23 *Mycobacterium leprae*

A 37-year-old Hispanic woman, a native of Southern Mexico, went to see her primary care physician after complaining of a persistent **rash** throughout her body. The woman had three children, was a nonsmoker, and appeared to be well-nourished.

Her symptoms had started 5 years before with spasms, with needle-like pain, in her arms. She also felt tired and stressed and had been initially diagnosed with depression. Her skin examination indicated **atopic dermatitis** and **urticaria** and she was prescribed ibuprofen, fluoxetine, and hydroxyzine.

Physical examination revealed numerous hypopigmented skin lesions (**Figure 23.1**), especially those on her arms, nasal bridge area, cheeks, abdomen, back, and her legs. Her eyebrows had started thinning and she had numbness in her forearm.

The patient had a biopsy of skin lesions on the abdomen. Acid-fast bacilli were detected and a diagnosis of lepromatous leprosy (LL) was made. The patient was counseled about leprosy and was prescribed a course of a standard multidrug therapy (MDT). As required by Mexican law, her case was reported to the Public Health Department.

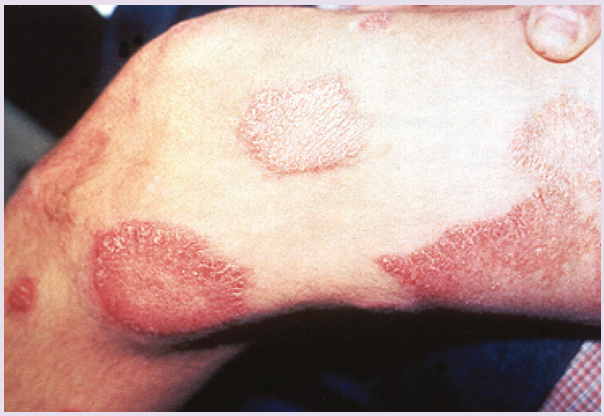

Figure 23.1 Skin lesions of a patient with lepromatous leprosy. This is usually accompanied by the loss of sensation around the affected area. *Courtesy of the US Department of Health and Human Services.*

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

CAUSATIVE AGENT

Leprosy (also called Hansen's disease, HD) is a chronic granulomatous disease of the skin and peripheral nervous system. For many years, *Mycobacterium leprae* was considered as a sole pathogen causing leprosy. However, in 2008, *Mycobacterium lepromatosis* was identified as second causative agent of HD. *M. lepromatosis* has been implicated in a small number of HD cases, and clinical aspects of the disease caused by *M. lepromatosis* are not yet clearly defined. *M. lepromatosis* was initially associated with diffuse LL, but subsequent studies have linked it to other forms of HD. *M. leprae* and *M. lepromatosis* comprise a so-called "*Mycobacterium leprae complex*". Based on their DNA sequences, both mycobacteria are classified as different species: *M. leprae* and *M. lepromatosis* might have diverged from a common ancestor more than 13 million years ago. However, they are both obligate intracellular organisms and share many important features. In this chapter, we focus on *Mycobacterium leprae* as the most frequent causative agent of leprosy.

M. leprae is a member of the Mycobacteriaceae family. It is an obligate intracellular gram-positive bacillus that requires the environment of the host macrophage for survival and propagation by binary fission. It shows preferential tropism toward macrophages and Schwann cells that surround the axons of nerve cells. The bacilli resist intracellular degradation by macrophages, possibly by escaping from the **phagosome** into the cytoplasm and preventing fusion of the phagosome with **lysosomes**.

M. leprae is an acid-fast microorganism. This means that it is resistant to decolorization by acids during staining procedures. The bacilli appear as straight or curved rod-shaped organisms, 1–8 µm long and approximately 0.3 µm in diameter. In common with all pathogens belonging to the genus *Mycobacterium*, *M. leprae* can be stained using the Ziehl-Neelsen method, in which the bacteria are stained bright red and stand out clearly against a blue background (**Figure 23.2**). A Fite modification of this method allows identification of more bacilli using their ability to accumulate large amounts of hyaluronic acid.

M. leprae, unlike *M. tuberculosis*, cannot be cultured in the laboratory. *M. leprae* can, however, be propagated in mouse

footpad and in its natural host – the nine-banded armadillo – for experimental purposes.

The genome of *M. leprae* has been sequenced and it includes 1605 genes coding for proteins and 50 genes for stable RNA molecules. The genome of *M. leprae* is smaller than that of *M. tuberculosis* and less than half of the genome contains functional genes but there are many pseudogenes, with intact counterparts in *M. tuberculosis* (**Table 23.1**). Gene deletion and decay compared with *M. tuberculosis* have eliminated many important metabolic activities. *M. leprae* is therefore even more dependent on host metabolism and this is why it is characterized by a slower growth rate than that of *M. tuberculosis*.

The cell wall of *M. leprae* is similar to that of *M. tuberculosis*, but it includes the species-specific phenolic glycolipid I (PGL-I) widely used for serodiagnosis of LL and disease pathogenesis (see Section 2); and genus-specific lipoarabinomannan (LAM) among other molecules (see Section 4).

