The History, Biology & Medical Aspects of Leprosy

Phillip Eichman

THROUGHOUT history, fear and superstition have often been associated with diseases, especially those that are not well understood. For example, Ryan White, the young hemophiliac who contracted HIV from contaminated blood products and later died of the complications of AIDS, became a nationally known figure when he was prevented from attending school. Parents had blocked his admission out of fear for their own children's safety (Ser-Vaas 1988).

AIDS is not, however, the only disease with societal implications. Social stigma has often been connected with certain diseases. One of the best examples of this is leprosy, or Hansen's disease, as it is known today. In some cultures lepers are still excluded from society. Such ideas are certainly not new, but rather can be traced back to ancient times. Herodotus, the Roman historian, for example, wrote that it was a custom in Persia, and throughout the Mediterranean region, to isolate leprous persons and exclude them from contact with others (Mettler & Mettler 1947).

Dr. Paul Brand, a leprosy specialist, has described the prejudice, discrimination and ill treatment that leprosy patients have received in recent times in the United Sates. Brand, who treated leprosy patients for many years at the U.S. Public Health Service Hospital in Carville, Louisiana, noted that as recently as the late 1950s, patients were required to be transported to the hospital in chains, and that for many years leprosy was grounds for divorce and incarceration (Brand & Yancey 1993).

The facility at Carville, today known as the Gillis W. Long Hansen's Disease Center, began in 1894 as the Louisiana Lepers Home. Because of fear and prejudice the land for the hospital was leased under the pretext that it would be used as an ostrich farm. In a recent history of the hospital (Parascandola 1994) it was noted that patients were confined to the hospital grounds and that a patient could not leave the hospital voluntarily until about 1960.

Attitudes toward those suffering from leprosy have greatly improved with successful medical treatment and prevention. Unfortunately, in some parts of the world leprosy remains, even today, shrouded in fear and superstitution.

Phillip Eichman, Ph.D., is Professor of Biology at the University of Rio Grande, Rio Grande, OH 45674.

History of the Disease

One of the most well known of all ancient writings on leprosy is found in the Old Testament. In Chapters 13 and 14 of the book of Leviticus is found a detailed description of leprosy and how it was to be treated. The symptoms and signs described there, however, do not appear to be consistent with leprosy as it is defined today. Some writers have suggested that the term was probably used originally to describe all skin diseases known at that time and to differentiate diseases that made the person ceremonially unclean from those which did not (Sussman 1967; Møller-Christensen 1967; Browne 1985).

Some of the confusion regarding the biblical term is related to difficulties with the language. The exact meaning of the ancient Hebrew word in question *(tzaraat)* is difficult to determine with certainty. Freilich (1982) has pointed out that there are at least four different diseases, or groups of diseases, described in the Old Testamant under the general term *tzaraat.*

The fact that no skeletal remains with indications of leprosy have been found in the regions corresponding with the biblical text (Møller-Christensen 1967) would suggest that the modern disease of leprosy was probably not intended. Rather, the word was used to describe a wide range of skin diseases.

When the Hebrew text was later translated into Greek (the Septuagint), the word *tzaraat* was translated as *lepra.* The Greek text was later translated into Latin, and finally into English. In the process, *lepra* was translated into "leprosy" (Meyer 1991), a word that is much more specific than the original Hebrew term. Interestingly, some of the modern English versions of the Bible have a footnote explaining that the original term referred to several diseases.

Another historian has pointed out that the purpose of these Old Testamant regulations was more preventative in nature (Major 1954). Indeed, the principles of sanitation, hygiene and quarantine of infectious diseases described in the Old Testament are very similar to those used today. Such rules regarding the quarantine of "leprous persons" were probably intended to prevent the spread of infectious skin

diseases. Unfortunately, these principles were later used, especially in the Middle Ages, as a basis of exclusion and social stigmatization of persons with leprosy.

