Nonhuman Sources of Leprosy

Over at least several millennia, leprosy as a disease and as a stigma were largely inseparable. In 1873, two men of considerable courage and perseverance changed these two aspects of leprosy for all time: Armauer Hansen, here in the town of Bergen, saw and depicted unstained intracellular "rods" or "sticks" in tissue fluid of lesions from leprosy patients, and declared them as the cause of leprosy.[1] Today we see these rods so easily and so clearly as the acid-fast *Mycobacterium leprae.* Halfway around the globe in Hawaii, a 33-year-old Belgian priest known as Father Damien first brought dignity and hope to the destitute and hopeless leprosy patients who had been cruelly isolated at Kalaupapa, on the island of Molokai. By his life, and by his death from leprosy 16 years later in 1889, Father Damien raised the social conscience of the world toward the alleviation of the stigma of leprosy.[2]

Our topic today, "Nonhuman sources of leprosy," is not a new subject. For example, Dr. Sand at the II International Leprosy Congress in Bergen in 1909 presented a paper entitled "Geschieht die Ansteckung der Lepra durch unmittelbare Übertragung?".[3] In this study, Dr. Sand addressed the question of whether leprosy was transmitted only by patients, or if there were other possible sources of the leprosy bacillus. From his observations there was no good evidence of transmission of leprosy within the leprosy hospitals in Norway, and he wondered if decaying soil or animals transmitted the disease. The importance of soil or other nonanimal materials, such as sphagnum moss, as sources of *M. leprae* is a relevant and continuing topic of great interest, especially to investigators here in Norway and elsewhere in Europe.[4] For reasons of brevity only, this topic will not be considered further.

Hansen's thesis that there was indeed a leprosy bacillus was revolutionary. In this context it is important to remember that *M. leprae* was only the third etiologic agent proposed for diseases of humans, and the first for a chronic disease. To substantiate his claim, Hansen attempted to cultivate the leprosy bacillus *in vitro* and to transfer the disease to experimental animals.[5–7] He had, as we know so well, no success in these attempts.

The problem of establishing suitable animal models of leprosy was first approached rationally when Dr. Chapman Binford noted in 1956 that, "In man the lepra bacillus has a natural preference for sites of lower body temperature."[8] Following on this hypothesis, Binford produced lesions in the ears and testes of hamsters,[9] Shepard[10] established the widely used mouse foot pad model of leprosy, and Kirchheimer and Storrs[11] transmitted leprosy to the nine-

---

[1] Hansen, G. A. Undersogelser angaende spedalskhedens arsager. Norsk Mag Laegevidensk **4** (1874) 1–88. [English translation: Hansen, G. A. Causes of leprosy. Int. J. Lepr. **23** (1955) 307–309].

[2] Daws, G. Stigma. In: *Holy Man. Father Damien of Molokai.* New York: Harper and Row, 1973, pp. 215–252.

[3] Sand, A. Geschieht die Ansteckung der Lepra durch unmittelbare Übertragung? In: *Proceedings II International Leprosy Conference, Bergen.* Vol. 3. H. P. Lie, ed. Leipzig: Johann Ambrosius Barth, 1909, pp. 39–46.

[4] Kazda, J., Irgens, L. M. and Kolk, A. H. J. Acid-fast bacilli found in sphagnum vegetation of coastal Norway containing *Mycobacterium leprae*-specific phenolic glycolipid-I. Int. J. Lepr. **58** (1990) 353–357.

[5] Johnstone, P. A. S. The search for animal models of leprosy. Int. J. Lepr. **55** (1987) 535–547.

[6] Rees, R. J. W. Animal models in leprosy. Br. Med. Bull. **44** (1988) 650–664.

[7] Rees, R. J. W. Evolution and contribution of animal models in leprosy. Indian J. Lepr. **63** (1991) 446–456.

[8] Binford, C. H. Comprehensive program for the inoculation of human leprosy into laboratory animals. U. S. Publ. Health Repts. **71** (1956) 995–996.

[9] Binford, C. H. Histiocytic granulomatous mycobacterial lesions produced in the golden hamster (*Cricetus auratus*) inoculated with human leprosy. Lab. Invest. **8** (1959) 901–924.