The major reservoir of *M. leprae* is in humans, rarely apes, and some species of monkeys: chimpanzees, nine-banded armadillos, mangabey monkeys, and cynomolgus macaque. These, especially armadillos, are characterized by a natural low body temperature of 34°C that favors the survival of *M. leprae*.

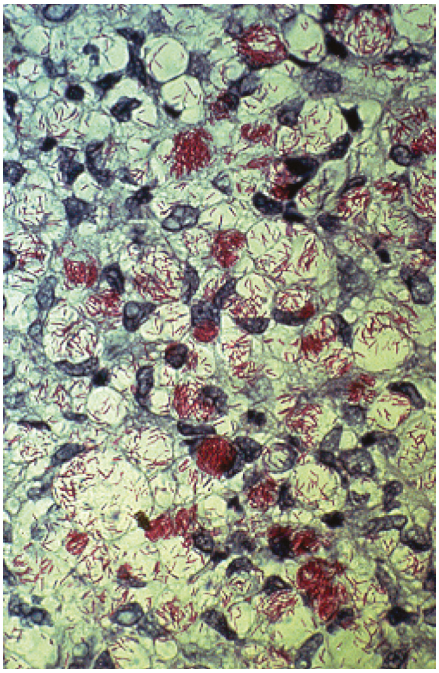

Figure 23.2 Skin lesion fluid from the leprosy patient stained by the Ziehl-Neelsen acid-fast method. The reagent stains *M. leprae* red against the blue background. *Courtesy of the US Department of Health and Human Services.*

ENTRY AND SPREAD WITHIN THE BODY

The current view is that *M. leprae* enters the body via nasal epithelial cells or poorly differentiated keratinocytes, fibroblasts and endothelial cells of the skin through minor injuries. Tropism for these cells is likely to be mediated via mammalian cell entry protein 1A (Mce1A). In the respiratory system, the microorganism is taken up by **alveolar macrophages** where they live and proliferate very slowly. In early infections, subsequent to entry into respiratory mucosa, the bacilli are spread by the circulation, and reach neural tissue where they infect Schwann cells. It is still unclear how *M. leprae* travels through blood but it is likely to be via macrophages and **dendritic cells** (**DCs**). Fibroblasts, which can be invaded by *M. leprae*, can also contribute to dissemination of the bacteria.

M. leprae binds to Schwann cells via the cell wall PGL-I (an **adhesin**), which attaches to the G-domain of α2-chain of laminin 2 isoform in the basal lamina of Schwann cells and is restricted to peripheral nerves. However, the subsequent uptake of *M. leprae* by the Schwann cells is facilitated by its α-dystroglycan – a receptor for laminin on the cell membrane. The bacilli live in the infected Schwann cells and macrophages and are characterized by slow growth (sometimes for years) that is reflected in the long incubation period of the disease. The average division rate of *M. leprae* is very low for microbes, 10–12 days for one division. Optimal temperature for growth of *M. leprae* is lower than core body temperature (27–33°C), thus it prefers to grow in the cooler parts of the body, that is skin and superficial nerves. Several factors enable *M. leprae* to survive in Schwann cells: affecting host-cell metabolism by increasing the uptake of glucose and lipid synthesis leading to the reduction in intracellular oxidative stress. To avoid

Table 23.1 Comparative genomics of *M. leprae* and *M. tuberculosis*

Parameter	*M. leprae* (strain TN)	*M. tuberculosis* (strain H37Rv)
Genome size (bp)	3268203	4411532
Protein genes	1614	3993
tRNA genes	45	45
rRNA genes	3	3
Unknown genes	142	606
Pseudogenes	1133	6
Gene density (bases/gene)	2024	1106
% protein coding	49.5	91.2
Single nucleotide polymorphism frequency	1/24000 bp	1/3000 bp

Adapted from Scollard et al., 2006

host-cell apoptosis, Schwann cell survival factor insulin-l like growth factor-I (IGF-I) is induced by *M. leprae* as well as 2′–5′ oligoadenylate synthetase-like (OASL), which impairs autophagy and antimicrobial peptide expression.

Another possible route of entry for *M. leprae* is through minor injuries in the epidermis which consists of almost 90% keratinocytes. The bacteria attach to keratinocytes probably via laminin- 5, the major form of laminin in the skin, prompting keratinocytes to launch innate immune responses.

PERSON-TO-PERSON SPREAD

Leprosy sufferers, particularly with multibacillary leprosy (predominantly those with LL – see Sections 2 and 3) represent the major source of the infection, and transmission is through aerosols to the respiratory tract. Its dissemination through skin lesions seems to be less important. There is increasing evidence that those infected individuals that do not develop the symptoms of the disease may nevertheless transiently excrete the microbe nasally and spread the infection. As a result, close proximal contacts of the infected individuals (household, neighbors, social contacts) have an increased risk of contracting the disease. The risk varies for different forms of the disease (see Section 3): 8–10 times higher for LL and 2–4 times higher for the tuberculoid form (TT). Factors such as probability of a frequent contact, similar genetic and immunologic background, and similar environment may all play a role. In the southern states of the US, molecular typing has proven that *M. leprae* can be transmitted from armadillos to humans. Immunosuppression is one of the contributing factors. In immunocompromised individuals, leprosy can develop after solid-organ transplantation, chemotherapy, anti-rheumatoid treatment or HIV infection, although the latter cases are rare.