References to leprosy, or at least to skin diseases, are found in other ancient writings as well. The Egyptian document, known as the Papyrus of Ebers, describes both tubercular and mutilating forms of leprosy (Major 1954). Some medical historians, however, question whether or not this was actually leprosy. Studies of skeletal remains from Egypt have resulted in very few examples (actually only two) of bone deformation commonly found with leprosy (Møller-Christensen 1967). Thus, the relative absence of skeletal evidence would suggest that leprosy may not have been found in this region at the time that the Papyrus of Ebers was written.

The earliest written records describing true leprosy are from India (ca. 600 B.C.). It is likely that leprosy actually began in India, spread from there to China in about 500 B.C., and from there was carried into Japan (Browne 1985).

Leprosy was first described in Chinese medical books as early as 6th century B.C. (Major 1954; Lu & Needham 1967). One of the more well known cases was that of Confucius' pupil, Pe Nieu, who contracted leprosy and eventually died of the disease. These Chinese records also mention the course of treatment for leprosy. This included diaphoretics (agents that increase perspiration), purgatives, and the use of arsenic (Major 1954).

The Greeks left a number of references to leprosy. The word leprosy *(lepra)* itself was derived from the Greek and is found in the writings of Hippocrates (460-377 B.C.) (Mettler & Mettler 1947). However, even though he used the word *lepra*, his description is more likely that of other forms of skin disease (Browne 1985).

It has been speculated that leprosy found its way into Greek medicine because it was carried to Greece by the soldiers of Alexander the Great as they returned from the Indian Campaign in ca. 327-326 B.C. (Browne 1985). Regardless of how it was brought to Greece, modern leprosy was definitely described by Greek physicians. One such physician, Aretaeus, wrote an accurate description of the disease of leprosy (although he called it *elphantos*). He clearly described the formation of skin nodules, the spontaneous loss of fingers and toes, atrophy, and loss of sensory functions known today to be the result of leprosy (Mettler & Mettler 1947).

In ancient times medical terminology was not as precise as it is today. Celsus (1st century A.D.), the Roman physician, used the term "elephantiasis" to describe scurvy, which is actually a vitamin deficiency. Another Roman, Lucretus, however, used the word *elephas* in a way that would suggest leprosy. Although there may be some superficial similarities, the modern term "elephantiasis" refers to a completely different disease. In this stage of the development of medicine, however, several distinct diseases could be easily confused for the same malady.

By Greek and Roman times, it appears that leprosy was a fairly common disease. Pliny (A.D. 23-79), the Roman historian, mentions the disease in his *Natural History.* He described perhaps the first known case of a disease being transmitted to a village and reaching epidemic proportions (Brothwell 1967). Pliny's description of the disease, including the loss of sensory function and disfigurement, would certainly suggest leprosy.

Even though leprosy had been described and was known to physicians, the means of transmission remained a mystery. Unfortunately, leprosy was often associated with sexually transmitted diseases. Avicenna (A.D. 980-1037), an Arab physician, was one who made this erroneous connection (Mettler & Mettler 1947). This association of leprosy with sexually transmitted diseases only further strengthened the negative social implications of this disease. It was not until centuries later when the connection between "germs" and disease was understood that this association was severed.

The highest incidence of leprosy appears to have occurred in Europe during the Middle Ages. Møller-Christensen (1967) reported that of the more than 18,000 skeletons studied, the majority of those with evidence of leprosy were found in the medieval cemeteries associated with leprosy hospitals in Denmark and Sweden. The medical writings, art, and literature of this time all confirm the presence of this dreaded disease.

