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184 Leprosy

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Leprosy Leprosy, also referred to as Hansen’s disease, is a chronic infectious disease caused by Mycobacterium leprae. The clinical manifestations are largely confined to the skin, peripheral nervous system, eyes, and upper respiratory tract. The differing immune responses to M. leprae result in a spectrum of disease ranging from tuberculoid to leproma tous leprosy. M. leprae has a predilection for peripheral nerves, and immunologically mediated reactional states can cause nerve damage to the face, arms, and legs; this damage often results in disability, which in turn can lead to stigma and social exclusion. The physical disfigurement that accompanies leprosy has left marks on society that have endured long after the disease’s disappearance in many countries. In everyday language, leprosy has become a metaphor for a horrible condition that warrants social exclusion. Leprosy is a neglected disease and is often thought no longer to exist. However, 174,087 new cases from 182 countries were reported in 2022. A general lack of awareness among both the public and medical practitioners often delays diagnosis and treatment and thus results in irreversible impairments. Early diagnosis and treatment of leprosy and leprosy reactions can cure the disease and prevent most chronic complications. ■ ■ETIOLOGY M. leprae is an obligate, intracellular, acid-fast staining, rod-shaped bacterium, measuring 1–8 µm in length and 0.3 µm in diameter.

M. leprae mostly appears irregularly stained and fragmented or granu lar, in which case the organism is usually considered to be dead. The few bacteria that are brightly and uniformly stained are thought to be solid, viable bacilli. The morphologic index is a measure of uniformly stained solid bacilli on slit-skin smear examination and is calculated as the percentage of viable bacilli among the total number of bacilli counted under oil-immersion microscopy. On slit-skin smear exami nation at the lepromatous end of the disease spectrum, M. leprae is pre dominantly found in clumps or globi within macrophages (lepra cells). Inside these cells, M. leprae multiplies in unrestricted fashion, and hun dreds of bacilli may be present; the organisms are arranged in parallel arrays placed side by side as a result of the presence of surface lipids (glial substances). The bacteriologic index is a logarithmic-scaled mea sure of the density of bacilli of all forms found in the dermis upon slitskin smear examination, varying from 0 to 6+ (with or without globi) from the tuberculoid to the lepromatous end of the disease spectrum. The bacteriological index falls an average of 1 log unit per year with multidrug therapy. M. leprae infects mainly macrophages and Schwann cells. It has never been grown in artificial media. Reproduction occurs by binary fission, and the organism grows slowly (over 12–14 days) in the footpads of mice. The temperature

required for survival and

proliferation—between 27°C and 30°C—explains the greater impact of the disease on surface areas such as the skin, peripheral nerves, testicles, and upper airways, with less inner visceral involvement. M. leprae remains viable for 9 days in the environment. PART 5 Infectious Diseases Ultrastructural Characteristics of M. leprae Electron micros copy reveals that M. leprae has a cytoplasm, plasma membrane, cell wall, and capsule. The cytoplasm contains structures common in grampositive microorganisms. The plasma membrane has a permeable lipid bilayer containing interacting proteins—the protein surface antigens. Similar to that of other mycobacteria, M. leprae's cell wall, which is attached to the plasma membrane, is composed of peptidoglycans bound to branched-chain polysaccharides; these peptidoglycans are arabinogalactans, which support mycolic acids, and lipoarabinoman nan (LAM). The capsule—the outermost structure—contains lipids, particularly phthiocerol dimycocerosate and phenolic glycolipid (PGL-1), which has a trisaccharide bound to lipid by a molecule of phenol.

Because this trisaccharide is antigenically specific for M. leprae, its detection is helpful in serologic diagnosis of leprosy. Genome of M. leprae Comparative analysis of the genomics of single-nucleotide polymorphisms indicates that four distinct strains of M. leprae originated in East Africa or Central Asia. A mutation spread to Europe and subsequently underwent two separate mutations that were then followed by spread to West Africa and the Americas. The genome of M. leprae is circular. Its estimated molecular mass is 2.2 × 109 Da, with 3,268,203 base pairs and a guanine-plus-cytosine content of 57.8%. Culture Difficulties Compared to the genome of Mycobacterium tuberculosis, that of M. leprae underwent reductive evolution, result ing in a smaller genome rich in inactive or entirely deleted genes. This reductive evolution, gene decay, and genome downsizing all may explain the unusually long generation time and may account for the inability to culture the leprosy bacillus in artificial media. As a result, propagation of M. leprae has been restricted to animal models, includ ing the armadillo and normal, athymic, and gene-knockout mice. These systems have provided the basic resources for genetic, metabolic, and antigenic studies of the bacillus. Growth of M. leprae in mouse footpads also provides a tool for assessing the viability of the bacteria and testing the drug susceptibility of clinical isolates. Immunologic Properties of M. leprae M. leprae induces both humoral and cell-mediated immune responses. The immunogenic components of M. leprae include polysaccharides and proteins. Poly saccharide components induce mainly a humoral immune response, whereas protein components induce both humoral and cell-mediated immune responses. The immunogens in M. leprae form two distinct groups: cytoplasmic antigens and antigens from the mycobacterial cell. As mentioned above, a species-specific phenolic glycolipid, PGL-1, has been identified in M. leprae. Other varieties of M. leprae antigens identified with monoclonal antibodies include antigens of 18, 28, 7, 14, 36, 65, and 70 kDa that may possibly induce an immune response. Mycobacterium lepromatosis In 2008, a new mycobacterial species, M. lepromatosis, was isolated from patients with a special type of dif fuse lepromatous leprosy known as diffuse leprosy of Lucio and Latapí. This clinical variety of leprosy is found mainly in Mexico and Central America. M. lepromatosis is very similar to M. leprae microbiologically and clinically. Microbiologically, both species are acid-fast and noncul tivable and preferentially infect skin and peripheral nerves. Clinically, differentiation of M. lepromatosis from M. leprae in individual patients is not diagnostically necessary since both organisms respond well to the same antimycobacterial regimens. ■ ■EPIDEMIOLOGY Incidence, Prevalence, and Disability The true incidence of leprosy is difficult to establish because the figure is very low and because the initial

signs and symptoms are often insidious, and thus not all cases are detected as they occur. In 2022, as stated earlier, 174,087 new cases were reported to the World Health Organization (WHO) from 182 countries. New case detection per year is commonly used as a proxy for incidence, but operational factors, such as the inten sity of case detection, the use of surveys, the use of contact tracing, the level of community awareness, and the quality and availability of health care, have a profound effect on case detection rates. In nonendemic countries around the world, leprosy is often misdiagnosed simply because it is not considered. The registered prevalence of leprosy is defined as the number of patients receiving treatment at a point in time (usually at the end of a calendar year). The registered prevalence is a proxy measure for true prevalence, which would include existing cases that have not yet been detected. The two factors that determine the registered prevalence are the new case detection rate and the duration of treatment; changes in either factor will affect the registered prevalence. The WHO leprosy disability grading system scores patients accord ing to the presence of disabilities of the eyes, hands, and feet. For the