It is a slowly developing disease with an incubation period from 6 months to up to 40 years or even longer! Again, the mean incubation time is different for TT and LL, being 4 years and 10 years, respectively.

EPIDEMIOLOGY

According to the World Health Organization (WHO) in 1997, 2 million people worldwide were infected with *M. leprae*. Introduction in the mid-1980s of MDT significantly reduced the prevalence of leprosy. In 2000, the WHO declared leprosy eliminated as a public health problem on the basis of overall reduction in prevalence to less than 1 case per 10 000 people. Since 2010, however, a fairly stable number of new leprosy cases of around 200 000 are reported each year indicating that MDT upon diagnosis is not sufficient to eliminate the disease. A high frequency (17%) of infection in children should be noted. In adults, the LL form is more common in men than women with an approximate 3:2 ratio. The risk for the acquisition of leprosy actually might be bimodal: first wave at 5–15 years of age and then after 30 years.

Leprosy can affect races all over the world. However, it is most common in warm, wet areas in the tropics and subtropics. Leprosy is endemic in Asia, Africa, the Pacific region, and Latin America. About 75% of the patients have been registered with the disease in South-East Asia, particularly in India where leprosy is epidemic (**Figure 23.3**). Significant regional clustering has been detected in individual countries and even communities. Interestingly, African blacks have a high incidence of TT, while people with white skin and Chinese people mostly have LL.

In the last decade of the 20th century, the case detection rate remained stable (India), decreased (China) or increased (Bangladesh). However, these data rely on the measurement

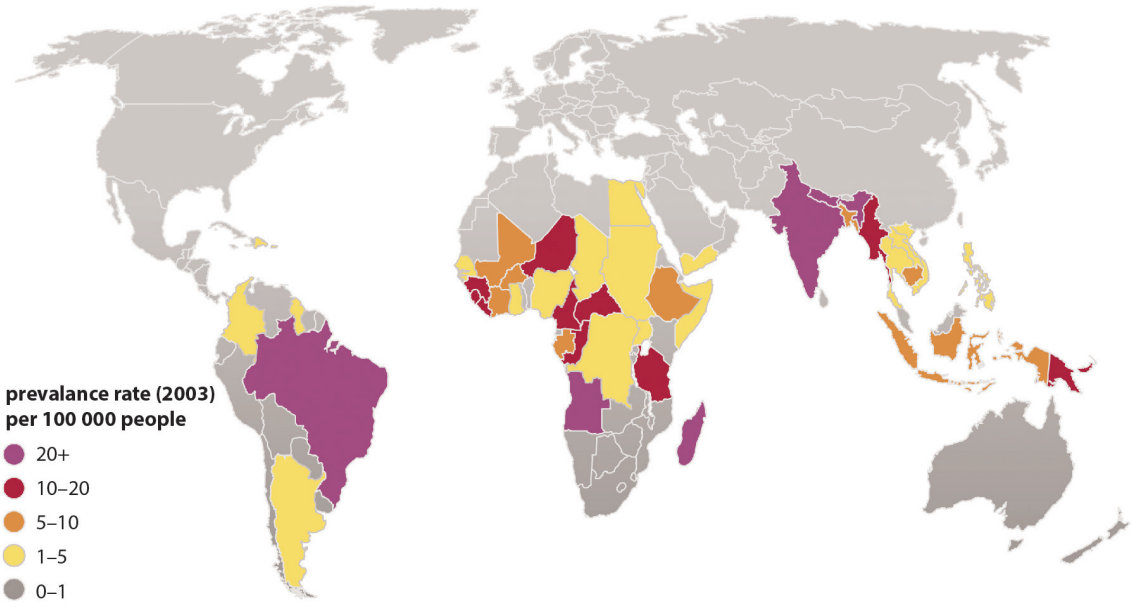

Figure 23.3 Global distribution of leprosy in 2003 according to WHO. South-East Asia, Africa, the Pacific region and South America are the regions the most affected.

of incidence through the number of patients registered for the treatment that is far from optimal. Often long sufferers from leprosy remain unregistered for various reasons (stigma, costs, lack of health services). For example, a door-to-door inquiry in Bangladesh, produced nearly a five-fold increase in cases compared to self-reported findings only. Consequently, the information currently available from endemic countries might often be inadequate and does not anticipate trends in leprosy epidemiology and transmission.

In non-endemic countries, the symptoms of leprosy are often overlooked. In the UK, in more than 80% of cases, leprosy was not suspected at the first visit to a medical doctor since it simply was not expected. This often leads to a median diagnostic delay of 1.8 years.

In the US, 75% of cases were shown to be from immigrants, and for the rest international exposure was the contributing factor, although transmission from infected armadillos remains a possibility.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

Host immune responses to *M. leprae* differ for TT and LL types of leprosy, with a prevalence of either T-cell immunity (TT) or antibody production (LL). For the definition of different types of leprosy see Section 3.

