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Neuropathy of Leprosy

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Author: **Ramaratnam Sridharan, MD, FRCP, FAAN**, Head of the Department of Neurology, Professor, Neurology, Chennai Neurospeciality & Research Institute

Ramaratnam Sridharan is a member of the following medical societies: American Academy of Neurology

Coauthor(s): **Nicholas Lorenzo, MD**, Chief Editor, eMedicine Neurology; Consulting Staff, Neurology Specialists and Consultants; **Lakshmi Narasimhan Ranganathan, MD**, Assistant Professor, Department of Neurology, Stanley Medical College, India; **Srinivasaraman Govindarajan, DMRD, DNB**, Staff Physician, Barnard Institute of Radiology, Madras Medical College, India

Editors: **Paul E Barkhaus, MD**, Professor, Department of Neurology, Medical College of Wisconsin; Director of Neuromuscular Diseases, Milwaukee Veterans Administration Medical Center; **Francisco Talavera, PharmD, PhD,** Senior Pharmacy Editor, eMedicine; **Agapito S Lorenzo, MD**, Laboratory Director, Associate Professor, Departments of Neurology, Creighton University and University of Nebraska Medical Center; **Matthew J Baker, MD**, Consulting Staff, Collier Neurologic Specialists, Naples Community Hospital; **Nicholas Lorenzo, MD**, Chief Editor, eMedicine Neurology; Consulting Staff, Neurology Specialists and Consultants

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Background

Leprosy is the most common treatable cause of neuropathy in the world. In all patients with leprosy, the nerve tissue is involved. The dermal nerves are infected in all skin lesions, including those due to indeterminate leprosy of childhood. Clinical examination is often sufficient to reliably diagnose leprous neuropathy.

Clinical leprosy lies between 2 extremes: tuberculoid (TT) and lepromatous (LL) disease. Between the 2 ends of the spectrum lies a broad group designated as borderline and subclassified as borderline tuberculoid (BT), midborderline (BB), and borderline lepromatous (BL). The disease does not remain static but evolves spontaneously or in response to therapy. Transition toward the TT pole is referred to as upgrading (and may lead to a reversal or type I reaction), and transition toward the LL pole as downgrading (leading to type II or erythema nodosum leprosum [ENL] reaction). The reactions reflect abrupt changes in the host-parasite immunologic balance and are associated with acute clinical exacerbations.

In classification based on skin smears, patients with negative smears at all sites are classified as having paucibacillary (PB) leprosy, whereas those with a positive smear at any site are classified as having MB leprosy. Persons with more than 5 skin patches and involvement of more than 1 nerve trunk also are considered to have MB leprosy. The PB group includes TT and BT types, whereas the MB group includes BB, BL, and LL types.

Leprosy is a common cause of neuropathy in developing countries, although it also is seen in developed countries. In the United States, the prevalence of leprosy may increase with increasing immigration from regions in which the disease is endemic.

Pathophysiology

Peripheral nerves and skin are affected most commonly. Although intense bacillemia is common in LL disease, and though organisms can be seen in stained smears of peripheral blood or buffy coats, high temperature or systemic signs of toxicity are absent. Bacilli are also found in the liver, spleen, and bone marrow; however, no clinical signs of visceral organ dysfunction are apparent. Even in the most advanced cases, destructive lesions are limited to the skin; peripheral nerves; anterior aspects of the eyes; and the upper respiratory passages above the larynx, testes, hands, and feet.

Frequency

United States

Leprosy is found in endemic foci in parts of Florida, Louisiana, and Texas that border the Gulf of Mexico. It is also seen in the Spanish-American population of New York City, and in the Asian and Mexican populations of California. As of 1998, 112 cases of leprosy had been reported.

International

The prevalence of leprosy is gradually declining. The registered prevalence as of December 2005 was 219,826 cases, of which 133,119 are from Asia. Brazil, Democratic Republic of Congo, Madagascar, Nepal, Mozambique, and Tanzania have prevalences of greater than 1 case per 10.000 inhabitants. The number of new cases worldwide in 2005 was 296,499, of which nearly two thirds are from Asia. Most cases are concentrated in Southeast Asia, Africa, and South America. Brazil accounts for more than 80% of all cases in Latin America.

Mortality/Morbidity

- Death is rarely immediate. The mortality rate of patients with LL disease is 4 times greater than that of the general population owing to the indirect effects of leprosy. In patients with non-LL leprosy, mortality rates are the same or slightly higher than that of the general population.
- Worldwide, 1-2 million people are visibly and irreversibly disabled because of past and present leprosy. Of these patients with LL disease, 70-75% have eye, hand, and/or foot disabilities.
- According to 1 study, the frequency of nerve function impairment at presentation in regions of endemic disease is 1.7 cases per 100 patient-years at risk in PB leprosy and 12 cases per 100 patient-years at risk in MB leprosy.
- Frequency of new nerve lesions during treatment is 2% in PB leprosy and 11% in MB leprosy.

Race

Leprosy has no racial predilection. Leprosy was endemic throughout the world until the late 19th century, when the incidence in Northern Europe and North America strikingly decreased. At present, leprosy is mostly limited to tropical areas. The LL form is most prevalent in Africa, while the TT form is most frequent in Asia.

Sex

Male individuals are affected more frequently than female individuals, except in some areas in Africa, where prevalence in females is equal or higher than of males.

Age

Leprosy occurs in people of all ages from early infancy to old age, though the disease is extremely rare in infants. About 20% of cases occur in children younger than 10 years.

History

Signs and symptoms vary depending on the type of leprosy.