Although leprosy reached epidemic proportions during this time, the spread of the disease was eventually brought under control. The basic method, avoidance of contact with infected persons, had been described centuries earlier in the Old Testament. History reveals, however, that the actual carrying out of these methods reached brutal efficiency. For example, in 1313 in France, Philip the Fair ordered that all lepers be burned. Although it was never completely enforced, this does indicate the type of measures that were used. Fortunately, to avoid such harsh treatment, the monasteries of St. Lazarus were set aside for the care of the lepers. These institutions, known as "lazarettos," became a haven for those suffering from leprosy. In western Europe alone, it is estimated that at one time there were 19,000 lazarettos (Haggard 1929).

During this time lepers were referred to as the "living dead," and indeed in the eyes of their family they were dead. Often, a symbolic funeral service was performed when it was discovered that a person had contracted leprosy. These unfortunate individuals

were removed from society and their families and were forced to live in the lazarettos. They were required to wear a mask and hideous clothing to hide their disfiguration, and to carry a bell to warn all of their coming (Haggard 1929). This separation of lepers from society, although harsh, did contribute to the decrease in the spread of the disease. By the end of the 16th century, leprosy was nearly wiped out in Europe (Haggard 1929).

One of the most complete medical descriptions of leprosy was written during the Middle Ages by Gilbertus Anglicus (c. 1180-1250), who wrote a medical textbook titled, *Compendium Medicinae.* In it, Gilbertus listed several means of contracting leprosy, including heredity, a poor diet, the breath of a leper, and living with a woman who had been promiscuous with lepers. Although Gilbertus' understanding of the transmission of the disease is questionable, his description of the signs and symptoms of leprosy was accurate. These included loss of pain sensation, atrophy of the skin, and deformation of the hands and feet (Talbott 1970).

The actual causative agent for leprosy was discovered several centuries after the time of Gilbertus by Gerhard Henrik Armauer Hansen (1841–1912) (Talbott 1970). Hansen was born in Bergen, Norway and devoted much of his life to the study of leprosy. He trained as a physician and began his medical career at a leprosy hospital. The director of the hospital had co-authored a monograph on leprosy, shortly before Hansen arrived, in which he strongly advocated that leprosy was hereditary rather than infectious in nature. Not long after joining the hospital, however, Hansen was able to describe the actual cause of the disease.

In 1869 Hansen first identified "large brown elements" in skin nodules removed from leprosy patients. Later, in 1873 he identified these elements as some type of bacteria. In 1874 Hansen presented a paper before the medical society in which he described the bacteria and also the epidemiological studies that he had conducted on leprosy (Talbott 1970; Vogelsang 1978).

Hampered by his inability to stain the bacteria, Hansen was unable to actually identify the organisms. In 1879 Neisser developed a staining method for bacteria similar to those that cause leprosy. Using Neisser's method, Hansen was able the following year to assign the name *Bacillus leprae* to these organisms (Talbott 1970). Today, we know the bacteria as *Mycobacterium leprae.* In honor of his discovery, leprosy is today commonly referred to as Hansen's disease.

Although the discovery of the causative agent was attributed to Hansen, he was never able to successfully culture the organism or transmit the disease to experimental animals. Even today, more than a

century later, our understanding of the organism and the disease remain limited.

Biology of Leprosy

Members of the genus *Mycobacterium* are slightly curved or straight rod-shaped bacteria which range in size from 0.2 to 0.6 by 1.0 to 10 μm (Nolte & Metchock 1995). They are nonmotile, nonencapsulating, and nonspore-forming (Rees 1985). The cell walls of the mycobacteria have a high lipid content which prevents normal uptake of the dyes in the Gram stain method. The cells can be stained, however, with the acid-fast method, and are referred to as acid-fast bacilli.

The genus *Mycobacterium* included saprophytes that are free living in soil and water, opportunistic pathogens, and two species, *M. tuberculosis* and *M. leprae*, which are obligate parasites and found only in the tissues of humans and other warmblooded animals (Nolte & Metchock 1995).

Members of this genus are typically slow growing bacteria with generation times ranging from 2 to > 20 hours (Nolte & Metchock 1995). The exact generation time for *M. leprae* is not known since the cells have never grown *in vitro*.