TUBERCULOID LEPROSY

A strong T-cell-mediated immunity combined with a weak antibody production leads to the development of a mild clinical form of TT with few nerves involved and low bacterial load. The replication of *M. leprae* in Schwann cells leads to the stimulation of T-cell response and subsequently to chronic inflammation. This is mediated through the bacterial cell wall glycolipid PGL-I. The Schwann cells can express HLA class II molecules and therefore stimulate **CD4**+ T cells. **γ-interferon** (**γ-IFN**)-producing CD4+ T cells are found infiltrating the lesions and forming **granulomas** with epithelioid and giant cells.

In addition, interaction of *M. leprae* with **Toll-like receptors** (TLR1 and TLR2) on Schwann cells in patients with TT is believed to induce **apoptosis** thus leading to nerve damage. A chronic inflammatory reaction results in swelling of perineural areas, **ischemia**, **fibrosis**, and death of axons. However, very little circulating antibody against *M. leprae* is present in TT.

Keratinocytes can also function as antigen-presenting cells (APC) by presenting *M. leprae* antigens to CD4+ T cells. In turn, production of γ-IFN by CD4+ T cells can activate keratinocytes in lesions of tuberculoid leprosy patients.

LEPROMATOUS LEPROSY

Antibody-mediated responses with no protective effect are a feature of this form of leprosy. In LL, PGL-I stimulates production of specific **IgM** that is proportional to the bacterial load and this has diagnostic and prognostic importance. These antibodies are not protective and are thought to down-regulate cell-mediated immunity. They form **immune complexes** that are deposited in tissues attracting neutrophils to the deposition sites and causing complement activation. This leads to the development of intense and aggravated inflammation and tissue/organ damage. A systemic inflammatory response mediated by the deposition of extravascular immune complexes is called **erythema nodosum** leprosum (ENL). Women with leprosy may develop post-partum nerve damage. Although pregnancy itself does not seem to aggravate the disease or cause a relapse, LL patients experience ENL reactions throughout pregnancy and lactation, possibly associated with earlier loss of nerve function.

As might be expected by the predominant cellular or humoral response, the clinical form of the disease is affected by the balance of **Th-1**/**Th-2** cytokines in TT and LL forms of leprosy. Since T-cell immunity is enhanced by the T helper 1 (Th-1) **cytokine** pathway (**interleukin** (**IL**)-2, IL-15, IL-12, IFN-γ), and humoral immunity is supported by Th-2 cytokines (IL-4, IL-5 and IL-10), the severity of antibody-dominated LL is dependent upon activation of Th-2 cytokines.

DCs are likely to encounter the bacilli in the nasal mucosa or skin abrasions, where they play a key role in the subsequent regulation of inflammation and balance of Th-1/Th-2 cell-mediated immunity – summarized in **Figure 23.4**.

Epithelial cells can direct local DCs to stimulate IgA switch in B lymphocytes. IgA can confer protection to *M. leprae* infection by efficiently clearing the bacteria in the airways. Elevated levels of IgA directed to PGL-I and LAM were detected in the saliva of untreated leprosy patients, their contacts and household members indicating a potential protective role of these antibodies.

Genetic polymorphism was also found to be associated with the pattern of the disease: HLA DR2 and DR3 alleles are associated with TT, and DQ1 with LL forms of leprosy (see Section 3).

The borderline cases appear immunologically unstable and susceptible to aggressive, inflammatory episodes affecting the peripheral nerves which can lead to leprosy-associated disabilities.

PATHOGENESIS

Hypersensitivity reactions vastly contribute to the pathogenesis of the disease. There are two types of reactions that can develop: type 1 reaction (T1R) also called reversal; or type 2 reaction (T2R) ENL. T1R are delayed hypersensitivity

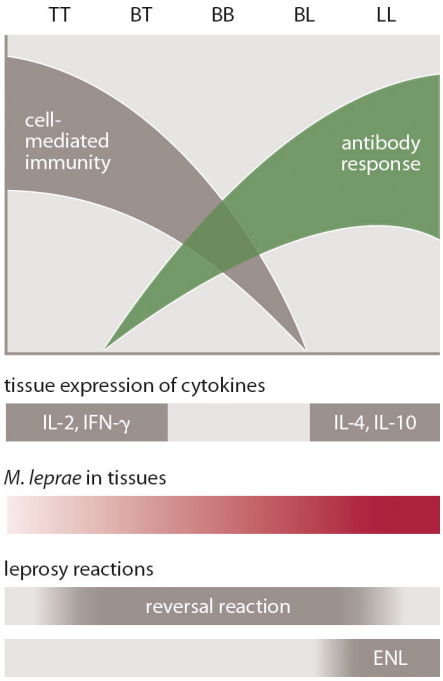

Figure 23.4 Spectrum of clinical and immunologic characteristics of leprosy. Immune responses regulated by Th-1 cytokines (IL-2, IFN-γ) are characteristic of the less severe TT form with the prevalence of T-mediated immune responses, while Th-2 cytokines (IL-4, IL-10) enhance the more aggressive antibody-dependent LL form of leprosy. Intermediate forms (BT, BB, and BL, see Section 3) are characterized by an increasing shift in balance from Th-1 toward Th-2 cytokine-mediated immune responses accompanied by a concomitant appearance of *M. leprae* in the tissues. Intermediate forms can revert to the less severe form of the disease, but LL is irreversible and presents as ENL. BT: borderline turberculoid leprosy; BB: mid-borderline leprosy; BL: borderline lepromatous leprosy. *From Britton WJ & Lockwood DNJ (2004) The Lancet 363:1209-1219. With permission from Elsevier.*

reactions associated with an increase in cell-mediated immune responses in the lesions. These are characteristic for the TT form of leprosy.