- General features of leprous neuropathy
  - Sensory neuropathy is far more common than motor neuropathy, but pure motor neuropathy can occur.
  - Mononeuropathy and mononeuritis multiplex can occur, with the ulnar and common peroneal nerves most often involved.
  - Symmetric peripheral neuropathy also may occur.
- Symptoms of leprous neuropathy usually include the following:
  - Anesthetic, painless, nonitchy skin patches: Patients with skin lesions overlying peripheral nerve trunks are at high risk for the development of sensory or motor impairment.
  - Deformities due to weakness and wasting of muscles innervated by the affected peripheral nerves (eg, claw hand or foot drop secondary to muscle weakness)
  - Sensory symptoms such as diminution to complete loss of sensation, paresthesias in the distribution of affected nerves, and neuralgic pain when the nerve is struck or stretched
  - Spontaneous blisters and trophic ulcers consequent to sensory loss
- Symptoms seen in reactions
  - Reversal reaction - Sudden onset of redness of the skin and appearance of new skin lesions

- ENL reaction - Multiple skin nodules, fever, joint pains, muscle pains, and redness of eyes
- Severe neuritic pain and rapid evolution of peripheral nerve damage resulting in claw hand or foot drop

Physical

The type of leprosy determines the evolution, pattern, and extent of sensory loss and paralysis. Distinction between TT and LL leprosy is discussed in detail in Leprosy. The Table below highlights the salient differences between the 2 extremes of the spectrum constituting clinical leprosy. Physical signs due to intracutaneous nerve damage may differ from those due to involvement of major nerve trunks.

Differences between TT and LL Leprosy

Clinical Feature or Test	TT Leprosy	LL Leprosy
Skin lesions		
Number	One or few	Numerous
Sensation	Absent	Not affected
Surface	Dry and scaly	Shiny
Hair grown in lesions	Absent	Not affected
Nerve enlargement		
Cutaneous nerves	Common	None
Large peripheral nerves	Rare	Symmetric
ENL reactions	None	Common
Lepromin test	Strongly positive	Negative
Bacillary index	0	5 or 6
Skin histology		
Granuloma cell	Epithelioid	Foamy histiocyte
Lymphocytes	Strongly positive	Positive or negative
Dermal nerves	Destroyed	Easily visible
Prognosis	Good	Poor

- Cutaneous (or integumentary system): Characteristic cutaneous lesions confirm the diagnosis in more than 50% of patients.
- Peripheral nerve hypertrophy
  - Nerve trunks are enlarged palpably in 40-55% of patients; this sometimes predates sensory loss in the corresponding nerve territory.
  - Nerve hypertrophy must be differentiated from a healthy nerve that may be palpable.
  - Sensory cutaneous nerves running to the proximal edge of a skin lesion may be thickened in TT and BT leprosy.
    - Nerves with a predilection for thickening include the great auricular nerves, supraclavicular nerves as they cross the clavicle, ulnar nerves just above the elbow, dorsal cutaneous branches of the ulnar nerve at the wrist, the median and superficial radial nerves, the femoral cutaneous and lateral popliteal (common peroneal) nerves as they wind round the neck of the fibula, the superficial peroneal nerves in front of the ankles, the posterior tibial nerves immediately below the internal malleoli, and the sural nerves. The ulnar nerve is most commonly thickened.
    - Thickening is usually confined to 1 nerve in TT disease.
    - In LL disease, increase in nerve size is symmetrical. However, degree of nerve thickening may differ between the 2 sides. The enlargement often may be segmental rather than diffuse and uniform.
    - Disparity may be noted between specific areas of thickened nerves and distribution of sensory/motor signs.
- Cranial nerves
  - Facial nerve palsy due to involvement of branches to the frontalis or orbicularis oculi leads to frontalis weakness or lagophthalmos. It may be unilateral or bilateral but spares other muscles innervated by the facial

nerve.
    - Sensory loss may occur in the malar region and cornea.

- Motor system
    - Wasting and weakness usually progress pari passu (ie, at the same rate). In some patients, however, wasting is more prominent than weakness.
    - These signs involve predominantly the ulnar nerve at the elbow, median nerve at the wrist, and common peroneal nerve at the fibular head.

- Sensory modalities
    - Thermal sensation is affected first, followed by pain and touch. Proprioception and vibration modalities often are preserved.
    - Topographical distribution of sensory loss is variable.
    - Graded sensory testing with standardized nylon microfilaments or computer-assisted sensory examination (CASE) may be helpful to detect early sensory loss.

- Deep tendon reflexes: These are generally preserved because the muscle spindles and large-fiber nerves are not involved.
- Extremities, deformities, and trophic changes
    - Claw-hand deformity (usually indicating ulnar nerve involvement) is most common, though it is a nonspecific manifestation of leprosy (see Media file 1).
    - Trophic ulcers, a common, nonspecific complication of pain sensation loss, occur on the sole of the foot and the hands/fingers (see Media file 2).
    - Absorption of fingers and toes may be noted.

- Autonomic system
    - Autonomic nerve involvement is manifest clinically as varying degrees of impaired sweating and possible anhidrosis.
    - Visceral autonomic nerves are not involved generally, though conflicting experiences with cardiac dysautonomia have been reported.

- Reversal reaction
    - Physical findings include erythema and edema in skin lesions. New skin lesions appear.
    - Affected nerves increase in size and become tender with signs of damage of involved nerves.

- ENL reaction
    - Reaction is characterized by acute peripheral nerve damage leading to claw hand or foot drop.
    - The involved nerve trunk—usually ulnar just above the elbow, median at the wrist, lateral popliteal at the fibular head—becomes tender and increases in size.
    - Other features include multiple acute and tender skin nodules, arthritis, edema, hepatosplenomegaly, lymphadenopathy, orchitis, and iridocyclitis.

Causes

- Microbiology
    - The agent that causes leprosy, *Mycobacterium leprae,* is the only mycobacterium known to infect nervous tissue; it was the first bacterial pathogen to be associated with a specific human disease.

    - The Koch postulates have never been fulfilled because the bacterium has not been cultured in vitro.

    - *M leprae* is an obligate intracellular organism that preferentially proliferates in tissues of cooler temperature.

    - *M leprae* is a strongly acid fast, rod-shaped organism. It has parallel sides and rounded ends, measures 1-8 µm in length and 0.2-0.5 µm in diameter, and closely resembles the tubercle bacillus.

    - Under an electron microscope, *M leprae* is seen as dark, osmiophilic inclusions located in a cytoplasmic vacuole containing a phenolic glycolipid-1 (PGL-1) and liporabinomannan, both of which *M leprae* produces in large amounts.