Although it has been attempted for more than a century, *M. leprae* has never been cultured with any artificial medium or in cell cultures. Leprosy has been successfully transmitted experimentally to mice via injection into their foot pads and to armadillos (Baron et al. 1994). Wolf and others (1985) reported that leprosy has been transmitted to certain species of monkeys by inoculating them with *M. leprae* derived from humans.

A naturally occurring leprosy-like disease was discovered in armadillos (Walsh et al. 1975). This discovery led researchers to further study the relationship between *M. leprae* and armadillos. A procedure was developed for extracting *M. leprae* from the diseased tissues of the armadillo (Storrs et al. 1974). This technique has been used successfully to increase the amount of *M. leprae* available for further study.

As a pathogen, *M. leprae* has a low degree of virulence, a long generation time, and a low optimum temperature. For these and other reasons the disease is not highly contagious. The bacteria do not easily invade tissues or secrete any serious toxins, but are able to produce a chronic infection in certain individuals. The pathology that is caused by an *M. leprae* infection results more from the response of the immune system than to the disease organism itself (Ridley & Job 1985).

The most obvious pathological effect of leprosy is the development of lesions or granulomas that result from a chronic infection with *M. leprae*. The area

becomes inflamed, and phagocytes, especially macrophages, infiltrate the tissues. The phagocytes, however, are not able to eradicate the invaders.

The cells of *M. leprae* are able to survive as an intracellular parasite within the phagocytic cells. The bacteria accomplish this by producing large amounts of phenolic glycolipids, called cell wall-associated glycolipids (Brock & Madigan 1991). This substance has been shown effective in neutralizing hydroxyl radicals and superoxide ions, toxic chemicals normally used by phagocytes to destroy engulfed bacteria (Brock & Madigan 1991). Thus, *M. leprae* cells survive intracellularly, producing a chronic infection.

Leprosy is best known, perhaps, for producing lesions on the skin. In addition to the skin, *M. leprae* has also been shown to cause lesions in peripheral nerves, eyes, nose, larynx, mouth, hard and soft palate; organs of the reticuloendothelial system, e.g. lymph nodes, liver, spleen, and bone marrow; and internal organs such as testes, adrenal glands, and kidneys (Ridley & Job 1985).

Leprosy is, however, primarily a disease of the peripheral nerves. The bacteria become established in the nerve bundle causing inflammation and infiltration of phagocytes. The nerve becomes swollen and enlarged, and may be visible externally on the surface of the skin. The swelling causes damage to the nerve cells resulting in loss of sensory and motor function, paralysis, and anesthesia of the affected area (Ridley & Job 1985).

Because of the low optimum temperature of *M. leprae*, leprosy tends to affect the cooler regions of the body, especially the skin, face, hands and feet. The loss of sensitivity in these areas may lead to further trauma or infection. Even serious wounds or injuries may go unnoticed. Untreated, these may develop into ulcerations, abscesses, and deeper infections that can lead to the loss of fingers and toes. Brand and Frischii (1985) have emphasized that the continued use of injured limbs leads to much of the crippling effects of leprosy. They, along with others, have developed techniques for immobilizing the limb to allow the ulcers to heal. Surgical procedures, special splints, shoes, and numerous other devices have been developed to facilitate treatment of damaged areas and to rehabilitate patients with leprosy.

Medical Aspects of Leprosy

It has been estimated that the number of leprosy patients in the world ranges from 10 to 12 million (Noordeen 1985; Nolte & Metchock 1995). Approximately 25% of these individuals have some physical disability as a result of the disease (Bullock 1990). Of the estimated cases, 62% are found in Asia, 34% in Africa, 3% in South America, and 1% in the rest of the world (Noordeen 1985). Even in the world of modern medicine the physical suffering, economic loss, and social consequences are difficult to comprehend. Most of the burden of this disease has fallen upon developing countries with few resources and limited medical care.

