Current Comments

Leprosy: Down But Not Out

Number 37 September 15, 1980

Where is the world's only leprosy museum? Calcutta? Louisiana? No. It's in Bergen, Norway. I visited the Leprosy Museum in Bergen last year, when visiting my friend, Jan Eggum, a well-known Norwegian singer and composer. The museum houses the original laboratories and surgeries where Dr. Armauer Hansen and his colleagues did the first systematic research on leprosy. The "leprosarium" where Hansen discovered the leprosy bacillus is also located in Bergen. Hansen's microscopes, historical records on the disease, and other memorabilia are preserved in rooms designated "The Armauer Hansen Commemorative Rooms."[1]

During a recent visit to the Center for Disease Control (CDC) in Atlanta, Georgia, I mentioned this museum to Dr. Roger A. Feldman, who is now chief of the Enteric Diseases Branch at CDC. During a pleasant dinner at his home, he told me some interesting facts about leprosy. Of course, most people still imagine leprosy to be the ancient scourge described in novels such as James Michener's *Hawaii*.[2] As we shall see, this impression is incorrect.

Leprosy, as described in *Dorland's*, is "a chronic communicable disease, caused by a specific microorganism, the *Mycobacterium leprae*, which produces various granulomatous lesions in the skin, the mucous membranes, and the peripheral nervous system."[3]

In general, clinical leprosy first appears as discolored patches of skin, which may develop into granulomas—inflamed lesions. Since peripheral nerves in the lesions are also attacked by leprosy bacteria, there is generally some loss of feeling at these sites.

Actually, the leprosy bacteria affects individuals differently, depending on their immunological response (resistance) to the *M. leprae* bacterium.[4] Consequently, researchers and clinicians use a classification scheme to describe the various expressions of the disease.[5] Most people who are infected by the bacteria do not develop clinical disease because they develop a resistance to *M. leprae*.[6] Individuals with this "subclinical infection" may never realize they are infected. People with a less effective resistance may develop *tuberculoid* leprosy. This may heal spontaneously, though if untreated it can result in some mutilation. *Lepromatous* leprosy is the disfiguring form with which most people are familiar. It is characterized by numerous lesions which may cover the whole body. An individual with this form of the disease has the least effective immunological response to the *M. leprae* bacterium. Untreated, lepromatous leprosy may heal after a number of years, but it is generally progressive. It is believed to be the most communicable form of the disease.

Sometimes the leprosy bacteria are responsible for disfigurement. For example, the depression of the nose is caused by the destruction of the cartilage which supports the bridge of the nose. Contraction of scar tissue pulls the

nose into the face, although the nose is still intact. This type of deformation, however, is rare. More often the bacteria attack nerve fibres. When these fibres, which supply sensation to the hands and feet, are destroyed, anesthesia of the extremities results. Once the hand or foot loses feeling, it can be cut, burned, or bruised without any sensation of pain. Continued bruising can result in absorption of bone, which is responsible for the foreshortening of leprosy patients' fingers and toes. Thus, the victim may cause his own injuries, since one inevitably bumps a limb accidentally and the bruises aren't even noticed. In addition, paralysis of the facial muscles and lack of sensation in the eyes may lead to blindness.

According to Dr. Feldman, serious deformations such as these can be prevented if the disease is treated early. Unfortunately, Dr. Feldman reports that the disease often goes untreated for a long time because individuals are ashamed of having leprosy and don't seek medical help.[7]

Today, leprosy affects between 10 and 20 million people mainly in tropical and subtropical areas. No one knows exactly why the disease is endemic to these areas, although it is widely believed poor socioeconomic conditions in these countries play a role.

