6</sup> Mitsuda, K. On the value of a skin reaction to a suspension of leprosy nodules. *Hifuka Hinyoka Zasshi* (Jpn. J. Dermatol. Urol.) **19** (1919) 697–708. (in Japanese) [English translation: *Int. J. Lepr.* **21** (1953) 347–358.]

<sup>7</sup> Lara, C. B. Leprosy in children: general considerations: initial and early changes. *Philippine J. Lepr.* **1** (1966) 22–57.

<sup>8</sup> Wade, H. W. The International Journal of Leprosy. An Editorial Statement. *Int. J. Lepr.* **1** (1933) 1–3.

<sup>9</sup> Leprosy News and Notes. Fifth International Leprosy Congress, Havana, April 3–11, 1948. *Int. J. Lepr.* **16** (1948) 187–253 (see p. 243).

<sup>10</sup> Faget, G. H., Pogge, R. C., Johansen, F. A., Dinan, J. F., Prejean, B. M. and Eccles, C. G. The Promin treatment of leprosy: a progress report. *Publ. Hlth. Repts.* **58** (1943) 1729–1941.

<sup>11</sup> Cochrane, R. G. A comparison of sulphone and hydnocarpus therapy of leprosy. *Int. J. Lepr.* **16** (1948) 139–144.

<sup>12</sup> Hemerijckx, F. The Belgian Leprosy Centre, Polambakkam. *India* **30** (1958) 24–25.

nerves.<sup>13</sup> Also during those years, surgical procedures were devised for correcting paralytic and other deformities, and protecting insensitive hands, feet and eyes. For these monumental efforts we are indebted largely to the pioneering work of Paul Brand in India.<sup>14</sup> The primary disease was now curable and many of its ravages could be corrected. These two advancements led to ambulatory treatment and physical rehabilitation, with an enormous salutary impact on patient care.

But still in the 1950s, much remained unknown. The bacillus could not be cultivated *in vitro*, despite the efforts of John Hanks and many other researchers over many decades,<sup>15</sup> and there were no animal models for leprosy. Thus, there were very few studies on, for example, the physiology of *Mycobacterium leprae* or the immunology and pathogenesis of the disease. In 1956, my late colleague, Chapman Binford, on the basis of Virchow's observations in 1863 and on his own clinical observations in Hawaii, proposed that *M. leprae* grew selectively in the cooler areas of the host—i.e., ears, skin, eyes, peripheral nerves and testes.<sup>16</sup> This concept led Binford to infect hamsters successfully (1958),<sup>17</sup> and ultimately, for Shepard to develop the mouse model (1960)<sup>18</sup> and Kirchheimer and Storrs to infect the nine-banded armadillo (1971).<sup>19</sup>

The mouse model became renowned for studies in the chemotherapy of leprosy. No

longer did investigators have to depend on clinical response or bacteriologic staining properties to screen drugs. There was now an experimental model on which to test new preparations. Besides dapsone, two of the many important antileprotics studied in the mouse were rifampin and clofazimine. These drugs had already been shown to be effective clinically, but experimental data were most welcome. Mice that were immunologically manipulated by chemicals, radiation or surgical procedures, and various genetic variants of mice, added valuable information on the pathogenesis of leprosy. Perhaps, however, the most important contribution of the mouse model with impact on patient care was the detection of sulfone-resistant strains by Pettit and Rees in 1964.<sup>20</sup> This set in motion the concept of alternative chemotherapeutic approaches, and eventually combined drug regimens.

Classification of leprosy had long been a topic of heated debate. Clinically, the current classification of leprosy into tuberculoid, dimorphous or borderline, and lepromatous disease was established at the Madrid Congress in 1953.<sup>21</sup> Beginning in 1962, Ridley and Jopling codified a classification system based on clinical, immunologic and histopathologic criteria. This Ridley-Jopling system has become the researchers "gold standard" for uniformity in assessing the host response in clinical investigations in leprosy, and provides excellent prognostic criteria for patient management.<sup>22</sup>

The formation in 1966 of the Coordinating Committee of European Leprosy Agencies (ELEP),<sup>23</sup> which in 1975 became the International Federation of Antileprosy Associations (ILEP),<sup>24</sup> was a highly significant move in the coordination of the worldwide

<sup>13</sup> Khanolkar, V. R. Perspectives in pathology of leprosy. Indian J. Med. Sci. **9** (1955) Suppl. 1, 44 pp.

<sup>14</sup> Brand, P. W. The value of surgical and physiotherapeutic measures in leprosy. Lepr. India **27** (1955) 131–143.

<sup>15</sup> Hanks, J. H. Assay of the fate of mycobacteria in cell and tissue cultures. Rev. Tuberc. Pulmon. Dis. **77** (1958) 789–801.