900,000 800,000 700,000 600,000 500,000 400,000 300,000 200,000 100,000

FIGURE 184-1 Global trend in leprosy new-case detection, 1990–2022. hands and feet, grade 0 means no anesthesia and no visible impair ment; grade 1 signifies anesthesia but no visible impairment; and grade 2 indicates visible impairment. For the eyes, grade 0 signifies no eye problems due to leprosy and no evidence of visual loss; grade 1 signifies eye problems due to leprosy without severe effects on vision; and grade 2 indicates severe visual impairment (vision score worse than 6/60; inability to count fingers at 6 meters) and also includes lagophthalmos, iridocyclitis, and corneal opacities. The sum score for these six body sites is called the Eye-Hand-Foot (EHF) score and is used as an overall indicator of the impairment status of a person with leprosy. Leprosyrelated grade 2 disability is usually reported as the proportion of people with such disability at any site among patients newly diagnosed with leprosy in a specific year. The global trend in new case detection since 1990 is presented in Fig. 184-1. The trend was remarkably static up to the year 2001, with a peak around the year 2000; fell dramatically between 2001 and 2005; and has leveled off from 2006 until 2016. Since 2017, a continuous decline has been observed, but the figures for 2020 and 2021 are unreli able due to underreporting during the COVID-19 pandemic. The most important factor contributing to the fast downward trend after the year 2000 was the decline in leprosy control activities following the decla ration by the WHO in 2000 that leprosy was eliminated as a “public health problem.” Elimination was defined as a prevalence of <1 case per 10,000 population at the global level. The decline in new case detection since 2016 to below 200,000 cases per year indicates that transmission of M. leprae is becoming less and that elimination of leprosy could become possible in the next 25 years or so. Sex, Age, and Geographic Distribution Approximately 40% of all reported leprosy patients are women, but the low proportion in some countries raises concerns about underdiagnosis in women due to poor access to health services, illiteracy, low status, and other cultural factors. The age-specific incidence often shows a bimodal pattern, with peaks in the teenage years and in adulthood. Around 8% of all newly detected cases are found in children (<15 years of age), a measure that is often taken as an indicator of continued (recent) transmission. Leprosy is rare among children <5 years of age. Around 5% of all patients have a grade 2 disability. There are large variations among world regions and countries in new case detection rates. Approximately 80% of global new case detec tion is reported from India, Brazil, and Indonesia. There are also dis tinct geographic variations within countries, with differences between urban and rural communities and clustering of cases at the

village or neighborhood level. Geographic variations can be due to differences in health service provision, socioeconomic development, isolation,

and poverty. Figure 184-2 depicts the geographic distribution of new leprosy cases in 2022. Transmission Understanding of the transmission of M. leprae is limited. The existing evidence is largely circumstantial because of the long incubation period from exposure to disease, the inability to culture M. leprae, and the difficulty of diagnosing both infection and early disease. M. leprae organisms can be shed in large numbers from the mouth and nose of patients with untreated multibacillary leprosy (droplet infection) and sometimes from damaged skin, but it is unclear whether patients with paucibacillary leprosy can spread the bacillus. There is evidence for transmission between humans and—in southern U.S. states—for zoonotic transmission through wild armadillos. The main route of entry into the body is assumed to be the respiratory tract, but in patients with wounds or tattoos, transmission through the skin also is possible. CHAPTER 184 Leprosy Reservoirs of Infection It is assumed that humans are the main reservoir of infection for M. leprae. The armadillo is also a reservoir for human infection. Certain species of monkeys and red squirrels are infected with M. leprae in the wild, but there is no evidence of transmission to humans through contact with these animals. Evidence is weak for the potential of water and soil as environmental sources of M. leprae. The higher incidence rate of leprosy among household con tacts of multibacillary cases than among those of paucibacillary cases suggests that multibacillary cases represent an important reservoir for undetected and untreated cases in the community; that is, a prolonged period between the onset of signs of leprosy and treatment due to a delay in diagnosis and initiation of multidrug therapy increases expo sure in the community. Persons with subclinical leprosy are likely to be a main source of infection, given that multidrug therapy for clinical leprosy apparently has not made an impact on transmission. Incubation Period, the Role of Contacts, and Genetic Sus ceptibility The incubation period of leprosy is estimated to range from 2 to ≥10 years. The incubation period for multibacillary leprosy appears to be longer (5 to ≥15 years) than that for paucibacillary lep rosy (~2–5 years). Poverty-associated factors such as low level of edu cation, poor hygiene, and food shortages have been identified as risk factors for leprosy, but the most important risk factors are associated with intimacy and duration of contact with a leprosy patient, in par ticular with an index case with multibacillary leprosy, and the intensity of contact with and physical distance from the index patient. Increasing evidence from studies in twins and from observational studies supports host genetic susceptibility to leprosy. Ongoing studies are exploring the

New leprosy cases, 2022 – Nouveaux cas de lèpre en 2022

1–10 11–100 101–1000 1001–10,000

> 10,000 No data – Aucune donnée FIGURE 184-2 Geographic distribution of new leprosy cases, 2022. (Reproduced with permission from Global leprosy (Hansen disease) update, 2022: new paradigm-control to elimination. Wkly Epidemiol Rec 98:409, 2023.) PART 5 Infectious Diseases mechanism underlying genetic susceptibility to leprosy and its clinical manifestations. ■ ■PATHOGENESIS Whatever the route of M. leprae’s entry into the human body, the pathogenic

> process usually starts in the peripheral nerves. Once bacilli are engulfed by Schwann cells, the histopathologic changes in nerve and skin—and thus the type of leprosy that develops—depend on the immunologic resistance of the person infected, in particular on the cell-mediated immune (CMI) response to the bacillus and its antigens. Ridley-Jopling Classification of Leprosy In 1962, Ridley and Jopling described five overlapping categories of leprosy: tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and lepromatous (LL). An early clinical manifes tation is recognized and referred to as indeterminate leprosy (IL). Immunologic resistance is strong at the tuberculoid end of the spec trum, gradually diminishes through the borderline spectrum, and is weakest in lepromatous leprosy. The LL and TT types of leprosy are relatively stable, with little or no change in clinical disease expression over time, while the BL, BB, and BT types are unstable both clinically and immunologically. Further distinction indicates that subpolar types of TT and LL leprosy (TTs and LLs) are less stable than polar types (TTp and LLp). The immune reaction depends on predisposing genetic factors and the extent of exposure to M. leprae. The host tissue's reac tion and related damage are largely due to delayed hypersensitivity. In response to the presence of M. leprae, a granuloma is formed either by macrophage–lymphocyte interaction when there is immunity or otherwise by macrophages only. The formation of a granuloma is pre ceded by a stage of infiltration by lymphocytes alone, as is seen in IL. Because of the strong immune response toward the tuberculoid end of the spectrum, macrophages, along with many lymphocytes, become fixed epithelioid cells, and groups of these cells become giant cells. The tuberculoid granuloma leads to nerve destruction resulting in anes thesia and muscle weakness. The cellular response is less focal and less destructive in the borderline portion of the spectrum; consequently, there is less damage to nerves and few bacilli are present. In BL leprosy, there are macrophage granulomas along with lymphocytes, but little nerve damage and more bacilli. In LL leprosy, bacilli multiply within

Schwann cells and perineural cells. Liberated bacilli from these cells are engulfed by histiocytes, becoming wandering macrophages and travel ing throughout the body to other nerves and tissues via blood, lymph, and tissue fluids. In addition, there are diffuse lepromas in LL leprosy that consist of histiocytes and/or macrophages, with very few lym phocytes and plasma cells. The bacilli are packed within macrophages called globi and outside macrophages either singly or in small groups. WHO Simplified Clinical Classification of Leprosy RidleyJopling classification requires clinical and pathologic expertise that does not exist in many settings. The WHO has therefore introduced a simplified classification system based on slit-skin smear: patients with negative slit-skin smear results at all body sites are classified as having paucibacillary leprosy, whereas patients with positive smears at any body site are classified as having multibacillary leprosy. However, because slit-skin smear facilities are not available or dependable in many countries, most leprosy control programs use clinical criteria only for classifying leprosy and deciding on the appropriate treatment regimen for individual patients. In this circumstance, paucibacil lary leprosy is defined as one to

five skin lesions and no or only one involved peripheral nerve, while multibacillary leprosy is defined as six or more skin lesions and/or more than one involved peripheral nerve. ■ ■CLINICAL MANIFESTATIONS Leprosy is a disease affecting mainly the skin, cutaneous and peripheral nerves, mucous membranes, and, less commonly, other sites such as joints, lymph nodes, eyes, and testes. Other systemic manifestations may occur, particularly in BL and LL disease, with or without leprosy reactions. Most dermal and cutaneous nerves feeding skin lesions are affected—e.g., the supraorbital, great auricular, radial cutaneous, infrapatellar, superficial fibular, and sural nerves and the cutaneous nerves of the thigh. The peripheral nerves involved include the ulnar, median, radial (in upper limbs), lateral popliteal, and posterior tibial (in lower limbs). The cranial nerves commonly involved are the tri geminal and facial. Indeterminate Leprosy (IL) This early clinical type manifests as one or a few hypopigmented or faintly erythematous, ill-defined to well-defined macular lesions measuring 1–5 cm in diameter. These lesions invariably occur on the external aspects of the limbs, buttocks,