Leprosy has also been a major problem throughout Europe and the British Isles, especially during the Middle Ages.[8] The disease is believed to have reached Western Europe with the Roman armies several hundred years before Christ. It peaked in parts of Europe in the 12th century, but had largely disappeared by the 17th.[8,9] Historians are still baffled by this mysterious decline. Theories suggesting that the plagues which swept through the continent or that improvements in diet and housing may have been responsible for the decline have not been supported.[9]

Although leprosy had largely disappeared from Western Europe by the 17th century, small pockets of the disease remained, most notably in Norway. It was here that the Norwegian physician Gerhard Henrik Armauer Hansen described the causative bacterium *M. leprae* 107 years ago.[10] For this reason, leprosy is often called "Hansen's disease" or "Hanseniasis." Use of these names has received a lot of support from individuals and organizations who believe that they will evoke less repugnance than the word leprosy. Incredibly, *Webster's Third International Dictionary* doesn't even mention this eponym in the entry for leprosy. There is, however, a cross-reference to leprosy from Hansen's disease.[11] The *Encyclopedia Americana* entry for leprosy says the disease is "...sometimes popularly known as Hansen's disease—though the term is not used by physicians."[12]

Historically, the term leprosy has been applied to the disease caused by the *Mycobacterium leprae*. However, it has also been used to describe a wide range of unrelated, and usually horrific, diseases including the bubonic plague. People with leprosy were given a special name, "lepers," and, in many societies, were considered the living dead.

Even the Bible has a prescribed set of laws for dealing with leprosy victims: "As for the person with a leprous affection, his clothes shall be rent, his head shall be left bare, and he shall cover over his upper lip; and he shall call out, 'Unclean! Unclean!' He shall be unclean as long as the disease is on him. Being unclean, he shall dwell apart; his dwelling shall be outside the camp."[13] Throughout history, biblical quotations such as this have been used to justify inhumane treatment of leprosy patients.

This treatment has been motivated by both the physical appearance of the disease and its seemingly mysterious origins. Since leprosy can have an incubation period of many years, victims and their families could not always make the association between prior exposure to a person with the disease and

its onset. So, instead, they attributed it to forces such as God's will, heredity, and sin.

There is no cure for leprosy. However, patients are administered drugs which control the disease. These drugs prevent deformations if the disease is caught in time, and are believed to eliminate the contagiousness of the disease. Since the 1940's sulfone drugs, specifically diamino-diphenyl-sulphone (also known as dapsone and DDS), have been used to treat leprosy patients. A number of other drugs, including rifampicin and clofazimine, are also administered, but these are more expensive than dapsone, and, therefore, difficult to obtain in the poorer nations where leprosy is endemic.[14] A patient with lepromatous leprosy may take drugs throughout his or her life.[15] People with tuberculoid leprosy must take them for at least two years.[5]

In recent years, the leprosy bacteria from some patients have developed a resistance to dapsone. In most cases this happens to lepromatous and borderline lepromatous patients who, over their life span of treatment, have not regularly taken their drugs.[5] But recently, it has been shown that new cases of leprosy were caused by dapsone-resistant bacteria. Much research is currently underway to find drugs, or drug combinations, which will successfully deal with these drug-resistant strains of the leprosy bacteria.[16,17]

A major problem faced by scientists conducting research on anti-leprosy drugs and vaccines has been their inability to cultivate the *M. leprae* bacillus *in vitro*.[18,19] This has limited their ability to test drugs and vaccines for safety, and to study various metabolic and immunological aspects of the disease. A number of investigators have reported the successful growth of *M. leprae in vitro*. So far, however, no one has been able to reproduce their results. Recently, Arvind M. Dhople, Florida Institute of Technology, reported the successful growth of rat leprosy *in vitro*.[19] Dhople stressed that this naturally occurring leprosy in rats, which can survive *in vitro* up to 24 weeks, is not identical to the disease in humans. He pointed out, however, that it does provide a good research model.[20]

At present, the two major animals used as models in leprosy research are the mouse and the armadillo. Since *M. leprae* will successfully multiply in the mouse footpad, drugs are being tested for their efficiency in suppressing this multiplication of bacteria in the mouse footpad.[21] Experimentally infected armadillos have, in the last ten years, been the major source of leprosy bacteria.[22] The bacteria, much of which have been produced at the US Public Health Service (USPHS) Hospital in Carville, LA, are used in many of the microbiological, immunological, and epidemiological research programs sponsored by the World Health Organization's Immunology of Leprosy Program (IMMLEP), and by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health.

A number of research projects have been conducted involving armadillos who were believed to have contracted a leprosy-like disease in their natural habitats in Louisiana and Texas. This research has been done at the Gulf South Research Institute, Louisiana, the Center for Disease Control in Atlanta, the University of Texas Medical School in Galveston, and the US Public Health Service Hospital in Carville, LA.