<sup>16</sup> Binford, C. H. Comprehensive program for inoculation of human leprosy into laboratory animals. Publ. Hlth. Repts. **71** (1956) 955–956.

<sup>17</sup> Binford, C. H. Histiocytic granulomatous mycobacterial lesions produced in the golden hamster (*Cricetus auratus*) inoculated with human leprosy. Int. J. Lepr. **26** (1958) 318–324.

<sup>18</sup> Shepard, C. C. The experimental disease that follows the injection of human leprosy bacilli into foot pads of mice. J. Exp. Med. **112** (1960) 445–454.

<sup>19</sup> Kirchheimer, W. F. and Storrs, E. E. An attempt to establish the armadillo (*Dasypus novemcinctus*, Linn.) as a model for the study of leprosy. I. Report of lepromatoid leprosy in an experimentally infected armadillo. Int. J. Lepr. **39** (1971) 693–702.

<sup>20</sup> Pettit, J. H. S. and Rees, R. J. W. Sulphone resistance in leprosy; an experimental and clinical study. Lancet **2** (1964) 673–674.

<sup>21</sup> Muir, E. Report on the Madrid Congress. An Editorial. Int. J. Lepr. **21** (1953) 477–557.

<sup>22</sup> Ridley, D. S. and Jopling, W. H. A classification of leprosy for research purposes. Lepr. Rev. **33** (1962) 119–128.

<sup>23</sup> News and Notes. Coordinating Committee of European Leprosy Agencies (ELEP). Int. J. Lepr. **34** (1966) 437–438.

<sup>24</sup> News and Notes. ILEP. Int. J. Lepr. **43** (1975) 155.

activities of numerous voluntary agencies, missions and foundations. In recent years ILEP members have contributed approximately \$70 million annually, provided expertise in training and service for the care of millions of patients, and promoted operational and basic research.

In 1971, with the development of experimental lepromatous leprosy in the nine-banded armadillo, for the first time there was an animal model of a form of leprosy in humans and one that was reproducible in laboratories around the world.<sup>19</sup> Tissue of these animals abounded with leprosy bacilli with as many as 10<sup>13</sup> bacteria per animal. It was most unfortunate that deep-seated controversy surrounded research on this animal model and, as a result, the armadillo was soon largely relegated to an "industrial" role—namely, the manufacture of large numbers of leprosy bacilli for *in vitro* biochemical, immunologic, chemotherapeutic, and eventually molecular biologic studies. In the era 1971 to the latter 1980s there were probably many missed opportunities in the use of armadillos for basic research on the epidemiology, transmission, and pathogenesis of leprosy.

The armadillo, nevertheless, opened new vistas in leprosy, most significantly the recognition of leprosy as a natural zoonosis in southern United States.<sup>25</sup> Today in some foci in Louisiana and Texas, as many as half of the armadillos in the wild have some form of naturally acquired leprosy, and humans in the U.S.A. have contracted the disease by direct or indirect contact with infected armadillos or their tissues.

The possible worldwide importance of zoonotic leprosy surfaced in the latter 1970s when West African chimpanzees and mangabey monkeys that had never been experimentally inoculated with leprosy bacilli developed leprosy while in captivity in the United States.<sup>26, 27</sup> Extensive experimental investigations revealed that other species of

nonhuman primates were susceptible and provided excellent models of leprosy for long-term studies.

The concept of zoonotic leprosy is now well established. Zoonotic leprosy could well contribute to maintaining the endemicity of leprosy in some geographic areas.

The question of a varying host response in the different clinical forms of leprosy introduced by Mitsuda in 1919 has provoked major immunologic investigations. While many of the immunologic findings have only academic meaning at this time, a few have had some direct application to leprosy control. For example, Godal in 1974 showed by antigen-specific lymphocyte transformation that in Ethiopia exposure rates were highest (56%) in occupational contacts, 47% in household contacts, and 29% of those with no known contact.<sup>28</sup> Brennan and Barrow (1980) for the first time isolated specific antigens of *M. leprae*,<sup>29</sup> but sensitivity in detecting antibodies to this antigen (PGL-I) was too low for practical usefulness in diagnosis or seroepidemiologic surveys.

Some *M. leprae*-based vaccines have been assessed in large-scale trials in humans, but thus far have not proved effective. While other cultivable mycobacteria-based vaccines are under study, reports thus far are insufficient for critical evaluation. BCG in some populations is highly protective against leprosy, but not in others. Serial BCG vaccination in one study was an effective immunoprophylactic approach.<sup>30</sup> This scheme, however, will probably not be used in large-scale studies because of potential adverse reactions in immunosuppressed individuals.

ford, C. H., Imes, G. D., Jr., Hadfield, T. L., Schlagel, C. J., Gerone, P. J., Wolf, R. H., Gormus, B. J., Martin, L. N., Harboe, M. and Imaeda, T. Leprosy in a mangabey monkey—naturally acquired infection. *Int. J. Lepr.* **53** (1985) 1–14.