    - PGL-1 is the best-characterized virulence factor; it is a prominent surface lipid specific to *M leprae.*

        - PGL-1 binds to complement component C3, which in turn mediates phagocytosis of the bacterium by mononuclear phagocytes via CR1, CR3, and CR4 receptors on their cell surfaces.

        - Once inside the phagocyte, PGL-1 helps to protect the bacterium from oxidative killing by chemically scavenging hydroxyl radicals and superoxide anions.
    - *M leprae* exhibits the longest reproduction time of any bacteria, requiring 13 days to double in experimentally infected mice.
    - *M leprae* has been cultured in vivo using the mouse footpad inoculation method (Shepherd) or by inoculating thymectomized irradiated (TR) mice.
        - The TR mouse has been used to detect small numbers of viable organisms and is used to detect persistent disease after treatment.
        - The mouse footpad model has been used to test the minimum required concentration of drugs and sensitivity of bacilli to new drugs.
    - Reservoirs of infections
        - The 9-banded armadillo (*Dasypus novemcinctus*) also can be infected with *M leprae.* This animal has become the main source of *M leprae* for genetic, biochemical, and immunological research, including development of a vaccine.
        - Approximately 5% of armadillos in Louisiana have naturally occurring clinical disease. About 20% have serologic evidence of infection with organisms indistinguishable from *M leprae.* However, only occasional cases are reported among individuals handling armadillos. Naturally occurring infection also has been reported in the African chimpanzee, sooty mangabey, and cynomolgus macaque.
        - Persons with MB leprosy are the most important reservoir of infection.
    - Portals of entry and exit
        - Portal of exit of *M leprae* - Skin and nasal mucosa
        - Portal of entry of *M leprae* - Skin and upper respiratory tract
    - Method of transmission of leprosy
        - Skin-to-skin contact
        - Respiratory route: Evidence in favor is inability to detect the organism on the surface of the skin.
        - Large numbers of morphologically intact organisms can be demonstrated in the nasal discharge.
        - *M leprae* may survive outside the human host for several hours or days.
        - Experimental transmission of leprosy has been accomplished through aerosols containing *M leprae* and by topical application in immune-suppressed mice.
    - Vectors
        - In experimental studies, acid-fast bacilli (AFB) have been demonstrated in biting insects.
        - Successful transmission of *M leprae* by intracutaneous inoculation in the mouse footpad model has been reported.
        - However, the question whether insects transmit the infection remains unanswered.
- The following mechanisms may explain the entry of *M leprae* into the nerves.
    - Bacilli may enter through naked nerve filaments in the epidermis and travel through the axon. However, intra-axonal bacilli are detected rarely.
    - Bacilli may be phagocytosed by Schwann cells in the skin, where they multiply and are passed to adjacent Schwann cells.
    - Macrophages in the upper dermis take up *M leprae,* which then aggregate around nerve bundles. They may release bacilli, which are ingested by perineurial cells (which pass the bacilli to Schwann cells), or *M leprae*–laden macrophages themselves infiltrate the perineurium.

- Perivascular intraneural granulomata may be found in TT Hansen neuritis; therefore, bacilli may spread through the bloodstream and reach the nerve by means of the intraneural capillaries.
- Inside the nerves, the bacillus is offered immunological protection by the Schwann cell basement membrane, multilayering of the perineurium, absence of lymphocyte recirculation within the fascicles, and the blood-nerve barrier.

- Possible factors in mechanism of nerve damage
  - Temperature: Nerves in cool body parts are involved preferentially.
  - Mechanical factors
    - Affected nerves are usually superficial nerve trunks, those commonly prone to compression, or those situated in confined spaces.
    - Angulation stresses due to joint movement and external pressure also contribute.
    - Edema, inflammation, and swelling at sites of predilection for entrapment result in increased intraneural pressure.
  - Vascular factors
    - Histologic studies have identified vasculitic changes in small-sized arteries and arterioles (intraneural blood vessels).
    - Angiographic studies have revealed abnormalities in medium-sized vessels as well.
    - The consequent ischemia may be one of the factors leading to neuropathy.
  - Genetic and immunologic factors
    - These are discussed in detail in the article Leprosy.
    - The basis for the conspicuous destruction of nerve structure is thought to be a delayed hypersensitivity reaction with specific helper T cells reacting with *M leprae.*
    - Leprae antigens are presented in the endoneurium by macrophages.
    - Activation of macrophages leads to release of secretory products including neural proteases, potent oxidizing agents, and free radicals.
    - A delayed hypersensitivity reaction in the endoneurium can cause major damage or even necrosis and intraneural abscesses.
  - Cytokines and chemical factors
    - Roles of interferon-gamma and interleukins are discussed in detail in the article Leprosy.
    - Tumor necrosis factor (TNF) has been shown to induce demyelination; therefore, chronic production of TNF in lesions of leprosy may be related to some aspects of nerve damage.

- Factors determining clinical expression after infection
  - Susceptibility
    - About 90% of the population is not susceptible. Children are more susceptible than adults.
    - Immunologic and epidemiologic studies suggest that only 10-20% of those exposed to *M leprae* develop signs of indeterminate Hansen disease; only 50% of those with indeterminate disease develop full-blown clinical leprosy.
    - Spontaneous healing has also been reported in TT leprosy.
  - Host immunity
    - When host immunity is intact, organisms are routed and no disease occurs.
    - If immunity is good, organisms are contained, and TT disease occurs.