T2R develops as a result of antibody responses to *M. leprae* antigens leading to the formation and deposition of immune complexes into tissues and subsequent infiltration by neutrophils and systemic effects such as high fever and edema. Bacterial antigens involved in the immune complex formation are PGL-I, LAM and major membrane protein II (MMP-II). T2R predominantly occurs in BL/LL patients (see Section 3) with high bacillary loads and leads to the nerve damage.

Patients with untreated LL might develop a rare condition, called the *Lucio phenomenon*, mostly present in cases with T2R which manifests with the onset of necrotizing vasculopathy.

Excessive accumulation of collagen as a result of chronic activation of fibroblasts can lead to fibrosis, causing irreversible nerve impairments and neuropathy.

Surprisingly, and different from *M. tuberculosis*, co-infection with *M. leprae* and HIV does not have any appreciable effect on clinical symptoms, although HIV infection impairs T-cell-mediated immune responses. However, in patients with preexisting leprosy and subsequent infection with HIV, a paradoxical clinical deterioration may occur after highly active antiretroviral therapy (HAART). This treatment would flair up a so-called reversal reaction (RR) which manifests as an increase of the inflammatory process in the skin, nerve, or both, leading to the appearance of new lesions.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

THE DIFFERENT FORMS OF LEPROSY

The forms of leprosy range from the mildest indeterminate form to the most severe lepromatous type. Severe forms arise because of a less effective immune response to the infection (see Section 2). Most of those infected develop an appropriate immune response and never develop signs of leprosy.

The classification of leprosy is currently based on clinical grounds. Some authors identify the least aggressive indeterminate leprosy (IL) as the very first stage of the disease.

According to the accepted Ridley and Jopling (1966) classification, there are five more advanced stages of leprosy, given here in increasing severity.

- Tuberculoid leprosy (TT), also called type I leprosy.
- Borderline tuberculoid leprosy (BT).
- Mid-borderline leprosy (BB).
- Borderline lepromatous leprosy (BL).
- Lepromatous leprosy (LL), also called type II leprosy.

IL is an early form with no loss of sensation and one or several skin hypopigmentation areas and **erythematous** macules. About 75% of these marks heal spontaneously. In some affected individuals, supposedly with weak immune responses, the disease progresses to other forms.

Both IL and TT forms are characterized by fewer than five skin lesions, with no bacilli being detected on smear tests and are collectively called paucibacillary (PB) leprosy.

In patients with TT, one or several erythematous plaques are usually found on the face and limbs, but not on intertriginous areas or the scalp. Loss of sensation and hair loss (**alopecia**) are also characteristic. Neural involvement includes thickening of peripheral nerves, their tenderness, and subsequent loss of function. The TT form can either resolve itself spontaneously after several years, or develop to borderline BT and, very rarely, can progress to the more aggressive LL form.

LL and, often, BL are characterized by more than five skin lesions and considerable numbers of bacilli in smears and are collectively called multibacillary (MB) leprosy. Patients with LL have small diffuse and symmetric macular lesions. Lepromatous infiltrations are called lepromas or plaques and lead to the development of leonine faces. The loss of sensation and nerve loss progress slowly. Bone and cartilage damage is common as well as alopecia of eyebrows and

eyelashes (**madarosis**). Testicular **atrophy** leads to sterility and **gynecomastia**.

Within each type of leprosy, a patient may remain in that stage, improve to a less debilitating form or worsen to a more debilitating form depending on their immune status (see Section 2). LL is the only form that never reverts to a less severe form.

CLINICAL PRESENTATION

The initial symptoms of leprosy are not demonstrative and often go unnoticed. Most often, patients start to lose sensation to heat and cold years before skin lesions occur (see Case details). The next sensation to be affected is light touch, then pain, and finally hard pressure. The most usual sites for numbness are hands and feet, and the first symptoms that patients report are usually burns and ulcers at the numb sites. However, the disease is often recognized through the development of dermal eruptions. At this stage, other symptoms appear such as damage to the anterior chambers of the eyes, chin, earlobes, knees or testes.

SKIN

The most common skin presentations are lesions in the form of **macules** or plaques, more rarely **papules** and nodules. The TT form is characterized by few hypopigmented lesions with lost or reduced sensation. In patients with LL, there are usually many lesions, sometimes confluent, with not so apparent loss of sensation. Alopecia is common in LL patients and eyebrows and eyelashes are affected. The scalp remains intact.

NERVES

Peripheral nerve damage occurs characteristically near the surface of the skin, particularly in the neck, elbow, wrist, neck of the fibula, and the medial malleolus (posterior tibial nerve). The latter is the most affected, followed by ulnar, median, lateral popliteal, and facial nerves. Involvement of small dermal nerves leads to **hypoesthesia** and **anhidrosis** in TT patients and "glove and stocking" loss of sensation in the case of LL. In the final stages of nerve injury segmental demyelination is quite frequent.