FIGURE 184-3 Tuberculoid (TT) leprosy. Hypopigmented macular lesion with a welldefined edge and loss of fine-touch sensation. (From Dr. H. K. Kar, with permission.) and face, with mild to moderate impairment of touch and/or thermal sensations. There is no thickening of the corresponding cutaneous and peripheral nerves. IL is often, but not always, the first clinical sign of leprosy. This type either heals spontaneously or progresses to a determinate form of the disease (TT, BT, BB, BL, or LL), depending on CMI status. Tuberculoid (TT) Leprosy TT leprosy (Fig. 184-3) presents either as a well-defined, hypopigmented macule or as a raised,

erythematous/brown/copper-colored plaque with a well-defined edge. The lesions may be found on any part of the skin and are characterized by complete loss of fine touch and temperature sensations over their surface. Skin lesions are single or few (up to three) in number and can be of any size, but they seldom measure >10 cm in diameter. In plaquetype lesions, the raised clear-cut edge often slopes inward to a flattened and sometimes hypopigmented central area, acquiring an annular con figuration. The skin surface of both macular and plaque lesions is dry, hairless, and anesthetic because of destruction of underlying superficial cutaneous nerves. Larger corresponding cutaneous nerves are thick ened in a limited number of cases. On the face, sensory impairment may be difficult to demonstrate because of the generous and bilateral supply of sensory nerve endings. Autonomic nerve damage within the lesion is responsible for surface dryness and loss of sweating over the lesion. A solitary peripheral-nerve trunk in the vicinity of a lesion may be thickened, with sensory loss of the area supplied and with or with out motor disfigurement. On slit-skin smear examination, no acid-fast bacilli (AFB) are normally found. The lepromin skin test is strongly positive, signifying good host CMI status. Borderline Tuberculoid (BT) Leprosy BT leprosy (Fig. 184-4) is characterized by either macular or plaque-type lesions numbering three to nine or more and asymmetrically located on any part of the body, with variable sizes and contours. The margins of the lesions range from poorly defined to well defined; sometimes both forms of margin are seen in one lesion. There may be smaller satellite lesions around a larger one, especially on sides where the margin is less defined; this characteristic indicates downgrading of the lesion from TT to BT leprosy. The edges of plaque lesions may slope outward in contrast to TT lesions, which slope inward; plaques may gradually fade outward and eventually blend into normal-looking skin. Loss of sensation is less intense than it is in TT lesions and dryness on the surface less conspicuous. Several peripheral nerves are likely to be enlarged in an asymmetrical pattern, with sensory and motor deficits. One of the most striking features of BT leprosy is susceptibility to a

type 1 leprosy reaction (T1R; see below) that exacerbates skin lesions and/or periph eral nerves. If not diagnosed and treated early, disease in these patients tends to downgrade across the spectrum to BB, BL, or LLs leprosy, with an increasing bacteriologic index and a regressed CMI response caus ing nerve damage along the way. Slit-skin smears show bacteriologic indices varying from negative to 1+.

FIGURE 184-4 Borderline tuberculoid (BT) leprosy. Macular lesion with irregular, moderately defined edge and satellite lesion, with loss of sensation. (From Dr. W. H. van Brakel, with permission from NLR.) Mid-Borderline (BB) Leprosy This form of leprosy is unstable. Many cases downgrade toward BL and LL disease, especially if not treated. There are multiple plaque lesions and, not infrequently, macu lar lesions; the lesions are of various shapes and sizes, are bilateral, and usually occur in a more or less symmetrical distribution. In annular lesions, the inner edge is well demarcated and "punched out," and the outer edge is ill defined and merges with normal-looking skin. The surface of the lesions is moderately shiny, and the central area looks pale. There is minimal loss of sensation over the lesions. Nerve dam age is variable in BB leprosy. Many nerves may be thickened, and this effect may be asymmetrical. BB leprosy is not commonly observed and rapidly changes its spectrum—rarely to BT leprosy but more often to BL disease. The lepromin test is negative. Slit-skin smears of lesions show a moderate number of AFB (2+ to 3+). CHAPTER 184 Leprosy Borderline Lepromatous (BL) Leprosy In BL leprosy

(Fig. 184-5), there are numerous bilateral, round or oval, macular, dif fusely infiltrated, erythematous or hypopigmented lesions with moder ately defined borders. The lesions are usually 2–3 cm in diameter, may have a coppery hue, and tend to become symmetrical. Some loss of FIGURE 184-5 Borderline lepromatous (BL) leprosy. Numerous diffusely infiltrated erythematous and hypopigmented macules, downgrading from borderline tuberculoid to lepromatous leprosy. (From Dr. C. L. M. van Hees, Department of Dermatology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands, with permission.)

FIGURE 184-6 Lepromatous (LL) leprosy. Multiple nodules on ears and face and loss of eyebrows. (From Dr. K. Mponda, Department of Dermatology, Queen Elisabeth Central Hospital, Blantyre, Malawi, with permission.) PART 5 Infectious Diseases sensation may be detected, particularly over older lesions; however, no loss of sensation is observed over fresh lesions. With disease progres sion, papules, nodules, and plaques develop over the macular lesions. In untreated patients, new ill-defined skin lesions continue to develop. Widespread but asymmetrical thickening of peripheral nerves, with or without tenderness, leads to sensory and motor deficits. The lepromin test gives negative results, as it does in all degrees of lepromatous lep rosy. Slit-skin smear examination of lesions shows a bacteriologic index varying from 3+ to 4+. Lepromatous (LL) Leprosy LL leprosy (Fig. 184-6) pres ents with innumerable bilateral, symmetrically distributed, diffusely indurated, erythematous, copper-colored or skin-colored patches or plaques. There is no loss of sensation over these lesions, which have a smooth, shiny surface. The lesions spread over the face, earlobes, ears, extensor aspects of the upper and lower extremities, back, and but tocks. Induration can readily be recognized when lesions are viewed tangentially under natural sunlight. The induration initially is of a finer type but gradually becomes coarse, and lesions then progress to papules, plaques, and nodules. Bilateral earlobe thickening and eyebrow loss occur. Coarse induration on the face sometimes results in gross skin folds that lead to an appearance referred to as "lion face," particularly when associated with loss of eyebrows and thickening of earlobes. Of all cases of LL

leprosy, 10–15% are of the polar type (LLp) from the time of lesion onset; the remaining cases downgrade from the untreated borderline spectrum to subpolar LLs leprosy. Patients with LLs disease develop nerve damage during the borderline stages. In LLp disease, involvement of peripheral nerves occurs late and is bilateral and symmetrical, with sensory loss in a “glove-and-stocking” distribu tion. Slit-skin smear examination shows a bacteriologic index of 4+ to 6+ with globi. SYSTEMIC INVOLVEMENT In LL leprosy, AFB are found in the lymph nodes, spleen, liver, bone marrow, adrenal glands, smooth and striated muscles, tooth pulp, testes, oral cavity, nose, larynx, and eyes. Involve ment of the testes leads first to sterility and then to gynecomastia and impotence. Eye involvement includes corneal anesthesia; early on, this manifestation is due to bacillary infiltration of corneal nerves, while

later it arises from damage to the ophthalmic division of the trigeminal nerve. In addition, eye involvement includes episcleritis, iridocyclitis, iris atrophy, cataract and glaucoma, lagophthalmos, corneal ulcer ation and perforation, and blindness. The nose is a portal of entry for

