Chapter 1

Introductory Chapter: Hansen´s Disease – The Forgotten and Neglected Disease

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Additional information is available at the end of the chapter

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1. Introduction

Leprosy has been one of the diseases most feared by mankind and has managed to stigmatize societies for its lamentable symptoms and consequences. It is known since the remote epochs of the Biblical Times, the Middle Ages, the modern era, the Renaissance, and its lyrical poems, dedicated to those patients with leprosy in which their suffering was interpreted as a curse, a divine punishment, or a hereditary disease. The condemnation of those patients diagnosed with Hansen's disease was despair, physical, integral, and social death, promoted by rejection, persecution, and exile, because they had to be expelled and live hiding their shame and physical decomposition, trying to adapt to the spiritual change and its real beauty as the disease spread through their bodies; being recruited forcibly in those "cemeteries for the living" known as leprosaria, leprocomios, or lazaretos were dragging their lives and awaited death face to face; being neglected by a society that considered that the disease was the worst abomination that could exist, and that at the same time it did not know that it was through no fault of their own that those Hansen's disease patients contracted the disease [1, 2].

Leprosy is a disease believed to be incurable and characterized by marked changes in physical appearance and evolutionary skin lesions affecting the skin, peripheral nerves, and nasal mucosa. It was discovered in 1873 by Gerhard Hansen, who demonstrated that it was an infectious disease and not a curse, helping to establish the fundamental principles of immunology, bacteriology, and also public health and thus putting an end to the idea of leprosy being un-curable. Even so, because of the social stigma and fear, humanity continued to consider those with the disease as cursed pariahs, and the patients had to take refuge in places where those suffering from the same ailment were housed, the lazaretos; hidden there, they were isolated from the horror and repugnance of an uneducated society [3].

Today, the scientific community recognizes *Mycobacterium leprae* as the causative agent of the disease, although the postulates of the scholar Koch do not apply to this bacillus. This is a microorganism that prefers the colder zones of the body, and the most documented way of transmission is the one which expresses that the disease is transmitted from person to person by prolonged contact with a baciliferous patient through the respiratory tract reaching the nerves, skin, and eyes where its incubation period is long and years may pass from the infection to the emergence of evident clinical manifestations in a leprosy patient. Belonging to the *Mycobacteriaceae* family, this slightly curved bacillus measuring from 1 to 8 microns in length and 0.3 microns in diameter is intracellular, with tropism toward the macrophages and Schwann cells of the peripheral nerves. It is an acid alcohol-resistant bacillus as its wall consists of polysaccharides and mycolic acids that make it hydrophobic and resistant to discoloration and is not cultivable, a factor that makes it difficult to identify the microorganism by conventional methods [3, 4].

M. leprae contains in its genome around 3,200,000 base pairs and has 57.5% of guanine-cytokine; its sequencing identifies 1614 genes that encode proteins, 1116 considered as pseudogenes and 50 genes that encode stable RNA (Cole, Eiglmeier et al. 2001). The recombination between repetitive sequences and chromosomal rearrangements, translocations, and genetic deletions probably caused the genome reduction and mutation of the metabolic areas of *M. leprae* (Eiglemeier, Parkhill et al., 2001), making it conserve only the genes necessary for its transmission, fixation, and survival in the host and making it a "really astute microorganism" [5, 6].

Symptomatic skin (SP) patients have a skin lesion, anesthetic, hypopigmented, or reddish with limited borders or diffuse, non-congenital, unlike a scar, and symptomatic peripheral nervous system (SSNP) are defined as people with anesthetic body areas with distal problems of the feet or eyelids. People affected by leprosy have historically been diagnosed according to medical criteria using conventional methodologies, such as sputum smear that identifies acid- and alcohol-resistant bacilli, as well as samples of mucus and lymph, and skin biopsy that allow to observe the acid- and alcohol-resistant bacilli or the destruction of the peripheral nerve, achieving the classification of the disease as paucibacillary or multibacillary and thus establishing the treatment determined by the World Health Organization (WHO). Once *M. leprae* infects the skin and nervous tissue, it replicates slowly for years, and several mechanisms of skin lesions are triggered, reflecting those clinical manifestations of the disease that depend on the immune status. Based on the above, the WHO established two categories of the disease: paucibacillary, characterized by sporadic lesions on the skin with low presence of bacilli and immunological reactions Th1 type with high production of cytokines that favor the formation of granulomas that include tuberculoid leprosy (LT) and borderline tuberculoid leprosy (TB), or multibacillary, characterized by numerous lesions on the skin and a high bacillary load, Th2-type immune response with the absence of granuloma, including lepromatous leprosy (LL), borderline lepromatous leprosy (LB), and borderline-borderline (BB) leprosy [7–9]. They are the unstable forms of leprosy, and if they are not treated on time, these can evolve into lepromatous or tuberculoid forms gradually causing the disfigurement of the extremities and the development of physical disabilities, which are defined by WHO in three degrees of disability: grade 0 indicates the absence of disability; grade 1 indicates the loss of sensitivity in eyes, hands, and feet; and grade 2 indicates severe visual impairment and deformity of hands and feet [10].