EYES

Both nerve damage and bacterial invasion can lead to blindness in up to 3% and potential blindness in almost 11% of MB patients (mostly the LL form). Patients suffer from loss of corneal sensation and dryness in the cornea and conjuctiva due to the reduction in blinking. This increases the risk of microtrauma and ulceration of the cornea. **Photophobia** and **glaucoma** can also develop.

SYSTEMIC

Systemic damage is mostly associated with the LL form of the disease and is a result of bacillary infiltration. Particularly important is testicular atrophy, followed by **azoospermia** and gynecomastia. Adequate treatment significantly decreases the risk of the development of renal damage and **amyloidosis**. However, **lymphadenopathy** and **hepatomegaly** can develop in LL patients. Joint invasions by the microorganism may lead to aseptic **necrosis** and **osteomyelitis**.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

Diagnosis of leprosy is mainly clinical, and a panel of clinical criteria has been developed that gives an average reliability of 91–97% for MB and 76–86% for PB leprosy. The panel consists of three major criteria, as follows:

1. Hypopigmentation or reddish patches of the skin with the loss of sensation. The latter can be tested by touching the skin (tactile test) with a wisp of cotton, while the patient's eyes are closed. Test tubes with hot and cold water may be used to test temperature perception.
2. Detection of acid-fast bacilli in biopsies or in skin smears.
3. Thickening of peripheral nerves. Enlarged nerves, especially in the areas where a superficial nerve may be involved, are examined by palpation. Attention should be paid for wincing during nerve palpation, indicating pain.

A skin biopsy for testing the presence of inflamed nerves is currently the standard criterion for diagnosis. Hematoxylin and eosin sectioning is used. In T2R, the polymorphonuclear leukocytes are characteristic, while in Lucio's phenomena lesions, fibrin thrombi can be found. In addition, biopsies are examined for the presence of acid-fast bacilli and the morphologic index (MI) is calculated that represents the number of viable bacilli per 100 bacilli. Histologic diagnosis is used as the gold standard.

Tissue/skin smear tests using the Ziehl-Neelsen staining method (see **Figure 23.2**) or Fite modification allow the visualization of bacilli under the microscope and calculation of the bacterial index (BI). However, this method is relatively insensitive and smears from almost 70% of patients are found to be negative.

Two tests can be used to diagnose nerve injury.

1. In the histamine test, a drop of histamine diphosphate is placed on non-affected and affected skin. It normally causes the formation of a wheal on normal skin, but not where the peripheral nerves have been damaged. However, this test is not very clear in dark-skinned patients.
2. In the methacholine sweat test, an intracutaneous injection of methacholine results in sweating in normal skin but no sweating in lepromatous lesions.

Establishment of neural inflammation histologically differentiates leprosy from other granulomatous diseases.

Serologic tests detect antibodies to *M. leprae*. Usually high titers of antibodies indicate untreated LL. Antibodies to PGL-1 are present in 90% of LL patients, but only in 40–50% of TT cases. They are also detected in 1–5% of healthy individuals.

Polymerase chain reaction (**PCR**) assay on biopsy material for *M. leprae* specific genes or repeat sequences has been able to confirm 95% of MB and 55% of PB cases. PCR is more applicable as a detector rather than an identifier of the disease with a sensitivity of more than 90% and specificity of 100%. However, in cases with TT, a sensitivity dropped to 34% and specificity – to 80%.

The **Lepromin test** allows the assessment of delayed hypersensitivity to antigens of *M. leprae* or other mycobacteria that cross-react with *M. leprae* by injection of a standardized extract of inactivated bacteria under the skin. A positive test indicates cell-mediated immunity associated with TT. This test is only of value in the classification of leprosy. It should not be used to establish a diagnosis of leprosy.

Early diagnosis is often prevented by difficulties in reaching some affected rural communities in developing countries. Delays in the diagnosis and treatment lead to an increase in leprosy-related disabilities. Overcoming the stigma of leprosy in certain countries and public education about this disease are important. Effective therapy further reduces the stigma attached.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

Leprosy control includes early detection of the disease, adequate treatment of patients, effective care for the prevention of disabilities, and patient rehabilitation.

MANAGEMENT

All forms and stages of newly diagnosed leprosy are normally treated with rifampicin, clofazimine, minocycline, ofloxacin, and dapsone as a part of a standard MDT recommended by the WHO. MDT was introduced for leprosy control as a result of a resistance to monotherapy with dapsone (diaminodiphenylsulfone). However, the doses and combinations of these antibiotics differ for PB and MB leprosy.

1. For the one lesion PB leprosy, a single shot of rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg (also known as ROM) is used, which is both acceptable and cost-effective.
2. For PB leprosy with more than one lesion, a 6-month treatment includes: daily self-administered doses of dapsone 100 mg and a monthly supervised administration of rifampicin 600 mg.
3. For MB leprosy, the treatment is prolonged over 24 months and consists of: daily self-administered combinations of dapsone 100 mg and clofazimine 50 mg, together with monthly supervised administration of rifampicin 600 mg and clofazimine 300 mg.

In 2018, the WHO issued new guidelines and introduced uniform MDT for administering three drugs: rifampin, dapsone, and clofazimine, to all patients irrespective of the classified type. The prior regimens are still used with the addition of daily clofazimine for the PB disease. No changes were introduced to the treatment of MB cases. Using the uniform MDT treatment decreases the chances of MB disease misclassified as PB.