With the increasing frequency of dapsone-resistant strains of *M. leprae*, the creation of a leprosy vaccine has taken on added importance. This has been a major objective of the World Health Organization's Tropical Disease Research Program's IMMLEP group. Dr. Charles C. Shepard, chief of the Leprosy and Rickettsia Branch at CDC, and colleagues reported the development of a vaccine using heat-killed *M. leprae*, which maintains the ability

to induce an immune reaction in the vaccinated mouse.[23] Similarly, Dr. J. Convit and colleagues (Instituto Nacional de Dermatologia, Caracas, Venezuela) recently reported their success using leprosy bacteria killed by heat in combination with Bacilli Calmette-Guerin (BCG), the vaccine used for tuberculosis.[24,25] According to Dr. Feldman, BCG has been used to increase resistance to the leprosy bacteria with variable results in Uganda, Thailand, Burma, and now in India. He said that BCG appeared most effective in reducing the frequency of tuberculoid leprosy.[7]

One of the major problems in devising a vaccine is being solved with the development of methods for obtaining a highly purified form of *M. leprae*.[26] A number of researchers have been working on methods of purifying the bacteria from armadillo tissue so that it can be safely injected into the human body.[17,27] Dr. Shepard of CDC pointed out that, because the purified bacteria must be tested before its use in leprosy-endemic areas, it may be 15 to 20 years before a vaccine is widely available.[27] In addition, the efficacy of an anti-leprosy vaccine cannot be evaluated for many years on account of the long incubation period of leprosy.

The National Institute of Allergy and Infectious Diseases of the National Institutes of Health in the US funds research on propagating the bacteria *in vitro*, growing the bacteria in armadillos, separating bacteria from infected armadillo tissue, and isolating protein and lipid antigens from purified bacteria. The Institute also funds studies on epidemiology, immunology, and serology of leprosy. According to Earl Beck, assistant to the director of the Microbiology and Infectious Diseases Program at the Institute, approximately $1.5 million is being spent annually in these areas of leprosy research.[28] The American Leprosy Missions (ALM), headquartered in Bloomfield, NJ, provides some funding for work done at the University of Hawaii School of Medicine, under the direction of Dr. Olaf K. Skinsnes.

A great deal of basic and clinical research is being conducted to determine why certain individuals respond to the bacteria by contracting lepromatous leprosy whereas most others only develop a subclinical form. Basic scientists and physicians are investigating the immunological systems of leprosy patients, factors that may control the immunological reaction to the bacillus, and a number of different theories on the transmission of leprosy. These studies bear directly on the development of a leprosy vaccine, on the development and testing of anti-leprosy drugs, and on the creation of tests to detect clinically inapparent infection and susceptibility to the disease.

It is generally agreed that an individual's susceptibility and response to the disease is determined by his or her immunological reaction to the bacteria. Individuals who contract the lepromatous form have been shown to have an ineffective immune response to the infection. Their bodies' natural defenses are unable to control the bacteria. Various mechanisms which might cause or affect this defect of the immunological system are being investigated.[29-32]

One of the most debatable issues among leprologists today concerns the host response to *M. leprae*.[33-37] Several investigators believe that genetic factors may be responsible for a lepromatous individual's faulty resistance. Others believe the bacteria itself may affect the immunological system in such a way that the body's normal mechanism for mounting a defense against *M. leprae* is suppressed.

P.E.M. Fine, Ross Institute of the London School of Hygiene and Tropical Medicine, is one of many scientists investigating the genetic factors underlying the immunological reaction of the leprosy patient. In a recent paper sug-

gesting the gene responsible for susceptibility to tuberculoid leprosy is recessive, Fine and his colleagues emphasize the practical implications of genetic research on leprosy. The authors state: "The ability to identify carriers of susceptibility genotypes would permit early recognition of individuals at high risk of developing disease. Second, it might provide a clue to the biochemical mechanism that underlies the different host responses to infection with *M. leprae*. Finally, it could have implications for the strategy and effectiveness of attempts to devise a vaccine against leprosy."[38]

The "inheritability" of leprosy was being investigated as early as the mid-1800s, even before Hansen discovered the infective agent, *M. leprae*. Daniel C. Danielssen, with whom Hansen later collaborated, and Carl W. Boeck, published a number of books in which they stated that leprosy was a hereditary disease.[10,39] They believed the disease itself, rather than susceptibility to the disease, was genetically transmitted. Hansen later disproved this theory in favor of one recognizing the infectious nature of the disease.