        - In subjects with moderately good immunity, a seesaw battle occurs and results in borderline types of leprosy.
        - In persons with poor immunity, LL disease occurs.
    - Route of entry of the organism
    - Previous infection with other mycobacteria
    - Genetic factors (type of human leukocyte antigen)
- Incubation period
    - This period is difficult to define because of the lack of adequate immunologic tools and because of the insidious nature of the onset of leprosy, which is usually 3 or more years in TT disease and 8 or more years in LL disease.
    - The minimum incubation period reported is as short as a few weeks; this is based on the rare occurrence of leprosy among infants just 3 weeks old.
    - The maximum incubation period reported is as long as 30 years or more, as observed among war veterans exposed for short periods in areas of endemic disease but otherwise living in areas where the disease is not endemic.
- Other diagnostic considerations
    - Diseases characterized by wasting of small muscles of the hand
        - Syringomyelia
        - Motor neuron disease
        - Cervical myeloradiculopathies
        - Carpal tunnel syndrome
        - Ulnar nerve entrapment at elbow
    - Mononeuropathy multiplex
        - Rheumatoid arthritis
        - Polyarteritis nodosa
        - Diabetes
    - Symmetric polyneuropathy due to other causes
    - Small-fiber neuropathies due to amyloid or hereditary sensory neuropathy
    - Entrapment neuropathies
    - Dapsone-induced motor polyneuropathy
    - Sensory perineuritis affecting subcutaneous sensory nerves
    - Hypertrophic neuropathies
        - Amyloidosis
        - Hereditary motor sensory neuropathies
        - Refsum syndrome
        - Neurofibromatosis
        - Recurrent trauma
    - Diseases characterized by trophic ulcers

        - Tabes
        - Diabetic neuropathy
    - Congenital indifference to pain
    - Hereditary sensory neuropathy
    - Hysterical and/or functional disease

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DIFFERENTIALS

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Radial Mononeuropathy
Sarcoidosis and Neuropathy
Spinal Muscular Atrophy
Syringomyelia
Ulnar Neuropathy

Other Problems to be Considered

Cervical myeloradiculopathies
Mononeuropathy multiplex due to rheumatoid arthritis
Symmetric polyneuropathy due to other causes
Small-fiber neuropathies due to amyloid or hereditary sensory neuropathy
Dapsone-induced motor polyneuropathy
Sensory perineuritis affecting subcutaneous sensory nerves
Hypertrophic neuropathies due to amyloidosis
Hypertrophic neuropathies due to recurrent trauma
Diseases characterized by trophic ulcers
Congenital indifference to pain
Hysterical and/or functional disease

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WORKUP

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Lab Studies

- Complete blood cell count
- Blood glucose, BUN, creatinine, liver function tests
- HIV serology, when appropriate
- Skin and nasal smears for AFB
- Immunologic tests
    - Lepromin test
        - Lepromin is a suspension of killed *M leprae* obtained from infected human or armadillo tissue. Following intradermal inoculation, early (48 h, Fernandez) reactions and late (3-4 wk, Mitsuda) reactions may be seen.
        - The Mitsuda reaction, a granulomatous response to the antigen, is more consistent. Patients with TT or BT leprosy have strongly positive (>5 mm) responses, whereas patients with LL disease do not respond.
        - The test is not useful in the diagnosis of leprosy because most of the population in both areas of endemic disease and areas in which disease is not endemic are Mitsuda positive.
        - The lepromin test is a guide to the cell-mediated immunity of the individual.
        - Lepromin is not available in the United States.
    - Cellular immune response against *M leprae* also can be studied by lymphocyte transformation test (LTT) and lymphocyte migration inhibition test (LMIT). Response decreases steadily in the progression from subpolar TT to subpolar LL leprosy.
    - Tests based on detection of *M leprae* antibodies or antigens include serologic tests, tissue tests, and polymerase chain reaction (PCR)–based genetic tests.
    - Serologic tests
        - Major serologic assays include fluorescent antibody absorption test (FLA-ABS), radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), passive hemagglutination assay (PHA), serum antibody competition test (SACT), and particle agglutination assays (PAA).
        - Important serologic tests are FLA-ABS test and PGL-1 ELISA, which have been simplified further as dot ELISA and dipstick ELISA.
        - However, serologic responses persist for considerable time after subsidence of disease and are not useful in assessing disease activity.
    - Estimation of *M leprae*–specific components in tissues
        - *M leprae*–specific antigens, nucleic acids, and lipids are assessed with thin-layer chromatography, high-pressure liquid chromatography, gas-liquid chromatography, and mass spectrometry.
        - Lipids such as mycolic acid and phenolic glycolipid are characteristic of mycobacteria, including *M leprae.*
        - Tests to detect the epitope on *M leprae* antigens by using monoclonal antibodies or ELISA have been devised, but their high rate of false-positive reactions, especially in tropical countries, has decreased their positive predictive value for activity of the disease.
    - Recombinant DNA and PCR techniques
        - Gene probes have been developed for demonstration of *M leprae*–specific sequences in various specimens, such as skin and/or nasal smears, biopsies, tissue sections, and blood.
        - DNA-targeting probes have sensitivity of 10,000-100,000 organisms. Hence, they are not likely to be useful for a PB leprosy relapse. The signals may persist after bacterial death.
        - RNA (ie, mRNA, rRNA) targeting probes: These probes can detect 100-1000 bacteria and correlate better than the DNA-targeting probes with the presence of viable organisms.
        - Various PCR techniques to amplify the DNA of *M leprae* have been described, and these amplified sequences of target DNA can be detected by either gel electrophoresis or specific gene probes.
        - Very low bacterial loads (<10 bacilli) can be detected.
        - About 60-75% of patients with smear-negative PB leprosy have positive results on PCR. After chemotherapy, signals become weaker; therefore, PCR can be used to monitor treatment, confirm relapses, or determine the need for chemotherapy in patients presenting with reactions.
        - PCR methods for identifying the DNA, which encodes *M leprae* proteins of 65 and 18 kd and repetitive sequences of *M leprae* have been developed.