[10] 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.

[11] Kirchheimer, W. F. and Storrs, E. E. Attempts to establish the armadillo (*Dasypus novemcinctus*) 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.

banded armadillo, a cool-blooded animal (32°C–35°C).

Armadillos. Contrary to popular belief, armadillos are not difficult to adapt to or maintain under laboratory conditions. After approximately 9–18 months, sometimes longer, nodules appear at sites of cutaneous inoculation of *M. leprae*. These nodules have typical features of lepromatous disease, with acid-fast bacilli in foamy structures in phagolysosomes. The disease then disseminates to many organs (e.g., the spleen and liver) and often involves major peripheral nerves.[12]

In 1975, Walsh, *et al.* reported the first naturally acquired leprosy in armadillos.[13] They first suspected the disease on seeing enlarged lymph nodes with histopathologic changes of leprosy in recently captured armadillos. Today many sites of naturally acquired leprosy have been found in Louisiana and Texas, U.S.A. Prevalence rates in wild armadillos, as determined by histopathologic findings, range from 2% to 10%, and recent data show that 10% to 16% are serologically positive to PGL-I antigen.[14, 15]

How is naturally acquired disease in armadillos contracted and transmitted to other armadillos? We have speculated that armadillos originally contracted the disease from human sources of *M. leprae*, most likely in the pre-sulfone era when there were many untreated lepromatous leprosy patients living in rural areas of Louisiana and Texas, and that the enzootic disease has been maintained by armadillo-to-armadillo transmission. The nasal mucosa and mammary ducts of armadillos are heavily infected with *M. leprae*, suggesting that this transmission could be by the nasorespiratory passage or in mother's milk. Placental transmission to armadillo fetuses also takes place.[16, 17]

We shall now consider the question of transmission of leprosy from armadillos to humans. Epidemiologic data on leprosy in the United States reveal very high ratios of native to foreign-born leprosy patients in Texas and Louisiana in comparison to all other states. These are the two states known to have the highest prevalences of leprosy in wild armadillos.[18, 19] The first published report of a patient presumed to have contracted leprosy from wild armadillos was of a Texan who had had frequent contact with armadillos.[20] A biopsy specimen from this patient, reviewed at the Armed Forces Institute of Pathology, shows typical features of lepromatous leprosy. There are published reports of 16 patients from Texas and Louisiana for whom armadillo contact was an exceedingly high risk factor, and at least five additional such cases are known.[21, 22] Armadillos may also be a risk factor for pa-

---

[12] Binford, C. H., Storrs, E. E. and Walsh, G. P. Disseminated infection in the nine-banded armadillo (*Dasypus novemcinctus*) resulting from inoculation with *M. leprae*; observations made on 15 animals studied at autopsy. Int. J. Lepr. **44** (1976) 80–83.

[13] 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.

[14] Truman, R. W., Job, C. K. and Hastings, R. C. Antibodies to the phenolic glycolipid-I antigen for epidemiologic investigations of enzootic leprosy in armadillos (*Dasypus novemcinctus*). Lepr. Rev. **61** (1990) 19–24.

[15] Walsh, G. P., Meyers, W. M. and Binford, C. H. Naturally acquired leprosy in the nine-banded armadillo: a decade of experience 1975–1985. J. Leuk. Biol. **40** (1986) 645–656.

[16] Job, C. K., Sanchez, R. M. and Hastings, R. C. Lepromatous placentitis and intrauterine fetal infection in lepromatous nine-banded armadillos (*Dasypus novemcinctus*). Lab. Invest. **56** (1987) 44–48.

[17] Meyers, W. M., Walsh, G. P., Brown, H. L., Binford, C. H., Imes, G. D., Jr., Hadfield, T. L., Schlagel, C. J., Fukunishi, Y., 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.

[18] Smith, J. H., Folse, D. S., Long, E. G., Christie, J. D., Crouse, D. T., Tewes, M. E., Gaston, A. M., Ehrhardt, R. L., File, S. K. and Kelley, M. T. Leprosy in wild armadillos (*Dasypus novemcinctus*) of the Texas Gulf Coast: epidemiology and mycobacteriology. J. Reticuloendothel. Soc. **34** (1983) 75–88.