Other potential drugs include minocycline, ofloxacin, moxifloxacin, levofloxacin, and clarithromycin.

A study on more than 1900 patients in 2009–2015 demonstrated rising bacterial resistance to some drugs: 3.8% to rifampin, 5.3% to dapsone, and 1.3% to ofloxacin.

Treatment of Inflammatory Responses

Severe neuritis may need immediate treatment with corticosteroids to minimize irreversible nerve damage: prednisone, 40 to 60 mg/day, is recommended. Treatment with elevated doses for extended time is preferable for reducing pain and inflammation as compared to smaller and shorter doses of corticosteroids. In patients with diabetes, methotrexate can be substituted for a steroid regimen.

T1R can be treated with cyclosporine in patients unresponsive to corticosteroids, although toxicity has to be taken into account.

In mild cases of acute T2R, clofazimine can be used in increasing doses of approximately 300 mg daily for one month with a gradual decrease to 100 mg/day in one year.

Thalidomide is a powerful drug for the treatment of T2R and especially ENL, but it should not be used in pregnancy. The initial dose of 300–400 mg daily should be soon lowered to a maintenance concentration of around 100 mg daily, every couple of months. Neuropathy advancement is an indication of an immediate withholding of treatment.

PREVENTION

Vaccines for Leprosy

Because of the dormant nature of *M. leprae*, the long incubation period, effective treatment with MDT, low prevalence of leprosy, and insufficient funding, vaccine development has not been a priority. However, both, BCG and *Mycobacterium indicus pranii* (MIP) have a potential preventive role against leprosy and tuberculosis and are generally well tolerated. The key challenge is the development of a vaccine that prevents *M. leprae*-associated neuropathy.

A major recent advance has been the identification of potent vaccine adjuvants capable of stimulating Th-1 responses by macrophages and DCs. These include formulated TLR ligands (TLRL). The vaccine prototype LepVax (containing LEP-F1, a fusion protein mixed with a cocktail of ML2055, ML2380, and ML2028 antigens, in conjunction with glucopyranosyl lipid adjuvant in stable emulsion GLA-SE) was successfully tested in armadillos. It appeared to be safe and effective, reducing sensory nerve damage and delaying motor nerve damage in animals, and is now progressing to stage 1 clinical trials.

Prevention of Disabilities and Rehabilitation

Twenty-five percent of leprosy patients, particularly with LL and BL forms, have some degree of disability. It increases with age and is more severe in males. The gravity of disability correlates with the duration of the disease. Hands are most frequently affected followed by the feet and eyes.

There are currently around 3 million people with physical deformities and disabilities caused by leprosy.

The socioeconomic impact of leprosy continues to be a burden in endemic countries. Rehabilitation strategies for leprosy should contain physical, psychological, social, and economic aspects. Up to now, most leprosy control programs have been focused on physical rehabilitation only. Socioeconomic rehabilitation has been introduced by some local governments, nongovernmental organizations (NGOs), and community-based rehabilitation (CBR) programs focused on the patient's self-awareness and combating the stigma attached to the disease. These are specifically adapted for the local needs and differ among countries and from area to area.

SUMMARY

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY, AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

- For many years, *Mycobacterium leprae* was considered as a sole pathogen causing leprosy. However, in 2008, *Mycobacterium lepromatosis* was identified as second causative agent of Hansen's disease (HD). *M. lepromatosis* has been implicated in a small number of HD cases, and clinical aspects of the disease caused by *M. lepromatosis* are not yet clearly defined. *M. lepromatosis* was initially associated with diffuse lepromatous leprosy, but subsequent studies have linked it to other forms of HD.
- *M. leprae* and *M. lepromatosis* comprise a so-called "*Mycobacterium leprae* complex".
- *Mycobacterium leprae* is the most frequent causative agent of leprosy. It is an obligate intracellular gram-positive bacillus that requires the environment of the host macrophage for survival and propagation by binary fission.
- It shows preferential tropism toward macrophages and Schwann cells that surround the axons of nerve cells.
- *M. leprae* is a straight or curved rod-shaped organism, 1–8 µm long and approximately 0.3 µm in diameter.
- An intracellular parasite, *M. leprae* cannot be cultured by conventional laboratory methods and can be propagated in mouse footpad or in its natural host – the nine-banded armadillo.
- The genome of *M. leprae*, contains less than 50% of the functional genes of *M. tuberculosis*. These lost genes coding for the metabolic pathways have been replaced in *M. leprae* by pseudogenes or inactivated genes, and it is even more dependent on host metabolism for survival than *M. tuberculosis*.
- The cell wall of *M. leprae* is similar to that of *M. tuberculosis*, but its cell wall includes the species-specific phenolic glycolipid I (PGL-I) used for serodiagnosis of lepromatous leprosy and disease pathogenesis and genus-specific lipoarabinomannan (LAM).
- *M. leprae* enters the body via nasal epithelial cells or poorly differentiated keratinocytes, fibroblasts, and endothelial cells of the skin through minor injuries. Tropism for these cells is likely to be mediated via mammalian cell entry protein 1A (Mce1A). In the respiratory system, the microorganism is taken up by **alveolar macrophages**.
- *M. leprae* binds to the G-domain of α2-chain of laminin 2 in the basal lamina of Schwann cells. Uptake of *M. leprae* by the Schwann cells is facilitated by α-dystroglycan – a receptor for laminin on cell membrane.
- Optimal temperature for growth for *M. leprae* is low (30–35°C), so it prefers to grow in the cooler parts of the body: skin and superficial nerves. Natural hosts of *M. leprae* – armadillos – are characterized by low body temperature.
- Asymptomatic infected individuals may transiently excrete the microbe nasally and spread the infection among close proximal contacts.
- In 1997, two million people worldwide were infected with *M. leprae*, with around 800 000 new cases of leprosy detected per year.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