Imaging Studies

- Chest radiography
- Radiography to detect bone involvement
  - Radiographs may reveal features of periostitis and osteomyelitis, commonly in the epiphyseal and metaphyseal regions of the small bones of the hands and feet, especially the phalanges.
  - The tubular bones of the extremities and the ribs may be rarely involved because of hematogenous spread.
  - Facial involvement may take the form of maxillary alveolar and nasal spine destruction resulting in a constellation of facial deformities known eponymously as Bergen syndrome. Symmetrical periostitis of the tibia, fibula and the ulna may occur.
  - In rare cases, leprous arthritis may result because of direct extension from a focus of leprous osteomyelitis.
  - Most commonly, neuropathy and secondary infection affects the joints of the hands and feet.
  - Motor denervation results in concentric atrophy and resorption of cancellous bone resulting in the licked–candy-stick appearance.
  - Neuropathic osteoarthropathy results in cartilage erosion and fragmentation, bony eburnation, fragmentation, and destruction with a large serous effusion.
  - Secondary infection may result in osteomyelitis.
- MRI or CT of neuropathic joints when appropriate
- Magnetic resonance (MR) neurography in special situations
  - MR neurography can be performed by using custom-made, high-resolution phased-array coils and a variety of fat-saturation sequences to study gross nerve morphology and internal fascicular architecture. This technique has been used to assess the presence of neuropathy, including active reversal reactions.
  - TT leprosy results in nerve thickening and abscesses that may be detected as thickened nerves with increased signal intensity on T2-weighted images.
  - Nerve entrapment in osseofibrous tunnels occur in leprosy. Compression of the nerve appears as flattening of the normal circular cross-sectional appearance of the nerve with increased signal intensity on T2-weighted images, and the presence and configuration of the osseofibrous tunnels may be apparent on MRI.
  - Alteration in the fascicular architecture, increased signal intensity on T2-weighted images, and gadolinium enhancement are observed in nerves affected by acute reversal reactions. With treatment, normal T2 signal intensity and reduced enhancement have been reported.
  - The fascicular architecture is completely lost in many patients with ENL.
- Ultrasonography and Doppler ultrasonography
  - High-frequency linear ultrasound probes can be used to demonstrate thickening of nerves and presence of osseofibrous compression.
  - Doppler study documents increased endoneurial blood flow in nerves in acute reversal reactions, which has been shown to resolve after treatment with steroids.

Other Tests

- Nerve-conduction studies
  - Abnormalities include the following:
    - Segmental slowing of conduction at common sites of entrapment (eg, elbow segment of the ulnar nerve)
    - Prolonged distal latencies
    - Reduced (sensory or motor) nerve conduction velocities
    - Reduced amplitude of compound muscle action potentials
    - Absent or low-amplitude sensory nerve action potentials

        - Pattern of abnormalities suggesting mononeuropathy, mononeuropathy multiplex, entrapment neuropathy, or generalized polyneuropathy
    - The ulnar, common peroneal, median, and tibial nerves are most commonly involved.
    - Changes in nerve conduction are more severe if the nerves are clinically affected than if they are not.
    - Nerve-conduction velocity may be decreased before any sensory deficit appears, and this finding can be used to detect asymptomatic nerve involvement.
    - Conduction velocity in the index branch of the radial cutaneous nerve can be reduced in early leprosy and even in the contacts of patients with leprosy.
    - Similar studies in the dorsal cutaneous branch of the ulnar and the great auricular nerves can also be useful.
    - In LL disease, nerve thickening is not correlated with impaired nerve conduction.
    - Palpably enlarged nerves may be functional, though they may eventually fail.
- Other neurophysiologic findings
    - Prolongation of the refractory period is considered a more sensitive parameter than conventional motor or sensory conduction in detecting early nerve damage in clinically asymptomatic nerves.
    - Abnormalities in visual and brainstem auditory evoked potentials have been reported in LL disease, suggesting CNS involvement.
- Autonomic tests
    - Sympathetic skin response (SSR) may be absent initially, but can be recorded in approximately 16% of patients after treatment.
    - Fingertip blood-flow velocity and its control by vasomotor reflexes (as tested by using a laser Doppler flowmeter), fingertip skin temperature, and SSR have been valuable in the evaluation of early leprous neuropathy. Findings may be abnormal even in preclinical infection.

Procedures

- Skin biopsy
    - May lead to a diagnosis when a skin patch is sampled
    - Useful for the diagnosis and proper classification of leprosy
    - Skin and nasal smears for AFB: Details regarding skin and nasal smears are given in the article on Leprosy.
- Nerve biopsy
    - Nerve biopsy occasionally reveals abnormalities, even in contacts of patients with leprosy.
    - Findings from nerve biopsy may rule out other diseases, such as polyarteritis nodosa, hereditary neuropathies, and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Even in regions of endemic disease, not all persons with thickened nerves have leprosy.
    - In purely neuropathic leprosy, nerve biopsy is the only way to confirm the diagnosis.
    - Nerve biopsy is probably more sensitive than skin biopsy, although false-negative histologic findings may be seen when clinically uninvolved nerves are sampled.
    - Skin and nerve histologic findings are often incongruous. Patients with MB leprosy in the nerves may have PB in the skin.
    - The best results are obtained when the results are interpreted in laboratories with special expertise in these diseases.
    - Biopsy of a clinically involved cutaneous nerve may be more informative than routine biopsy of the sural nerve, radial cutaneous nerve, or dorsal branch of the ulnar nerve.
    - Sural nerve biopsy is usually performed at the level of the lateral malleolus, where it passes between the calcaneum and the lateral malleolus.

- Biopsy of the radial cutaneous nerve or dorsal branch of the ulnar nerve is at the level of the dorsum of the wrist.
- Fascicular nerve biopsy causes less sensory deficit than full-thickness biopsy.
- The nerve-biopsy specimen is divided into 5 pieces, each treated with 1 of the following fixatives:
  - Formalin for hematoxylin and eosin and silver stains for axons
  - Flemming solution for myelin stains (Weigert-Pal technique)
  - Glutaraldehyde for electron microscopy
  - Formol-calcium solution for teased-fiber preparations
  - Frozen specimen for enzyme histochemical techniques

- Aspiration cytology
  - The first step is performing a nerve block proximal to the site of aspiration.
  - A syringe filled with isotonic saline and fitted with an 18-gauge needle is used.
  - The nerve to be aspirated is fixed between the clinician's thumb and index finger, and the needle is inserted into the nerve as parallel to the fascicles as possible.
  - The aspirated material may demonstrate AFB.
  - Cytologic studies of fine-needle aspirates from skin lesions and lymph-node aspirates of patients with LL disease may be diagnostically useful.

Histologic Findings

Histologic findings on skin biopsies vary according to the type of leprosy.