M. leprae and is the earliest site of involvement in LL leprosy. Edema and mucosal thickening occur in the inferior turbinate and nasal septum, with crusting and epistaxis. Later, patients develop chronic rhinitis with loss of smell sensation. Septal perforation due to bony destruction, with typical saddle-nose disfigurement, is common in advanced LL disease. In late-stage LL leprosy, ulceration of the tongue, pharynx, hard and soft palates (leading to palate perforation), tonsillar pillars, and uvula occurs. In the hands, slow resorption sets in, starting from the distal end of the terminal phalanx and proceeding proximally to involve the middle and proximal phalanges. HISTOID LEPROSY Histoid leprosy is a rare form of LL leprosy in which waxy, shiny, firm, symmetrical or asymmetrical nodules and plaques are observed over normal-looking skin. Histologic examina tion of these lesions shows specific spindle-cell granulomas. Slit-skin smear examination reveals high bacteriologic and microbiologic indi ces without globi in most cases. DIFFUSE LEPROSY OF LUCIO AND LATAPÍ This rare form of nonnodu lar LL leprosy occurring in Mexico and Central America is character ized by diffuse shiny infiltration of the skin and widespread sensory loss. The skin looks waxy and has a shiny appearance (“lepra bonita,” or beautiful leprosy), with obvious diffuse induration of the earlobes and forehead as well as loss of eyebrows, sometimes eyelashes, and not infrequently all body hair. This form of leprosy can be complicated by an unusual reaction known as Lucio’s phenomenon (see below). Primary Neuritic Leprosy In some countries, such as India and Nepal, primary neuritic disease is observed in 2–10% of all leprosy cases, with only peripheral nerve involvement and no skin lesions. Nerve thickening and sensory loss occur in the affected area, with or without a motor deficit. Primary neuritic leprosy, even though not described by Ridley and Jopling, can manifest at different points along the disease spectrum. For practical purposes, primary neuritic leprosy is classified as paucibacillary or multibacillary on the basis of the absence or presence of AFB in nerve biopsy sections or the number of thickened nerves (single or multiple). ■ ■LEPROSY REACTIONS Leprosy reactions are immunologic phenomena that occur before, dur ing, or after treatment. They are severe complications that need to be diagnosed and treated early to prevent nerve function impairment and subsequent disfigurement as well as blindness. Type 1 Leprosy Reaction (T1R) T1R is a delayed hypersen sitivity reaction associated with sudden alteration of CMI status and leading to a shift in the patient’s position on the leprosy spectrum. This reaction is marked by infiltration of lesions by activated CD4+ T lymphocytes, especially T helper cells. T1R is also called a reversal reaction because of the upgrading of CMI status. T1R is usually observed in the borderline portion of the spectrum. Skin lesions are characterized by acute swelling

and redness (Fig. 184-7). Nerves may be painful and tender because of neuritis, with consequent nerve damage and disfig urement. In the severe form of T1R, nerve abscesses may be formed. Loss of nerve function can be much less obvious than usual when it occurs without other signs of inflammation. This “silent neuritis” may lead to sensory and motor impairment in the hands, feet, and face. Arthralgia or arthritis sometimes occurs. Rarely, the patient may develop fever and malaise, tenosynovitis, and edema of the feet and hands. Type 2 Leprosy Reaction (T2R) T2R, also known as ENL (erythema nodosum leprosum), is an immune complex–mediated syndrome (i.e., an antigen–antibody reaction involving complement) that causes inflammation of the skin, nerves, and other organs as well as general malaise. ENL is an example of a type III hypersensitivity reaction (Coombs and Gell classification) or Arthus phenomenon.

FIGURE 184-7 Type 1 leprosy reaction. Increased inflammation of existing lesions. (From Dr. W. H. van Brakel, with permission from NLR.) This reaction occurs mostly during multidrug therapy but can also develop in untreated patients. Evanescent, pink-to-red, maculopapular, papular, nodular, or plaque lesions suddenly appear and are usually accompanied by constitutional symptoms like malaise and fever, with or without painful swelling in the joints (Fig. 184-8). These crops of skin lesions present on the outer aspects of the thighs, legs, and face. They are painful or tender and warm, blanch with light finger pres sure, and last for a few days. The lesions change in color from pink/ red to bluish and brownish after 24–48 h and turn dark in a week. Rarely, ENL lesions become vesicular, pustular, bullous, and necrotic and break down to produce ulceration (erythema nodosum necroti cans). The patient may have other associated signs such as lymph node enlargement, myositis, arthritis, synovitis, rhinitis, epistaxis, laryngitis, iridocyclitis, glaucoma, painful dactylitis, acute epididymoorchitis, nephritis and renal failure, hepatosplenomegaly, anemia, and—at a later stage—amyloidosis. Severe T2R may include swollen, painful, and tender nerve trunks with sensory and motor deficits. Lucio’s Phenomenon Lucio’s phenomenon is observed in diffuse leprosy of Lucio and Latapí and may be a variant of erythema nodosum necroticans. Marked vasculitis and thrombosis of the superficial and deep vessels result in hemorrhage and infarction of the skin. Clinically, the skin reaction begins as slightly indurated, bluish-red, ill-defined, painful, and rarely palpable plaques with an erythematous halo, usu ally developing on one limb but sometimes on other areas of the body. The lesions are irregular or triangular. After a few days, they become purplish at the center; a central hemorrhagic infarct may develop with or without blister formation, and a necrotic eschar that detaches easily FIGURE 184-8 Type 2 leprosy reaction. Erythema nodosum leprosum, with pustular lesions. (From Dr. H. K. Kar, with permission.)

and leaves an ulcer of irregular shape may follow later. The ulcer heals, leaving a superficial scar. Patients remain afebrile throughout.

Nerve Function Impairment, Neuritis, and Disfigurement

The terms nerve function impairment, nerve damage, neuropathy, and neuritis are often used interchangeably for the sensory, motor, and/ or autonomic nerve deficits that occur because of the pathologic pro cesses resulting from M. leprae infection of the nerve. Neuritis (nerve inflammation) in leprosy is usually a subacute, demyelinating, and unremitting event involving cutaneous nerves and larger peripheral nerves. “Silent neuritis” or “quiet nerve paralysis” is defined as progres sive sensory or motor impairment in the absence of symptoms such as pain, paresthesia, or tenderness

of the nerve and with no obvious signs of leprosy reactions. Neuritis can occur at any time during leprosy but is more common and severe during leprosy reactions, mainly in T1R. Sensory and motor neuropathy can lead to secondary impairments in the upper and lower extremities, such as muscle atrophy, mobile- and fixed-joint contractures, bone absorption of digits, and cracks and wounds. ■ ■DIAGNOSIS Clinical Diagnosis Three cardinal signs indicate a diagnosis of leprosy. The diagnosis can be established when at least one of these three signs are present:

1. Hypopigmented or erythematous skin lesion(s) with definite loss or impairment of sensation: The clinical presentation of skin patches or plaques is diagnostic when it is associated with a definite loss or impairment of sensation (light touch, pain, and/or temperature). Diagnostic dilemmas arise in the indeterminate stage of leprosy because of variable loss of sensation and the presence of facial lesions (i.e., because the density of innervation in the face can com pensate for damage to certain nerve branches).
2. Involvement of the peripheral nerves, as demonstrated by definite CHAPTER 184 Leprosy thickening with sensory impairment: Thickening of a peripheral nerve should be assessed by palpation of the affected nerve and comparison with the corresponding contralateral nerve. In mul tibacillary leprosy, thickening of nerves is often bilateral. Nerve tenderness is established by the application of mild pressure on the nerve during palpation with the fingertips. The peripheral nerves commonly palpated in a leprosy patient are the greater auricular, ulnar, radial, radial cutaneous, median, lateral popliteal, posterior tibial, sural, and superficial peroneal nerves.
3. A positive result for AFB in slit-skin smears, establishment of the presence of AFB in a skin smear or biopsy sample, or a positive result in a biopsy polymerase chain reaction (PCR). Diagnostic Tools • TESTING OF SKIN SENSATION Light-touch sensation is tested with cotton, wool, or a feather. Pain is assessed as the patient’s ability to distinguish between the sharp and blunt ends of a wooden or bamboo toothpick. Thermal sensation thresholds are assessed with computer-assisted sensory testing equipment. SLIT-SKIN SMEAR Normally a slit-skin smear is taken from four sites: the right earlobe, the forehead above the eyebrows, the chin, and the left buttock in men or the left upper thigh in women. The mate rial is stained with Ziehl-Neelsen reagent and examined with a light microscope. The bacteriologic index is determined with a standard logarithmic scale and graded from 0 to 6. The microbiologic index is determined as the percentage of solid, stained AFB. SKIN BIOPSY A skin biopsy is done to confirm the diagnosis of leprosy, to classify the disease, to support the diagnosis of reactions, and to deter mine cure after the completion of multidrug therapy. When macular lesions are suspected of reflecting IL, a biopsy sample should be taken from the middle of a lesion; with plaques, a sample should be obtained from the active indurated edge. When there are numerous skin lesions with different morphologies, more than one biopsy sample is required for proper evaluation of the disease spectrum. Identification of early lesions of leprosy by histopathologic techniques is enhanced by immu nochemical staining, which reveals the presence of M. leprae antigens.

PGL-1 ANTIBODY TEST PGL-1 is a specific lipid on the M. leprae cell wall. A PGL-1 enzyme-linked immunosorbent assay (ELISA) has been used for serologic diagnosis of leprosy, yielding positive results in 90–95% of multibacillary cases and in 25–60% of paucibacillary cases. Using PGL-1 antigen and adopting an immunochromatographic technique, a rapid lateral-flow assay—the ML

flow test—has been developed for detection of antibody to PGL-1. This assay gives posi tive results in 92–97% of patients with multibacillary leprosy and in 32–40% of patients with paucibacillary disease. Recently, a quantitative UPC-LFA (upconverting phosphor lateral flow assay) test has become available, which has a higher specificity in paucibacillary disease.

LEPROMIN TEST The lepromin (or Mitsuda) skin test measures cel lular immunity against lepromin. A bacillary suspension standardized by the number of inactivated M. leprae it contains is injected just under the skin. The reaction to lepromin is measured as induration in

millimeters 3–4 weeks after intradermal inoculation. The result pro vides information about the ability of an individual's T cells to respond to M. leprae and the likelihood of granuloma formation in that indi vidual. A negative lepromin test is generally seen in patients with LL or BL leprosy, indicating the lack of a protective cellular response. GENE AMPLIFICATION (PCR) TECHNIQUE Gene amplification signifi cantly enhances the detection of M. leprae, especially in bacteriologic index–negative leprosy and cases that do not fulfill the criteria for the cardinal signs of leprosy. The several PCR methods developed to amplify different gene stretches in M. leprae include conventional DNA-based PCR, reverse-transcription PCR, and multiplex PCR. As major genes for detection of disease targets, PCR uses M. leprae–specific genes encoding 36-kDa antigen, 18-kDa antigen, 65-kDa antigen com plex 85, 16S ribosomal RNA (rRNA), and repetitive sequences. These assays are sensitive to as few as 1–10 bacilli and yield positive results in 60–75% of smear-negative cases. Multiplex PCR employing the genes encoding the repetitive element RLEP, SodA, and 16S rRNA can be used for early diagnosis and for the diagnosis of subclinical infection among household contacts. PART 5 Infectious Diseases Differential Diagnosis Leprosy is often diagnosed late, with a consequent increase in the risk of nerve damage and its ensuing dis abilities. The hypopigmented macules of leprosy must be differentiated from a variety of conditions, including pityriasis alba, vitiligo, pro gressive macular hypomelanosis, pityriasis versicolor, pityriasis rosea, postinflammatory hypopigmentation, sarcoidosis, post–kala-azar dermal leishmaniasis, and morphea. In the analysis of plaques and nodular lesions, conditions such as granuloma annulare, cutaneous sarcoidosis, cutaneous leishmaniasis, lupus miliaris disseminatus faciei, nodu lar histiocytosis, lupus erythematosus, cutaneous T-cell lymphomas (especially mycosis fungoides), and secondary syphilis should be kept in mind. ENL lesions must be differentiated from erythema nodosum of other etiologies, nodular vasculitis, and cutaneous polyarteritis nodosa. In the case of mononeuropathy lesions, diabetes, amyloidosis, and myxedema must be considered. With polyneuropathy lesions of acute onset, Guillain-Barré syndrome and toxic polyneuropathy must be given consideration. Diagnostic Tools for Nerve Function Impairment All sen sory modalities, autonomic function, and motor function of motor nerves may be affected in leprosy to varying degrees. The modalities mediated by small unmyelinated fibers, such as pain and warm tem perature sensation and autonomic function, are often affected first. Clinically detectable impairment of touch sensation and motor func tion frequently follows after several months. Unfortunately, tools that allow reliable and safe testing of pain and temperature sensation and autonomic function often are not available at peripheral health facili ties, but simple and reliable tests of touch sensation and motor function do provide a reflection of the underlying neuropathy. TOUCH SENSATION TESTING The ulnar and median nerves and the posterior tibial nerve are usually tested for touch sensation. The most reliable test is the Semmes-Weinstein monofilament (SWM) test. If the impairment is of <6 months' duration and/or new nerve function