<sup>28</sup> Godal, T. Growing points in leprosy research. 3. Immunological detection of sub-clinical infection in leprosy. *Lepr. Rev.* **45** (1974) 22–30.

<sup>29</sup> Brennan, P. J. and Barrow, W. W. Evidence for species-specific lipid antigens in *Mycobacterium leprae*. *Int. J. Lepr.* **48** (1980) 382–387.

<sup>30</sup> Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet* **348** (1996) 17–24.

<sup>25</sup> Walsh, G. P., Storrs, E. E., Burchfield, H. P., Cottrell, E. H., Vidrine, M. F. and Binford, C. H. Leprosy-like disease occurring naturally in armadillos. *J. Reticuloendothel. Soc.* **18** (1975) 347–351.

<sup>26</sup> Leininger, J. R., Donham, K. J. and Meyers, W. M. Leprosy in a chimpanzee. Post-mortem lesions. *Int. J. Lepr.* **48** (1980) 414–421.

<sup>27</sup> Meyers, W. M., Walsh, G. P., Brown, H. L., Bin-



Finally, we consider the multidrug therapy of leprosy. The pioneer prospective multidrug therapy program with limited duration of treatment was started in Malta in 1973 by Depasquale and Freerksen. These investigators employed Isoprodian and rifampin. Long-term observation of 275 patients treated for approximately 2 years revealed only one relapse.<sup>31</sup>

The World Health Organization (WHO) in 1982 issued recommendations for multidrug therapy (MDT) of leprosy.<sup>32</sup> These recommendations were based largely on empirical judgments on efficacy, practical administrative constraints in field programs, and cost. Goals were to treat the disease, prevent bacterial resistance, and interrupt transmission. The choice of one of two regimens is based on a simplified field classification of patients and administered for 6 or 24 months, depending on the form of disease. Cooperative efforts between WHO, ILEP and the governments of endemic countries have proved highly effective. By 1991 the estimated number of leprosy patients worldwide had dropped from a high of 10–20 million to 5.5 million. This prompted the WHO in May 1991 to approve a resolution “. . . to attain the global elimination of leprosy as a public health problem by the year 2000.”<sup>33</sup> Elimination as a public health problem was defined as one patient or less per 10,000 population by country. Whether or not this goal is achievable within the timeframe is not known, but remarkable progress has been documented. By July 1997, application of MDT has reduced prevalence of leprosy since 1981 by an astounding 85%. There are now slightly less than one million known patients world-

wide. In the period 1981–1997, 8.4 million leprosy patients were treated and approximately 97% of all known leprosy patients have been or are being treated.

Paralleling these remarkable achievements in chemotherapy, advances in the understanding of social rehabilitation programs have reduced, but not eliminated, the stigma. Today we can affirm that the plight of the leprosy patient has greatly improved, but many questions remain:

1) Can the current programs be sustained? With fewer patients public interest declines and financial support and specialized care diminish. Will this lead to exacerbation of the disease?

2) How accurate are prevalence data? Around 600,000 new patients continue to be diagnosed each year, and some focal surveys suggest that significant numbers of patients remain undetected.

3) Are diagnostic methods adequate? Early diagnosis remains a problem, with one in five new patients already showing disability at diagnosis. Given the present low level of support for leprosy research, can the burgeoning biochemical technology infrastructure provide accurate and cost-effective early diagnostic tools?

4) Can leprosy be eradicated? Without an effective vaccine and with known zoonotic sources, and possibly other sources, eradication is unlikely very soon. Improved socioeconomic conditions in endemic countries would probably accelerate eradication of leprosy in humans as much or more than medical interventions.

I close by calling to mind, for example, the history of pronouncements of the elimination of tuberculosis and malaria. Essential “elimination” disrupted research and control programs in these plagues, and today worldwide they are among our most dangerous infectious diseases. Whither will leprosy go?

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<sup>31</sup> Depasquale, G. Rifampicin and Isoprodian in combination in the treatment of leprosy. *Lepr. Rev.* **46** Suppl. (1975) 179–180.

<sup>32</sup> World Health Organization. Chemotherapy of leprosy for control programmes. Geneva: World Health Organization, 1982. Tech. Rep. Ser. 675.

<sup>33</sup> News and Notes. Report of the First Meeting of the WHO Working Group in Leprosy Control, 1–3 July 1991. *Int. J. Lepr.* **60** (1992) 114.