[19] Vogelsang, T. M. Gerhard Henrik Armauer Hansen, 1841-1912, the discoverer of the leprosy bacillus, his life and work. Int. J. Lepr. **46** (1978) 257–332.

[20] Freiberger, H. F. and Fudenberg, H. H. An appetite for armadillo. Hosp. Practice **16** (1981) 137–144.

[21] Job, C. K., Kahkonen, M. E., Jacobson, R. R. and Hastings, R. C. Single lesion of subpolar lepromatous leprosy and its possible mode of origin. Int. J. Lepr. **57** (1989) 12–19.

[22] Lumpkin, L. R., III, Cox, G. F. and Wolf, J. E., Jr. Leprosy in five armadillo handlers. J. Am. Acad. Dermatol. **9** (1983) 899–903.

tients registered in California, but who contracted leprosy elsewhere.[23]

If we make some conservative assumptions, the extent of the problem of leprosy in wild armadillos in Louisiana becomes apparent, and should be of concern to environmentalists. Assuming that: 1) the average annual population of armadillos in Louisiana is 10^6; 2) every year, 4% have advanced infection and die; 3) each dead armadillo harbors 10^{12} *M. leprae*; and 4) 10% of the *M. leprae* are viable, there would be 4×10^{15} viable *M. leprae* discharged into the environment each year, or 1.1×10^{13} daily. If the half-life of the total number of viable *M. leprae* discharged by dead armadillos into the environment is 21 days, the mean daily number of viable *M. leprae* in the environment of Louisiana could be as many as 10^{14}.

Chimpanzees. In 1976, Donham, *et al.*[24] detected leprosy in a chimpanzee in the state of Iowa, U.S.A. The animal had been imported from Sierra Leone, and had never been inoculated experimentally with *M. leprae*. Hubbard,[25] and Alford and Matherne[26] have reported two chimpanzees with naturally acquired advanced multibacillary leprosy. These animals were, at the time of detection, housed in two separate institutions in Texas. All three animals had typical histopathologic features of leprosy and had high levels of antibody to PGL-I. Some chimpanzees that had been contacts of these animals also had elevated PGL-I antibody levels. The significance of enzootic leprosy in chimpanzees vis-a-vis leprosy in humans is unknown.

Sooty mangabey monkey. In 1979, a sooty mangabey monkey with lepromatous leprosy was detected at the Gulf South Research Institute in Louisiana, and transferred to the Delta Regional Primate Research Center where it was studied extensively. This animal had typical histopathologic features of lepromatous leprosy, and neuropathic deformities of the extremities, including clawing of the digits. Response to therapy was excellent and the etiologic agent satisfied all available criteria for identification as *M. leprae*.[27] A cagemate developed similar disease in 1987, and is believed to have acquired leprosy in captivity by natural transmission.[28]

M. leprae from the index animal induced leprosy in other sooty mangabey monkeys, and in rhesus and African green monkeys.[29] One mangabey had severe erythema nodosum leprosum involving nerves. Experimental data to date show that 80% of 36 mangabeys, 18% of 38 rhesus, and 26% of 19 African green monkeys developed disease following intravenous and intracutaneous inoculation.

Some of the inocula used in transmission studies contained both *M. leprae* and the mangabey strain of the simian immunodeficiency virus (SIV_{sm}), and the results suggest that SIV_{sm} promotes the susceptibility of rhesus monkeys to leprosy.[30, 31] Although

---

[23] Thomas, D. A., Mines, J. S., Thomas, D. C., Mack, T. M. and Rea, T. H. Armadillo exposure among Mexican-born patients with lepromatous leprosy. J. Infect. Dis. **156** (1987) 990–992.

[24] Donham, K. J. and Leininger, J. R. Spontaneous leprosy-like disease in a chimpanzee. J. Infect. Dis. **136** (1977) 132–136.

[25] Hubbard, G. B., Lee, D. R., Eichberg, J. W., Gormus, B. J., Xu, K. and Meyers, W. M. Spontaneous leprosy in a chimpanzee (*Pan troglodytes*). Vet. Pathol. **28** (1991) 546–548.