The treatment of the disease occurred in three stages: firstly, the incurability when there were no accurate studies of the disease and the patients had to be isolated and removed from the society. Secondly, the monotherapy that began in 1941 when Guy Farget found a derivative of dapsone as a cure for leprosy and was the only medicine available until then in the world, but in the middle of the 1960's *M. leprae* began to show resistance to the drug, causing the health authorities to begin the fight to maintain control over the disease and the search for strategies to eliminate it since it was a public health problem. Finally, rifampicin and clofazimine were discovered and added to the treatment of the disease known as polychemotherapy. In 1981, the WHO recommended multidrug therapy (MMT) consisting of the administration of dapsone, rifampicin, and clofazimine in multibacillary patients, with treatment for prolonged periods to completely eliminate the causative agent of the disease [11].

Worldwide, the diagnosis of Hansen's disease is based on criteria established by the WHO, and it is determined by a careful and thorough clinical examination in the search for characteristic lesions of the disease, such as looking for hypopigmented spots accompanied by loss of sensitivity, temperature, and pain or thickening of the peripheral nerves. However, there are disadvantages in the effectiveness of the diagnosis due to the nonexistent standard method that differentiates the infection from the disease. Laboratory tests are still established as a diagnostic support through the visualization of the bacillus by smear microscopy, the histopathology, or the intradermal reaction to lepromin. Since the advent of molecular biology techniques, a great impact has been made in different fields of science. They are currently used not only in the diagnosis of diseases but also in the study of pathologies, finding and understanding a wide variety of infectious diseases (immunological and genetic) [12].

Following the arrival of a highly sensitive and specific technique such as the polymerase chain reaction (PCR), used in the detection and quantification of DNA to differentiate species and aid the rapid identification of drug resistance, this molecular methodology has been fundamental in the investigation of infectious diseases, thus developing methods based on PCR. It is certainly necessary to adopt it to detect and identify *M. Leprae* in the shortest possible time and as a diagnostic support for the amplification of nucleic acids with high purity of different molecular targets, thus interrupting the chain of transmission and the sequelae of disability, since leprosy is an unheeded disease despite WHO's efforts to improve leprosy control programs [13].

For Hansen's disease, the use of PCR is based on the knowledge of gene sequences that code proteins and repeated sequences, allowing the analysis of different sequences on the genome of *M. leprae*, preparing specific complementary primers of the opposite strand of DNA, and achieving in vitro dissociation and reassociation by heating and cooling. The primers are incubated with the DNA to amplify it, and a DNA polymerase synthesizes the complementary chain through a series of specific temperatures that seeks its denaturation, binding and synthesizing the nucleotides corresponding to the *Mycobacterium* [14]. Through the cyclical application of these processes, exponential copies of the nucleic acid fragment of the microorganism are achieved.

2. Conclusion

Although the control of leprosy in the world was achieved, it has not yet been eradicated, and the lack of an effective diagnostic method is one of the limitations in the control of the disease, since the long period of incubation of the disease and the dissemination of *M. leprae* mean that the conventional methodologies used are not conclusive and are only useful in symptomatic patients or in those with physical changes, and infected cohabitants or patients without symptoms or injuries are not diagnosed in a timely manner. Therefore, molecular methodologies are an alternative of causality and are needed for the diagnosis of the disease. The evolution of the disease and the continuous use of basic methodologies for its diagnosis highlight the importance of implementing molecular methods to achieve early diagnosis of the disease and thus diminishing the emergence of disabling forms, since methods based on PCR are capable of generating large amounts of DNA, analysis of genetic variability, typing of strains, either through the use of genetic markers, repeated sequences, genetic polymorphisms, microsatellites, and white sequences, among others, demonstrating that PCR is the method of the future for the diagnosis of leprosy, its sensitivity, specificity, diversity, and simplicity allows identifying sources of infection, patterns of transmission, monitoring treatment, and detecting resistance to drugs of the disease, which would be of great support for follow-up and timely treatment sought by health programs, and thus maintaining the control of a disease considered as unattended.

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