impairment is diagnosed, glucocorticoid treatment should be given. Because filaments are not available in most peripheral health centers, the WHO recommends that a ballpoint pen be used instead. The test ing protocol is the same as in the SWM test: the stimulus is delivered by touching the test sites with the tip of a ballpoint pen held at an angle of ~45° relative to the skin. VOLUNTARY MUSCLE TESTING Motor function of the hands and feet should be evaluated by voluntary muscle testing. The muscle functions most affected in leprosy are eye closure (facial nerve), finger abduc tion (ulnar nerve), thumb opposition (median nerve), wrist exten sion (radial nerve), and ankle extension (common peroneal nerve). Strength is assessed with a WHO-recommended system as strong, weak, or paralyzed. NERVE CONDUCTION TESTS Testing of nerve conduction parameters is sensitive in detecting early signs of peripheral neuropathy in lep rosy. Sensory nerve conduction parameters are often affected several months ahead of clinical tests (e.g., the SWM test). However, a trial of glucocorticoid treatment of such early changes did not show improved long-term outcomes, perhaps suggesting that the glucocorticoids are unable to switch off or reverse the pathologic process. ULTRASOUND TESTING OF NERVES Palpable enlargement of certain peripheral nerves is one of the cardinal signs of leprosy. Definite enlargement is easy to establish, but milder degrees are much harder to diagnose by palpation. Ultrasound imaging and measurement of nerve diameters—even with portable equipment—can detect nerve enlarge ment accurately. This technique may be used to support the diagnosis of leprosy and may indicate the onset of neuropathy that warrants antiinflammatory treatment. OTHER TESTS OF PERIPHERAL NERVE FUNCTION Pain and tempera ture sensation are commonly affected in leprosy neuropathy. However, these sensations are difficult to test safely and reliably under field conditions. Studies have shown that heat detection thresholds are often affected several months before touch sensation is impaired. Laser Doppler measurement of autonomic vasomotor reflexes is a sensitive method for detection of peripheral autonomic nerve damage in leprosy patients. TREATMENT Leprosy, Leprosy Reactions, and Other Major Manifestations TREATMENT OF LEPROSY Multidrug Therapy Only one multidrug regimen is recommended by the WHO for the treatment of leprosy. This regimen consists of a combination of two or three of the following drugs: rifampin, dapsone, and clofazimine (Table 184-1). The keystone of WHOrecommended multidrug therapy for multibacillary leprosy is a monthly dose of rifampin together with daily doses of dapsone and daily and monthly doses of clofazimine. Patients with paucibacil lary leprosy are treated with two drugs, receiving monthly doses of rifampin and daily doses of dapsone. The treatment duration is 12 months for multibacillary disease and 6 months for paucibacil lary disease. Provided that patients complete therapy, treatment failure rates are very low. Some studies have investigated a uniform regimen of three drugs for 6 months. In a recent systematic review of evidence on the potential benefits and risks of this shorter regimen, the WHO concluded that relevant evidence is limited and inconclusive, with a potential increase in the risk of relapse. Therefore, the WHO does not recommend a shortened treatment duration for multibacillary leprosy. The WHO further recommends supervised intake, but actual practice varies among countries. Through the WHO, multidrug therapy is provided free of charge as blister packs for adults to all countries reporting leprosy. Blister packs are also provided for

TABLE 184-1 WHO-Recommended Multidrug Treatment for Leprosy PAUCIBACILLARY LEPROSYa MULTIBACILLARY LEPROSYb DRUG, AGE GROUP Dapsone Adult 100 mg/d 100 mg/d Child age 10–14 years 50 mg/d 50 mg/d Child <10 years Dose adjusted to body weight Dose adjusted to body weight Rifampin Adult 600 mg monthly 600 mg monthly Child 10–14 years 450 mg monthly 450 mg monthly Child <10 years Dose adjusted to body weight Dose adjusted to body weight

Clofaziminec Adult — 50 mg/d plus 300 mg monthly Child 10–14 years — 50 mg/d plus 150 mg monthly Child <10 years — Dose adjusted to body weight aDuration: 6 doses (6 blister packs). bDuration: 12 doses (12 blister packs). cIn 2018, the World Health Organization (WHO) suggested including clofazimine in the multidrug therapy regimen for paucibacillary leprosy as well, but it is questionable whether this suggestion will be implemented because of the possibility that skin discoloration might compromise compliance. In addition, this alteration would involve a major change in the production of blister packs, which currently do not include clofazimine for paucibacillary leprosy patients (in line with the original WHO recommendation). 10- to 14-year-olds, while younger children are given doses adjusted according to body weight (Table 184-1). Adverse Events • Rifampin Rifampin acts by inhibiting DNA-dependent RNA polymerase, thereby interfering with bacte rial RNA synthesis. Rifampin is well absorbed orally. Hepatotoxicity may occur with a mild transient elevation of hepatic aminotrans ferases, but this reaction is rare at the dosages and intervals recom mended for leprosy and is not an indication for discontinuation of treatment. Because rifampin is given only monthly in WHOrecommended multidrug therapy regimens, the adverse effects recognized from its use in tuberculosis probably do not occur. A monthly dose of rifampin does not cause induction of hepatic cyto chrome p450. Urine discoloration occurs but is harmless. Dapsone Dapsone (4,4-diaminodiphenyl sulfone [DDS]) acts by blocking folic acid synthesis and is only weakly bactericidal. Oral absorption is good, and the drug has a long half-life averaging 28 h. Dapsone has a poor safety profile, and its use should be monitored carefully. In the doses recommended for leprosy, it can cause mild hemolysis and may cause anemia or, rarely, psychosis. Glucose6-phosphate dehydrogenase deficiency seldom causes a problem, and enzyme levels are not routinely tested before the start of mul tidrug treatment. On the other hand, the “DDS syndrome” (also called the dapsone hypersensitivity syndrome) is a severe adverse event that is not uncommon in some countries. It usually devel ops 6 weeks after the commencement of dapsone administration and manifests as fever, skin rash, eosinophilia, lymphadenopathy, hepatitis, and encephalopathy. Other rare but severe cutaneous adverse reactions are erythema multiforme, Stevens-Johnson syn drome, toxic epidermal necrolysis, and exfoliative dermatitis. The fatality rate for DDS syndrome is 10%, with death occurring from liver failure, sepsis, and bone marrow failure. Most patients require treatment with systemic glucocorticoids. In all cases, dapsone treat ment must be stopped. Agranulocytosis, hepatitis, and cholestatic jaundice occur rarely with dapsone therapy. Clofazimine Clofazimine is a brick-red, fat-soluble crystalline dye. The mechanism of its weakly bactericidal action against M. leprae is not known. High drug concentrations are found in the intestinal

mucosa, mesenteric lymph nodes, and body fat. The most notice able adverse event is skin discoloration ranging from red to purple or black, with the degree of discoloration depending on the dosage. Clofazimine can accumulate in active leprosy skin lesions, thus making them more prominent. The abnormal pigmentation usually fades within 6–12 months of clofazimine discontinuation, although traces of discoloration may remain for up to 4 years. The skin dis coloration associated with clofazimine is psychologically distressing for many people. Patients often stop taking the drug because the discoloration is socially disabling for them, alerting their social environment to the fact that they are taking anti-leprosy medication and thus breaking confidentiality about treatment. Urine, sputum, and sweat may become pink during clofazimine administration. Clofazimine also produces a characteristic ichthyosis on the shins and forearms. Adverse gastrointestinal events ranging from mild cramps to diarrhea and weight loss may result from clofazimine crystal deposition in the wall of the small bowel.

Relapse The cure rate for leprosy with multidrug therapy is 99%, but relapse is possible. In multibacillary leprosy, relapse is defined as the multiplication of M. leprae, with an increase of at least 2+ over the previous value in the bacteriologic index at any single site; this change usually occurs in conjunction with evidence of clinical deterioration (e.g., new skin patches or nodules and/or new nerve damage). Relapse rates are well below 1% except among a small pro portion of patients who have a very high bacillary load at the start of treatment (bacteriologic index ≥4). In different studies, four to seven relapses were recorded per 100 person-years. These relapses usually occurred <5 years after the end of multidrug therapy. Since antimicrobial resistance to the combination of drugs used in multi drug treatment is rare, patients with relapse can be re-treated with the same multibacillary regimen. CHAPTER 184 Recognizing a relapse in paucibacillary leprosy can be difficult, as symptoms may resemble T1R. However, relapse of paucibacil lary disease is very rare. Administration of a therapeutic trial with glucocorticoids to patients with new lesions may help distinguish between these two phenomena: a definite improvement within 4 weeks of initiation of glucocorticoid therapy indicates T1R, whereas a lack of response favors the diagnosis of a clinical relapse. Patients with multibacillary disease who present with a relapse are re-treated with the multidrug regimen regardless of any change in classification. Patients with paucibacillary disease require 2 years of monitoring after treatment and patients with multibacillary disease at least 5 years. Reinfection by different strains of M. leprae is possible and can be confused with relapse. Leprosy Rifampin Resistance and Second-Line Drugs Resistance to rifampin has been reported from several countries, although the number of patients involved is small. Evidence on the potential benefits and risks of using alternative regimens for drug-resistant leprosy is not available. Therefore, recommendations provided by the WHO for second-line regimens are based on expert opinion and the known activity of alternative drugs, including the likeli hood of cross-resistance. For rifampin-resistant leprosy, the WHO guidelines recommend daily treatment with at least two second-line drugs—clarithromycin, minocycline, or a quinolone (ofloxacin, levofloxacin, or moxifloxacin)—plus clofazimine for 6 months, followed by clofazimine plus one of the second-line drugs daily for an additional 18 months. Leprosy patients infected with M. leprae resistant to both rifampin and ofloxacin may be treated daily with the following regimen: clarithromycin, minocycline, and clofazi mine for 6 months, followed by clarithromycin or minocycline plus clofazimine for an additional 18 months. TREATMENT OF LEPROSY REACTIONS Type 1 Reactions Oral, short-acting glucocorticoids are the treat ment of choice for T1R. Prednisolone is used most often in an initial dose of 1 mg/kg of body weight once a day, usually with a maximum of 60–80 mg. If standard treatment protocols are followed, as they are in most leprosy programs in endemic countries, an initial dose