[26] Alford, P. and Matherne, C. Leprosy in two wild-born outdoor housed adult chimpanzees. Book of Abstracts, Am. Assn. for Lab Sci. (1989).

[27] Meyers, W. M., Binford, C. H., Brown, H. L. and Walsh, G. P. Leprosy in wild armadillos. In: *Comparative Pathology of Zoo Animals* (Proceedings of a symposium on Comparative Pathology of Zoo Animals, National Zoological Park, Washington, D.C., October 1978). Washington, D.C.: Smithsonian Institution Press, 1980, pp. 247–251.

[28] Gormus, B. J., Wolf, R. H., Baskin, G. B., Ohkawa, S., Gerone, P. J., Walsh, G. P., Meyers, W. M., Binford, C. H. and Greer, W. E. A second sooty mangabey monkey with naturally acquired leprosy: first reported possible monkey-to-monkey transmission. Int. J. Lepr. **56** (1988) 61–65.

[29] Wolf, R. H., Gormus, B. J., Martin, L. N., Baskin, G. B., Walsh, G. P., Meyers, W. M. and Binford, C. H. Experimental leprosy in three species of monkeys. Science **227** (1985) 529–531.

[30] Baskin, G. B., Gormus, B. J., Martin, L. N., Murphey-Corb, M., Walsh, G. P. and Meyers, W. M. Pathology of dual *Mycobacterium leprae* and simian immunodeficiency virus infection in rhesus monkeys. Int. J. Lepr **58** (1990) 358–364

[31] Gormus, B. J., Murphey-Corb, M., Martin, L. N., Zhang, J.-Y., Baskin, G. B., Trygg, C. B., Walsh, G. P. and Meyers, W. M. Interactions between simian immunodeficiency virus and *Mycobacterium leprae* in experimentally inoculated rhesus monkeys. J. Infect. Dis. **160** (1989) 405–413.

the original sooty mangabey monkey was negative serologically for SIV, the mangabey monkey frequently carries this lentivirus, but the virus is apparently nonpathogenic in this species. The concept is intriguing, however, that the sooty mangabey is rendered more susceptible to *M. leprae* because of some subtle effects of the virus.

Summary. Our findings establish that there are known extrahuman reservoirs of *M. leprae* in three animal species. There is considerable evidence that the armadillo plays a role in the epidemiology of leprosy in humans in Texas and Louisiana.

The elimination of leprosy as a public health problem (defined by the World Health Organization as one active patient per 10,000 population)[32] may be attainable by the wide application of current control measures; however, the ultimate eradication of leprosy must take into account extrahuman reservoirs of *M. leprae.* The impact that attempts to control or to eliminate leprosy in such reservoirs (e.g., the armadillo in Louisiana and Texas) would have on environmental and wild-life considerations would be profound.

Whether or not similar situations prevail in other leprosy-endemic geographic areas is not known. Based on the armadillo experience, there seems to be ample justification for undertaking, forthwith, carefully designed surveys for enzootic leprosy in some of the major endemic areas of leprosy. At the current state of our knowledge of the subject, such surveys should be initiated in the natural habitats of the mangabey monkey and chimpanzees—in West Africa.

—Wayne M. Meyers, M.D., Ph.D.
Chief, Mycobacteriology
Department of Infectious and Parasitic Diseases Pathology
Room 4071
Armed Forces Institute of Pathology
Washington, D.C. 20306-6000, U.S.A.

—Bobby J. Gormus, Ph.D.
Research Chemist
Tulane Regional Primate Research Center
18703 Three Rivers Road
Covington, Louisiana 70433, U.S.A.

—Gerald P. Walsh, Ph.D.
Leonard Wood Memorial Center for Leprosy Research
Eversley Childs Sanatorium
P.O. Box 727
Cebu City, The Philippines

Acknowledgment. We thank Esther K. Meyers for assistance in preparing the manuscript, and Dr. Susanne Pritze for translating relevant portions of the article cited in footnote 3.

[32] News and Notes. Forty-Fourth World Health Assembly—elimination of leprosy by the year 2000, W.H.O. Lepr. Rev. **62** (1991) 442.