- Indeterminate leprosy
  - A few cells cuffing the dermal appendages and neurovascular bundles
  - A few *M leprae* in cutaneous nerves
- TT leprosy
  - Noncaseating granulomas formed by epithelioid cells, lymphocytes, and giant cells
  - Destruction of normal dermal nerves
  - Loss of normal skin organs (eg, sweat glands, hair follicles)
  - Bacilli frequently absent or difficult to demonstrate
- LL leprosy
  - Normal epidermis: The rete is flattened, and clear space separates the epidermis from the diffuse granulomatous reaction with macrophages, large foamy histiocytes (Virchow or lepra cells), and many intracellular AFB, which are frequently in spheroidal masses (globi).
  - Absent epithelioid cells and giant cells
  - Granulomas, most numerous around blood vessels, nerves, and skin appendages.
  - Plasma cells (occasional)
  - Easily visible dermal nerves
- BT leprosy
  - Epithelioid granulomas with lymphocytic preponderance

- Dermal nerves mostly destroyed
- Scanty or absent bacilli

- BB leprosy
  - Epithelioid granulomas
  - Possibly visible dermal nerves
  - More frequent bacilli than in BT leprosy
- BL leprosy
  - Granulomas formed by histiocytes
  - Dermal nerves visible
  - Bacilli seen in greater numbers than in other types
- Reversal reaction
  - Granulomas formed by epithelioid cells and lymphocytes
  - Extracellular edema in dermal collagen with dilated lymphatics and/or proliferation of fibrocytes
  - As the reactions clear, lesions healing with reduction or eradication of bacilli
- ENL reaction
  - Massive influx of polymorphonuclear cells
  - Possible deposition of complement and immunoglobulin in a granular pattern around dermal vessels
  - More numerous bacilli than in other reactions
  - Histologic studies not useful for assessing clinical activity because granulomas persist after clinical improvement.
- Nerve biopsy findings in LL
  - Light microscopy
    - Overall nerve structure is preserved.
    - Involvement is asymmetric between and within individual fascicles.
    - Nerve cross-sections show an inflammatory reaction affecting the epineurium and perineurium, causing increased nerve volume.
    - Macrophages and Schwann cells filled with organisms and debris (foamy cells) appear in the epineurium, endoneurium, and perineurium. In the perineurium, foamy macrophages infiltrate and separate individual layers, fibroblasts and perineurial cells proliferate, and collagen is deposited. This produces onion skinning of the nerve fascicles.
    - Proliferation of connective tissue (peri and endoneurial fibrosis) is not as prominent as in TL disease.
    - Lymphocytic vasculitis affects nerve blood vessels in all nerve compartments. The vessels remain permeable to blood. This feature is seen in persons who have received treatment for leprosy prior to the biopsy.
    - *M leprae* are extremely numerous, often found in globoid clumps on Ziehl-stained paraffin-embedded specimens. They are found in all nerve compartments and affect a large variety of cells, including perineurial cells, fibroblasts, cells of the macrophage histiocyte lineage, Schwann cells, and endothelial cells. Fite, auramine rhodamine, or toluidine blue (in plastic-embedded sections) also demonstrates *M leprae.* A few viable *M leprae* in Schwann cells persist even after treatment completion.

- Myelin and silver (axon) stains
  - Small myelinated and unmyelinated fibers are lost in early stages. Large myelinated fibers are lost in later stages.
  - Symptomatic neuropathy is associated with severe axonal loss. Nerve fiber density decreases to 5% of the control, compared to 25-30% in silent hypertrophy of the radial cutaneous nerve.
- Electron microscopy
  - Organisms are seen as membrane-bound, round- or rod-shaped, electron-dense structures. They often are surrounded by a clear halo, which is composed of bacterial metabolites and/or denatured host cytoplasmic components.
  - Bacteria are found easily in macrophages and Schwann cells of unmyelinated fibers but less frequently in Schwann cells associated with myelinated fibers.
  - In early leprous neuropathy, electron microscopy demonstrates naked or thinly myelinated axons, suggesting primary demyelination. Axonal pathology appears at a late stage.
  - Endothelial cells may appear swollen, with loss of cell junctions and other signs of damage to the blood-nerve barrier. Multilayering and thickening of the basement membrane around vessels occurs in all types of leprosy but is a nonspecific change of many chronic neuropathies.
- Teased-fiber preparation
  - In patients with silent hypertrophy of the superficial radial cutaneous nerve, this preparation reveals segmental abnormalities of the myelin sheath, including segmental demyelination, a wide nodal gap between 2 internodes, and short remyelinated internodes.
  - Demyelinated fibers often are clustered and linked closely with debris-laden macrophages.
  - Axonal degeneration of nerve fibers predominates in some.
  - In experimental animals, segmental demyelination was predominant during early infection. Axonal degeneration was evident in advanced infections.
- Pathological findings in PB (TT) leprous neuropathy
  - The nerve may be completely destroyed and normal nerve structures may not be identifiable.
  - Involvement also may be multifocal, with damaged fascicles found adjacent to entirely normal ones.
  - Perineurium is thickened markedly, often fused with the epineurium into a thick fibrotic mass and infiltrated by inflammatory cells and small vascular channels.
  - The entire endoneurium may be replaced by a single granuloma. Caseation necrosis may occur and may even progress to a nerve abscess.
  - Granulomas consist of epithelioid histiocytes, multinucleated giant cells, and variable numbers of lymphocytes and plasma cells.
  - Bacilli are absent in the lesions, but *M leprae* antigens may be demonstrated in nerves by immunohistochemical methods.
  - When no evidence of infection with *M leprae* can be found, differentiating sarcoid neuropathy from TT leprous neuropathy may be impossible. Immunologic and molecular techniques may be needed to confirm the etiology.