PART 5 Infectious Diseases of 40 mg of prednisolone is recommended by the WHO. The dose is tapered slowly, usually by 5 mg every 2 weeks over a period of 20 weeks—a schedule that results in better outcomes and lower reaction relapse rates than the previously recommended 12-week glucocorticoid regimen. However, the clinical response should guide treatment. Patients should be examined every 2 weeks, and the examination should include a quick nerve function assessment. Not infrequently, the reaction flares up again once the daily gluco corticoid dose is tapered to <10–20 mg. The potential benefits of longer treatment should be balanced against the risks of prolonged glucocorticoid use, especially at higher doses. Type 2 Reactions Mild first-time T2R (or ENL) reactions with localized skin nodules may be treated with aspirin and pentoxifyl line. If a rapid effect is needed, the most effective drug to date is tha lidomide, which rapidly suppresses clinical signs, including nerve impairment and iritis. However, the drug is blacklisted in many countries

because of its teratogenicity. If available, it should be given with great caution to women of childbearing age—only after careful counseling and a negative pregnancy test and with strict adherence to contraception. A dose of 100–200 mg is given either once or twice daily. In acute first episodes, thalidomide treatment should be tapered down and stopped after 1–2 weeks. If tissues other than the skin are affected—e.g., the eyes (iritis/uveitis), testes (orchitis), kidneys (nephritis), or joints (arthritis)—longer treatment may be needed until signs and symptoms have resolved. In patients with severe recurrent ENL, a daily thalidomide maintenance dose of 50 mg may be effective in suppressing new episodes. Because of the restricted availability and use of thalidomide, patients with acute ENL are usually treated with glucocorticoids. T2R tends to be transient, often resolving in ~2 weeks. The treatment strategy is therefore to suppress the acute signs and symptoms with high-dose oral prednisolone, quickly tapering treatment in 2–3 weeks either to zero or to a low maintenance dose if the patient has had previous attacks. High-dose clofazimine also is effective in preventing recur rent ENL, but attainment of a maximal effect takes several weeks. The usual regimen is 300 mg daily for 1 month, followed by 200 mg daily for 1 month and, subsequently, 100 mg daily as a mainte nance dose for as long as necessary. Prolonged use of high-dose clofazimine may cause significant adverse gastrointestinal effects. An important side effect of clofazimine is a dark discoloration of the skin. While discoloration resolves gradually after the drug is discontinued, it is one main reason that patients dislike or even refuse to take clofazimine. TREATMENT AND PROGNOSIS OF NERVE FUNCTION IMPAIRMENT Episodes of sensory or motor nerve function impairment without skin signs are common. Neuropathy may occur without obvious neuritis. Still, the treatment of such “silent neuropathy” is the same as that for T1R. High-dose prednisolone is the drug of choice. Some experts think that patients will benefit from nerve decompression surgery, but evidence from randomized controlled trials is lacking. If glucocorticoid treatment is started shortly after the develop ment of nerve function impairment, the prognosis for full recov ery is good. Generally, some recovery can still be expected up to 6 months after onset, but the likelihood of recovery diminishes with every new episode. Generally, nerve function impairment that has persisted for >6 months does not benefit from glucocorticoid treatment. TREATMENT OF (NEUROPATHIC) PAIN Pain is common in people affected by leprosy and is often of neuro pathic origin. Little evidence-based information is currently avail able on the origin and treatment of pain in leprosy. Generally, for the treatment of neuropathic pain, three classes of medication are available: tricyclic antidepressants, phenothiazines, and anticonvul sants (carbamazepine, oxcarbazepine, gabapentin, and pregabalin). These agents can be combined with analgesics and anti-inflamma tory drugs according to the patient’s needs. DISEASE MANAGEMENT DURING TREATMENT Leprosy can be cured effectively, but the long duration of multidrug therapy means that careful management is needed to help the patient complete treatment. Regular visits to a health center may invoke questions from community members that may threaten the patient’s privacy, thus causing the patient mental distress and jeopardizing treatment adherence. Counseling is essential, as are patient-friendly arrangements for collecting treatment drugs. The disease, its treat ment, and its possible complications should be discussed, including a consideration of disease prognosis, the resolution of skin patches, skin discoloration by clofazimine, the lack of contagiousness during multidrug therapy, and the capacity for unrestricted family relations, including marital life and sexual activity. Possible stigmatization, including self-stigmatization, also should be discussed. Because of the diverse complications that are possible, especially in patients with multibacillary leprosy, a multidisciplinary approach to patient management is required. In low-income countries, the responsibility for treatment usually lies with a leprosy control offi cer or a general medical practitioner. In middle- and high-income countries,

the main treatment responsibility usually falls to a der matologist. Additional support should come from a neurologist or neurophysiologist for the diagnosis of nerve function impairment, and a rehabilitation physician, physiotherapist, infectious disease specialist, and/or psychologist may be needed. Occasionally, spe cialist support with regard to orthotics as well as in ophthalmology, occupational therapy, reconstructive surgery, and/or communitybased rehabilitation is indicated. Supervised Multidrug Therapy Regular treatment is important, especially the supervised 4-weekly dose of rifampin and clofazi mine. However, treatment adherence can be facilitated by flexible arrangements; for example, patients can be allowed to take home more than one 4-week blister pack if they will be away for travel or seasonal labor. In such cases, a family member or another respon sible person can be asked to supervise the monthly dose. Monthly Nerve Function Assessment Since nerve damage can be insidious and silent, it is important to conduct a brief nerve function assessment at each clinic visit during multidrug therapy. This regular assessment is especially important in patients with known risk fac tors for nerve function impairment. At highest risk are patients with multibacillary disease, who already have nerve damage at the start of treatment. Their risk of additional nerve damage is as high as 65%. Multibacillary leprosy patients without nerve function impairment at diagnosis and paucibacillary leprosy patients with such impair ment at diagnosis have a 16% chance of developing damage and additional damage, respectively. Patients with paucibacillary disease who do not have nerve function impairment at diagnosis are at low est risk (3%); for them, an assessment at the start and completion of multidrug therapy can be sufficient. Leprosy reactions and new nerve damage may also occur after completion of multidrug treat ment. While the risk diminishes with time, these manifestations can occur up to 3 years after the conclusion of therapy. Health Education During treatment, patients will have questions that need to be addressed in order to ensure their treatment adher ence. Sensitive questions may arise regarding everyday life within the family and at work that, if not addressed properly, could lead to social withdrawal and mental health issues. Crucial points for health education are at diagnosis and at completion of treatment. When communicating the diagnosis, the physician must explain that the disease is caused by a curable microbial infection and must cover the possible discomforts of drug intake, the interruption of disease transmission through drug intake, and the importance of adhering to treatment to achieve a cure. At the completion of multidrug therapy, the emphasis should be on separating the con cept of cure (bacterial activity) from the sequelae of the disease (nerve function impairment, leprosy reactions, and disabilities) and explaining that the patient may need to continue receiving health care, including reconstructive surgery, for the sequelae. Patients often associate cure with the absence of symptoms, which