Although feared throughout much of history, leprosy is not a highly contagious disease, but rather transmission of the infection requires prolonged and close contact (Cruickshank et al. 1973). The precise mechanism of transmission is not completely understood. The reservoir for *M. leprae* appears to be humans. As pointed out previously, a naturally occurring leprosy-like disease has been found in armadillos, but this is not thought to be the source of the disease in humans (Noordeen 1985).

The bacteria appear to be spread from the skin and nasal mucosa of persons suffering from leprosy (Noordeen 1985). The exact portal of entry is not known. Although there is no conclusive evidence, the respiratory tract appears to be the most likely means of contracting the disease. Skin, especially broken skin, is also a possible source of infection (Noordeen 1985).

Studies have shown that leprosy has a very long incubation period. The longest reported cases were 30 years or more, but the average is about eight years (Noordean 1985).

The cardinal signs of leprosy are: (1) anesthetic skin lesions; (2) enlarged peripheral nerves; and (3) isolation of *M. leprae* bacilli from skin smears or nasal mucus (Pfaltzgraff & Bryceson 1985). The extent to which the patient is affected by the disease depends on the response of the immune system to the infection.

There are two forms of leprosy. Lepromatous (or nodular) leprosy is characterized by lesions or granulomas in the skin, mucous membranes, and various organs (e.g. lungs, liver and spleen) (Cruickshank et al. 1973). In this form of the disease, the immune response is impaired. Bacteria proliferate within the macrophages, giving them a foamy appearance. The bacteria eventually invade cutaneous nerves causing gradual loss of sensation. Further damage may then result from trauma and secondary infections in the affected areas (Baron et al. 1994).

In the second form, or tuberculoid leprosy, the bacteria multiply at the site of entry and invade peripheral nerves, where they proliferate in the Schwann cells of the nerve tissue. In this case the immune system responds vigorously. While few bacteria are found in the skin lesions, the nerve tissue becomes inflamed and swollen, resulting in damage to the nerve cells and loss of sensory and motor function (Baron et al. 1994).

Through the centuries various remedies have been used to treat leprosy. An oil pressed from the ripe seeds of the plant, *Hydnocarpus wightiana*, called chaulmoorga oil, or its derivatives was used for centuries

in India and China (Browne 1985). This treatment was introduced into Western medicine in the 19th century and was used into the 1930s (Parascandola 1994).

Dr. Guy Faget, a tuberculosis specialist, began working at the Carville hospital in 1940. Faget was aware of a sulfone drug called promin that had been shown experimentally to be effective in treating tuberculosis (another mycobacterial disease) in guinea pigs. Learning of promising experiments with promin in the treatment of rat leprosy, Faget began clinical trials with promin using volunteer patients at Carville in 1941. By 1946 he was able to publish positive results from the use of promin in treating leprosy in humans (Parascandola 1994). As a result of this work by Faget and others in the field, a new era began in the treatment of leprosy.

In the 1960s another sulfone drug, dapsone, was developed and quickly became the standard treatment for leprosy. In time, certain strains of *M. leprae* became resistant to dapsone. Consequently, two other antimicrobial agents, clofazimine and rifampin, are typically used in combination with dapsone in the treatment of leprosy. The treatment requires from six months to two years (Jacobson 1985; Baron et al. 1994), but the success rate is high for this combination drug therapy. The use of antibiotics, along with surgical techniques and rehabilitation programs, has allowed many persons suffering from this terrible disease to live more normal and productive lives.

Closing Remarks

Leprosy was the first disease to be associated with a "germ." Hansen's work preceded Koch's identification of the tuberculosis bacilli and the development of his "postulates" by several years. Ironically, however, leprosy remains one of the few infectious diseases not conquered by modern medicine. More than a century after Hansen's important discovery, there still is much to learn about *Mycobacterium leprae* and the disease which it causes.

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