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TREATMENT

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Medical Care

- General treatment: Inflammatory reaction in the nerve is suppressed by corticosteroid treatment with antileprosy treatment.
- Specific treatment
    - In the United States
        - PB disease: Dapsone 100 mg daily plus rifampin 600 mg daily for 1 year, then stop treatment.
        - MB disease: Dapsone 100 mg daily plus rifampin 600 mg daily plus clofazimine 50 mg daily for 2 years, then stop treatment. Some physicians continue to prescribe dapsone indefinitely after this therapy as prophylaxis to reduce whatever risk of relapse is present. This approach appears logical but difficult to maintain in all patients. The National Hansen's Disease Programs (NHDP) believes that stopping therapy after 2 years should be safe if close follow-up can be maintained for the recommended intervals when relapse is most likely to occur so that therapy can promptly be restarted if necessary. Furthermore, use of daily rifampin may also decrease the risk of reactivation. In the event of intolerance or toxicity to the usual drugs, the NHDP may be contacted for recommendations about alternative regimens
    - Internationally
        - The World Health Organization (WHO) Multidrug Therapy (MDT) is widely followed internationally. A WHO study group first recommended this treatment in 1981.
        - For adults with MB leprosy, rifampicin 600 mg once a month, dapsone 100 mg daily, clofazimine 300 mg once a month and 50 mg daily are recommended for 12 months. In the rare patient with evidence of deterioration, he or she can be treated with MDT for an additional 12 months.
        - For adult PB leprosy, rifampicin 600 mg once a month and dapsone 100 mg daily is given for 6 months.
        - For children, dapsone dosage is 2 mg/kg/d. Clofazimine dosage is 6 mg/kg once a month under supervision and 1 mg/kg/d self-administered. Rifampicin is administered 10 mg/kg once a month.
    - The use of other drugs such as ofloxacin and minocycline is discussed in the article Leprosy.
- Local treatment
    - Appropriate splints (eg, wrist drop or foot drop)
    - Exercises
    - Prevention of corneal exposure when the facial nerve is involved
    - Prevention of injuries to anesthetic areas
    - Prevention and protection of plantar ulcers by wearing special controlled-rigidity footwear for redistributing pressure
- Treatment of reactions
    - Reactions require urgent treatment as they can lead to irreversible deformities. Therefore, early diagnosis and timely initiation of anti-inflammatory measures are crucial. MDT should be continued at full doses without interruption. Aspirin or paracetamol should be given to reduce pain and fever, and rest is essential. In specific cases, prednisolone should be prescribed as follows:
        - 40 mg/d for weeks 1 and 2
        - 30 mg/d for weeks 3 and 4
        - 20 mg/d for weeks 5 and 6
        - 15 mg/d for weeks 7 and 8
        - 10 mg/d for weeks 9 and 10
        - 5 mg/d for weeks 11 and 12
    - The patient should be examined every week, and the dose of corticosteroids is reduced every 2 weeks. The maximum dosage of prednisolone is 1 mg/kg.
    - Mild reversal reactions may respond to salicylates, chloroquine, or nonsteroidal anti-inflammatory drugs (NSAIDs). Corticosteroids are used for patients with severe nerve involvement, nerve abscess, impending paralysis, or extensive and acutely inflamed skin lesions. Rest, splints, and physiotherapeutic measures may be appropriate. Thalidomide is not useful for reversal reactions.
    - Severe ENL reaction is often recurrent and chronic and may vary in presentation. The management of severe ENL is best undertaken by physician at a referral center. The physician can adjust dose and duration of antireaction drugs according to the needs of the individual patient. WHO guidelines for the management of severe ENL reaction are given below.
        - If the patient is still receiving antileprosy treatment, continue the standard course of MDT. If the MDT is already completed, MDT does not need to be restarted.
        - Use adequate doses of analgesics to control fever and pain.

- Use standard course of prednisolone 1 mg/kg/d for a total of 12 weeks.
- In patients with severe ENL that does not satisfactorily respond to corticosteroid treatment or in patients at high risk for corticosteroid toxicity, combination of clofazimine and corticosteroids may be used. Start clofazimine 100 mg 3 times a day and continue for a maximum of 12 weeks, along with a standard course of prednisolone. Then, taper the dose of clofazimine to 100 mg twice a day for 12 weeks and then 100 mg once a day for 12-24 weeks.
- Management with clofazimine (dosage as given above) alone is indicated in patients with severe ENL when corticosteroids are contraindicated: The total duration of treatment with high-dose clofazimine should not exceed 12 months. Clofazimine requires 4-6 weeks to achieve full effect in controlling ENL.
- Other drug claimed to be useful in ENL are pentoxifylline, alone or in combination with clofazimine-prednisolone.
- Because of the well-known teratogenic adverse effects, thalidomide should not be used for first-line management of ENL in leprosy. In exceptional cases, thalidomide may be used for men from countries where the drug is licensed for use. The initial regimen is 100 mg 3 or 4 times daily, which usually controls the reaction in 48-72 hours. The dose is then tapered over 2 weeks to a maintenance level, usually 50-100 mg/d. Regular attempts should be made to taper or discontinue the drug, but patients may need to continue taking thalidomide for months to years before ENL reactions no longer recur.

- Difficult cases: Other anti-inflammatory agents, such as cyclosporine and cytotoxic drugs, have been used in difficult cases.

- Immunoprophylaxis and immunotherapy

  - No specific and effective vaccine against leprosy is available. Indian trials of bacille Calmette-Guérin (BCG) plus killed *M leprae* and of International Committee of the Red Cross (ICRC) bacillus have yielded 65-70% protective efficacy. Other candidate vaccines have been tested (eg, those against *Mycobacterium W, Mycobacterium habana, Mycobacterium vaccae,* and others). However, none of the candidates or combinations provide a level of efficacy that can be considered a cost-effective intervention for a public health program.