Incidentally, Hansen was involved in a highly controversial episode of scientific plagiarism.[40] The "Hansen-Neisser controversy" involved a pupil named Albert Neisser who came to Bergen in 1879 to study leprosy with Hansen and his associates. After returning to Germany and staining the bacteria samples given him by Hansen, Neisser claimed he had "discovered" the leprosy bacterium. Following Neisser's claims, Hansen published his own findings in English, German, and Norwegian periodicals "partly to maintain his priority and partly to provide additional details."[10]

The familial nature of leprosy is now being researched by basic scientists and clinicians as well as social scientists. A number of studies have been made of the geographic and language similarities among leprosy patients. However, as S. Serjeantson and colleagues of the Australian National University point out, "Whether heritable factors are implicated in leprosy remains controversial.... Attempts to identify genetic factors in leprosy by pedigree analysis, genetic marker associations and epidemiological studies have been largely unsuccessful...."[41]

Similarly, attempts to identify the different ways leprosy can be transmitted have been less than successful. It has, however, recently been shown that *M. leprae* is contagious, although it causes overt disease in only a small proportion of infected people.[42] According to a working group on epidemiology at the 1978 International Leprosy Congress, "The available information indicates that leprosy is a disease of high infectivity and low pathogenicity [rarely causes clinically apparent disease]. With regard to transmission of the disease, there is more and more evidence of the importance of airborne spread, although other modes of transmission cannot be ruled out. The available evidence on arthropod transmission is inadequate to permit definite conclusions. However, there is less and less justification for insisting on the necessity for direct, prolonged, intimate contact for transmission of the disease."[43]

With the amount of research now being done on leprosy, it's hardly surprising that there are journals devoted almost exclusively to the subject. This is in addition to journals in such subject areas as infectious diseases, immunology, and microbiology, which also carry leprosy papers. Most of the literature on leprosy research is published in the *International Journal of Leprosy and Other Mycobacterial Diseases*, *Leprosy Review*, *Infection and Immunity*, and *Bulletin of the World Health Organization*. The first-mentioned is the leading journal in the field, usually called *International Journal of Leprosy*. This journal, *Infection and Immunity*, and the *Bulletin* are covered by *Current Con-*

tents®/Life Sciences. The *Bulletin of the WHO* is also covered by *Current Contents/Clinical Practice*, as is *Leprosy Review*. All four journals are indexed in the *Science Citation Index® (SCI®)*, and all except *Infection and Immunity* are selectively covered by the *Social Sciences Citation Index®*.

It is unusual for a journal on as specific a subject as leprosy to have as high an impact as does the *International Journal of Leprosy and Other Mycobacterial Diseases*. The impact is a measure of how often the average article it publishes is cited. According to the 1978 *SCI Journal Citation Reports®*,[44] it ranked in the top third of the journals covered by the *Science Citation Index* that year. Even more impressive is the journal's ranking in terms of how quickly authors cite the articles it publishes. When the journals covered by ISI® in 1978 were ranked by immediacy—by the number of times their 1978 articles were cited in 1978—the *International Journal of Leprosy* appeared in the top 20 percent.

Unlike these purely scientific journals, the magazine, *The Star*, carries general news items on leprosy and articles describing, rather than reporting, clinical and research findings. Published by leprosy patients at the US Public Health Service Hospital in Carville, LA, since 1941, this bi-monthly publication boasts a circulation of 70,000. The circulation of the *International Journal of Leprosy*, in contrast, is 1,400.

The major Indian leprosy journal, *Leprosy in India*, is published by the Indian Leprosy Association. It is a quarterly and deals with scientific and general aspects of the disease.[6]

A number of organizations exist purely for the funding and conduct of leprosy research and for providing aid to the victims of this disease. Frederick A. Leonard, deputy scientific director of the Leonard Wood Memorial for the Eradication of Leprosy (also called the American Leprosy Foundation), has identified 66 such organizations in the US alone.[45] One umbrella organization which coordinates leprosy research and treatment programs is the International Federation of Anti-Leprosy Associations (ILEP), 4 Rue Saint-Geoffrey, 80000 Amiens, France.