- A strong T-cell-mediated immunity, combined with a weak antibody production, leads to the development of a mild clinical form of tuberculoid leprosy (type I or reversal) with few nerves involved and low bacterial load.
- In the tuberculoid form of leprosy, the most damage is inflicted by chronic inflammation caused by immune responses.
- In lepromatous (type II) leprosy high titers of antibodies in combination with unappreciable cellular immune response result in widespread skin lesions, extensive nerve involvement, and a high bacterial load.
- In LL, systemic inflammatory response to the deposition of extravascular immune complexes leads to erythema nodosum leprosum (ENL) resulting in neutrophil infiltration and complement activation.
- The borderline forms of leprosy are characterized by an increasing reduction of cellular immune responses associated with increasing bacillary load.
- The clinical form of the disease is affected by the balance of Th-1/Th-2 cytokines that favor T-cell- or B-cell-(antibody) mediated immune responses, respectively.

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3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

- The forms of leprosy distinguished by the Ridley-Jopling classification are: indeterminate leprosy (IL), tuberculoid leprosy (TT), borderline forms (BT, BB, and BL) and lepromatous leprosy (LL).
- IL and TT are characterized by fewer than five lesions, no bacilli on smear tests, and are called paucibacillary (PB) disease.
- LL and, often, BL are characterized by more than five lesions with bacilli and are called a multibacillary (MB) disease.
- *M. leprae* is not very pathogenic and most infections do not result in leprosy. Some early symptoms such as skin lesions are self-limiting and can heal spontaneously.
- The initial symptoms of leprosy are the loss of sensation of temperature, followed by the loss of the sensation of a light touch, then pain, and finally hard pressure.
- The disease is mostly recognized through the development of dermal eruptions such as lesions in the form of macules or plaques, more rarely papules and nodules.
- The TT form is characterized by few hypopigmented lesions with lost or low sensation. The LL form is characterized by many lesions, sometimes confluent, with less apparent loss of sensation.
- Peripheral nerve damage appears near the surface of the skin, particularly in the neck, elbow, wrist, neck of the fibula, and medial malleolus.
- Both nerve damage and bacterial invasion can lead to blindness in up to 3% and potential blindness in almost 11% of multibacillary patients.
- Systemic damage in the patients with the LL form is a result of bacillary infiltration and comprises testicular atrophy, azoospermia, and gynecomastia.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

- The three main diagnostic criteria are: hypopigmentation or reddish patches of the skin with the loss of sensation; acid-fast bacilli in biopsies or in skin smears; thickening of peripheral nerves.
- Skin biopsy for testing of the presence of inflamed nerve is currently the standard criterion for diagnosis.
- Tissue/skin smear test using Ziehl-Neelsen staining method or Fite modification allows bacilli to be visualized under the microscope, but this method is not highly sensitive and smears from almost 70% of all patients are found to be negative.
- Serologic tests are used to detect antibodies to *M. leprae*. High titers of antibodies indicate untreated LL.
- To confirm diagnosis, automated PCR- and RT-PCR-based techniques have been implemented in many reference laboratories in countries with endemic leprosy.
- Early diagnosis is often prevented by difficulties in reaching some affected rural communities in the developing countries.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

- Leprosy control includes early detection, adequate treatment, comprehensive and effective care for the prevention of disabilities, and rehabilitation.
- Newly diagnosed leprosy is treated with a combination of rifampicin, clofazimine, minocycline, ofloxacin, and dapsone as a part of a standard multidrug therapy (MDT) recommended by the WHO.
- For the one lesion, PB leprosy a single shot of rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg (also known as ROM) is used.
- For PB leprosy with more than one lesion a 6-month treatment includes: a daily self-administered dose of dapsone 100 mg and a monthly supervised administration of rifampicin 600 mg.
- For MB leprosy, the treatment is prolonged to 24 months and consists of: daily self-administered combination of dapsone 100 mg and clofazimine 50 mg together with monthly supervised administration of rifampicin 600 mg and clofazimine 300 mg.
- BCG administration, together with killed *M. leprae*, leads to a shift in immune response from multibacillary to paucibacillary leprosy, which is beneficial for a patient.
- The development of BCG-based and recombinant vaccines is currently under way.
- Rehabilitation strategies for leprosy should contain physical, psychological, social and economic aspects.

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Students can test their knowledge of this case study by visiting the Instructor and Student Resources: [www.routledge.com/cw/lydyard] where several multiple choice questions can be found.