is not accurate in leprosy. Some patients will experience discomfort during bacterial activity but will have no sequelae after treatment. In others, nerve function impairment or leprosy reactions may cause disfigurement with physical discomfort after cure. These sequelae will need further management and patients at risk should be warned that such posttreatment complications may occur and to report without delay should this happen. Disabilities such as claw hand or neuropathic foot require chronic care. Guidelines After the Completion of Multidrug Therapy Patients should receive counseling at release from treatment. The topics covered should include reassurance that the person is no longer contagious, that in some patients hypopigmentation in skin lesions may not resolve for a long time, and that skin discoloration due to clofazimine will gradually disappear in the following months. Nerve impairment may continue to improve after release from treatment, but this is by no means certain. Most important, patients should be instructed to return to the clinic if

any new skin signs or fresh nerve damage occurs. This situation is not uncommon, is usually due to a leprosy reaction, and should be managed carefully from both a medical and a social perspective, since patients and persons in their environment will interpret this development as “leprosy coming back.” Patients at risk of further episodes of reaction and/or addi tional nerve function impairment (e.g., patients with preexisting nerve function impairment and multibacillary infection or patients who have experienced a reactional episode during therapy) should be asked to return for a check-up every 6 months for at least 3 years after being released from treatment. ■ ■REHABILITATION AND SOCIAL ASPECTS Physical Rehabilitation Peripheral neuropathy and its second ary disabling consequences often require physical rehabilitation. This effort may include reconstructive surgery in the case of facial, ulnar, median, or posterior tibial paralysis. In this case, pre- and postopera tive physical therapy is of crucial importance. Physical therapy is also indicated when muscles are not completely paralyzed or when con tractures are too stiff to allow surgery. Since paralysis is usually accom panied by sensory and autonomic neuropathy, occupational therapy also is helpful; therapists teach patients how to minimize the risk of further injury and other techniques for prevention of disabilities. The key principle is teaching patients and former patients to self-manage their disabilities. In many programs, this teaching occurs in the setting of self-care groups. A well-tested and evidence-based self-care routine for hands and feet consists of inspection, soaking, scraping, and oiling (ISSO). Specifically, in ISSO, the person inspects the affected limbs for hotspots (evidence of too much stress on an area of skin): wounds, cracks, and calluses. Next, the affected limb(s) are soaked in plain water for 15 minutes. While the skin is wet, areas with excess calluses are scraped with a rough stone or another rough object. The skin is then rubbed with petroleum jelly or another nonfragrant oil in order to trap moisture in the skin. If this routine is performed daily, the skin can be kept supple and in good condition, despite sensory and autonomic damage. If sensation on the soles of the feet is impaired, the person must wear protective footwear. Simple footwear (e.g., sandals or sneak ers) available at the local market is adequate as long as it has a strong sole and a soft insole of ethylene-vinyl acetate or microcellular rubber that distributes pressure—an especially important feature when foot muscles are weak or paralyzed or the architecture of the foot is dam aged, as is often the case with neuropathy. In high-resource settings, tailor-made orthopedic shoes can be provided. Mental and Social Support Like other chronic health conditions, leprosy requires patients to cope with the burden of new routines in everyday life. In addition to coping with stigma, they must organize themselves for prolonged treatment, prevention of disabilities, and rehabilitation activities. Moreover, like other neglected tropical dis eases (see “Neglected Tropical Diseases,” below), leprosy may lead to poor mental health. Such diseases are accompanied by social exclusion in the form of poor access to services such as health care, education,

employment, and housing. This exclusion accounts for common mental health comorbidities in leprosy patients and their family mem bers, including depression, anxiety, and suicidal thoughts. Leprosy is probably the most notorious of all stigmatized health conditions, and social stigmatization is the most common issue that triggers mental suffering. Other infectious diseases that raise this issue include HIV infection, tuberculosis, and neglected tropical diseases like lymphatic filariasis, Buruli ulcer, and dermal leishmaniasis. Although the rea sons for stigmatization vary, the manifestations and interventions that effectively reduce stigma are similar across conditions and countries. Therefore, joint interventions addressing health-related stigmas for multiple conditions would be strategically and financially attractive. The need to introduce mental health care in leprosy services is press ing. Therapeutic group meetings among institutionalized

patients and self-care groups at the community level, with a focus on prevention of disabilities and mental well-being, are known to ameliorate depression, encourage self-acceptance, and promote confidence.

NEGLECTED TROPICAL DISEASES Leprosy is one of a medically diverse group of 20 neglected tropical diseases (NTDs). This group includes infectious diseases caused by bacteria, viruses, fungi, and parasites as well as some noninfectious conditions, such as podoco niosis and snakebite. NTDs have been grouped together because they affect 1.5 billion of the poorest people on Earth and have been widely neglected in domains such as public policy, funding, and the develop ment of diagnostics and treatments. Leprosy is the archetypical NTD, featuring all of the common characteristics: a treatable infectious dis ease, a known population at risk, available preventive chemotherapy, disease complications that may lead to severe disabilities, and a per vasive social stigma that leads to discrimination, social exclusion, and severe mental health consequences. Nevertheless, the priority accorded to leprosy on the public health agenda of most endemic countries is very low. By joining hands in advocacy, fundraising, and development of joint control strategies, health care organizations can substantially raise the priority profile of NTDs, benefiting each of the individual disease control programs. Such a joint approach serves the goal of universal health coverage and helps to strengthen health services more effectively than vertical programs are ever able to do on their own. CHAPTER 184 Leprosy ■ ■PREVENTION AND CONTROL Interruption of Transmission and Novel Preventive

Strategies Leprosy control was traditionally based on early case detection and multidrug treatment. Apart from health education and leprosy awareness campaigns, no preventive measures were available. In the 1990s, authorities hoped that the transmission of M. leprae in the community could be interrupted through timely detection of cases and provision of multidrug therapy, leading to a decline in leprosy incidence. Unfortunately, this has not been the case (Fig. 184-1). The inability to reduce leprosy incidence in many countries and the heightened interest in NTDs have invigorated research into new techniques for the diagno sis of disease and infection, leprosy vaccines, enhanced postexposure chemoprophylaxis regimens, epidemiologic tools (e.g., geographic infor mation systems for identifying leprosy hotspots), surveillance of antimi crobial resistance, and alternative drugs and drug treatment regimens. Vaccines Against Leprosy The bacille Calmette-Guérin (BCG) vaccine used against tuberculosis provides varying degrees of protec tion against leprosy and is used routinely as postexposure immuno prophylaxis for contacts of leprosy patients in Brazil. Two promising vaccine candidates are in the pipeline: the MIP vaccine from India, which is based on killed Mycobacterium indicus pranii, and the syn thetic LepVax vaccine developed by the University of Washington’s Infectious Disease Research Institute in the United States. If proven effective, these vaccines, like the BCG vaccine, will be used as postex posure prophylaxis for contacts of leprosy patients. Trials are in early stages, and sufficient proof of efficacy will take years. Postexposure Chemoprophylaxis The introduction of post exposure chemoprophylaxis (PEP) for household and other close contacts of leprosy patients is an important innovation. A large

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