Another is the International Leprosy Association, 1262 Broad Street, Bloomfield, NJ 07003. The association publishes the *International Journal of Leprosy* and coordinates the International Leprosy Congress, which is held in a different country every five years. The 11th International Leprosy Congress, held in Mexico City in 1978, was attended by delegates from 83 countries. The transactions of the most recent congress, published in the June, 1979 issue of the journal, provide a good state-of-the-art review of leprosy research.[43]

The majority of leprosy organizations are "pass through" organizations which collect and disseminate money for leprosy research and treatment. Several also maintain treatment centers, particularly in India. Many of these, such as the Damien Dutton Society, the International Christian Leprosy Mission, the American Leprosy Missions, and Nobel Peace Prize Winner Mother Teresa's Missionaries of Charity, have a religious affiliation. Private organizations, such as the John A. Hartford Foundation, the Schleider Foundation, and the Public Welfare Foundation, also contribute to leprosy work.

The major sites of leprosy research in the US are the USPHS Hospitals in Carville, LA, San Francisco, CA, and Seattle, WA; the Armed Forces Institute of Pathology in Bethesda, MD; the Leonard Wood Memorial for the Eradication of Leprosy laboratories at the George Washington School of Medicine in Washington, DC, and in the Philippines; the University of Hawaii; the Center for Disease Control in Atlanta, GA; and SRI International in Menlo Park, CA.

Research efforts at the George Washington University Leprosy Laboratory are currently directed toward develop-

ing a simple blood test to identify "...subclinical cases of leprosy or at least identify those persons whose exposure to the leprosy organism may someday result in clinical leprosy..." and developing a procedure for screening new anti-leprosy drugs.[45] H.D.Caldwell, University of California—San Francisco, T. Buchanan, University of Washington and the USPHS Hospital in Seattle, and Dr. W.F. Kirchheimer, USPHS Hospital in Carville, are working on a similar project to identify subclinical leprosy through a blood test.[46,47]

Research at SRI International is directed toward developing animal models and drug regimens for the treatment of leprosy patients. Dr. A.H. Fieldsteel and colleagues, using immunosuppressed rats, are trying to develop drug regimens for killing persistent strains of *M. leprae*.[48]

By the way, the USPHS Hospital in Carville offers courses on all aspects of leprosy several times a year. Physicians and paramedicals may attend them free of cost. In addition, Carville has a library of audio-visual cassettes dealing with leprosy which are available to appropriate groups. For information concerning the courses and the audio-visual material, contact Dr. Richard O'Connor, Chief, Training Branch, USPHS Hospital, Carville, LA 70721.

Other major leprosy funding organizations include the German Leprosy Relief Association in the Federal Republic of Germany, and the Sasakawa Memorial Health Foundation in Japan. Naturally, a great deal of research—particularly of a clinical nature—is being done in tropical countries where leprosy is endemic. This is especially true of India which contains several hundred treatment and quite a number of research centers. These include the Acworth Leprosy Hospital in Bombay, Goa Medical College in Goa, and the All-India Institute of Medical Research in New Delhi. Two of the major leprosy treatment and research centers in Ethiopia, a country which experiences serious leprosy problems, are the Addis Ababa Leprosy Hospital and the Armauer Hansen Research Institute. A great deal of research is also conducted at the National Institute for Medical Research in London, the University of Quebec's Institut Armand-Frappier, the Australian National University in Canberra, and the University Medical Center in Leiden, the Netherlands.

While leprosy is still a major problem in tropical and subtropical areas of the world, research is progressing at a steady pace. Advances have been made recently toward understanding the mechanisms that contribute to leprosy's development and spread, and developing a vaccine and test for subclinical infection. But, as our literature review has shown, progress in leprosy research will depend not only on continued support for basic and applied research on the obvious manifestations of leprosy and related phenomena, but also on fundamental breakthroughs in molecular genetics and other areas of the life sciences.

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My thanks to Joan Lipinsky Cochran and Patricia Heller for their help in the preparation of this essay.

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