  - Trials of BCG immunoprophylaxis have revealed 20% protection in Burma and 80% in Uganda. Researchers in India, Papua New Guinea, and Malawi report intermediate protection rates. The endemicity, background saprophytic mycobacterial flora, and age at vaccination all may be relevant factors. Because vaccination may precipitate clinically apparent TT leprosy in apparently healthy contacts, immunoprophylaxis is most effective at an early age.
  - A recent meta-analysis of 7 experimental studies revealed an overall protective effect of 26% (95% confidence interval, 14-37%). An analysis of 19 observational studies overestimated the protective effect at 61% (95% confidence interval, 51-70%). The age at vaccination did not predict the protective effect of BCG vaccine. An additional dose of BCG vaccine was more protective in the prevention of leprosy compared with a single dose. An additional dose of BCG may be warranted for contacts of leprosy patients in areas where leprosy continues to be a public health problem.
  - India has approved a leprosy vaccine prepared from a killed, nonpathogenic mycobacterial strain for limited clinical observations. This intradermal vaccine is an adjunct to standard MDT. It accelerates healing and reduces the duration and cost of treatment. These first-generation vaccines are likely to be replaced by genetically engineered products. A live, nonpathogenic bacillus that replicates in the host is more likely to induce cellular immunity than a killed bacillus.
  - Other immunotherapeutic agents under investigation include immunomodulatory drugs, transfer factor, gamma interferons and interleukin 2, acetoacetylated *M leprae,* and delipidified cell components of *M leprae.*
  - Combined immunotherapy and chemotherapy have not increased incidence of reactions. The combination is well tolerated and beneficial. Modification of defective cell-mediated immunity may be associated with more efficient killing and faster clearance of dead bacilli.

- Management of decreased sensation

  - Most damage to insensitive tissues is preventable. Wounds in insensitive tissues heal as promptly as those in normal tissues.

  - Every wound must be splinted and protected from recurrent injury.
  - Instruct patients to inspect eyes, hands, and feet daily for evidence of injury. Encourage them to seek early medical attention.
  - Find suitable, safe occupations for patients.
  - Modify tools and everyday items (eg, door keys) to remove sources of high pressure and shear.

- Have patients wear gloves for potentially damaging tasks.
- Footwear must be soft, have total contact, and avoid shearing and direct forces.
- Goggles must be worn to prevent drying of cornea and introduction of foreign bodies.
- Tarsorrhaphy may be beneficial in lagophthalmos.
- When sympathetic denervation results in anhydrosis, keep hands and feet soft by soaking in water morning and night. This should be followed by occlusive cream or ointment application to lock in moisture.
- Once wounds have occurred, treatment is often prolonged and difficult. If a wound is infected acutely, antibiotics, bed rest, and elevation of the limb may be required. After the acute infection settles, the leg and foot may require a plaster cast to allow healing. Severely diseased tissue may require surgical amputation.

Surgical Care

- Surgery improves sensation in selected patients and often prevents further deterioration. Optimal timing for nerve decompression needs to be established. A multidisciplinary team comprising a leprologist, a neurologist, physical and occupational therapists, and a surgeon with experience in peripheral nerve surgery is needed.
- Surgical treatment of an acute nerve abscess is careful incision of the nerve sheath and draining the abscess. Surgical neurolysis or even fascicular dissection has been advocated to relieve intraneural pressure. Although generally irreversible, simple longitudinal epineurotomy often ameliorates sensory loss.
- Surgical treatments for eliminating anatomically restricted areas (constrictions) include medial epicondylectomy, anterior transposition of ulnar nerve, deroofing the carpal tunnel, and decompressing the posterior tibial nerve at the flexor retinaculum.
- Nerve decompression is used when signs of entrapment have not cleared after 3-4 weeks of steroid therapy, when function deteriorates despite steroid therapy, or when signs of nerve abscess or chronic entrapment are evident.
- Posterior tibial neurovascular decompression by release of flexor retinaculum with systemic administration of steroids may be beneficial in early acute or silent neuritis. Distal compression of plantar branches should be relieved by slitting the calcaneal bands and ensuring free passage of the plantar branches to the sole of the foot. Nerve function (particularly autonomic and sensory modalities) can recover considerably. In some cases, vascular decompression may help heal chronic plantar ulcers and prevent recurrence.
- Peripheral nerve reconstruction performed by using denatured muscle autografts may help to restore protective sensation in hands and feet.
- Nerve grafts may be helpful for patients with localized nerve lesions.
- Cosmetic surgery may be contemplated after leprosy is medically controlled. Procedures include excision of redundant skin in ear lobes and eyelids, excision of excessive breast tissue in gynecomastia, implantation of islands of scalp hair to replace lost eyebrows, and nasal reconstruction.
- Facial-nerve palsy with associated lagophthalmos may be corrected by performing tarsorrhaphy or canthoplasty to prevent exposure of cornea or by tunneling a slip of temporalis muscle attached to tendon through the lid and attaching it to the inner canthus. Re-education involves closing the jaws to effect eye closure.
- Tenodesis to stabilize joints, arthrodesis to correct clawing, and tendon-transfer surgery may be considered. Tendon-transfer procedures may be used to replace paralytic muscles with functioning ones, especially to restore dorsiflexion of foot, abduction-opponens action of thumb, extension of the proximal interphalangeal joint, and flexion at the metacarpophalangeal joint.

Consultations

- Gillis W. Long Hansen's Disease Center (formerly the NHDC) in Louisiana and its regional centers provide consultation and assistance in patient care. In the United States, patients are eligible for treatment by the public health service. Contact the Gillis W. Long Hansen's Disease Center, Bureau of Primary Health Care, HRSA 1770 Physician Park Drive, Baton Rouge, LA 70816. Phone: 1-800-642-2477 or e-mail: mtemplet@hrsa.gov.
- In the United States and in countries where leprosy is uncommon, patients with leprosy are best referred to specialized centers with expertise in leprosy management.
- Consultation with an orthopedic surgeon is recommended for the management of trophic ulcers and for tendon-transfer surgery.
- Consultation with an ophthalmologist is recommended for the management of ocular complications.

- Consultation with an otorhinolaryngologist may be helpful for patients who have nasal symptoms.
- Reconstructive surgeon with special interest in leprosy and peripheral nerve surgery may be of assistance.
- Specialists in physical medicine and orthotics should be consulted.
    - Physiotherapy and occupational therapy are essential in patients with paralysis because of neural involvement. In patients who undergo rehabilitative surgery, such as tendon transfers, muscle-reeducation exercises are essential.
    - The most effective healing tools for plantar ulceration are the total contact cast (TCC) and the posterior walking splint (PWS). If the TCC and PWS are not appropriate, alternative pressure-relieving or healing devices (eg, Carville custom sandal, Plastizote boot, prefabricated healing sandals and/or shoes) can be made, modified, or augmented to reduce loads on foot. The foot bed of the Plastizote boot is molded the same way as that of a Carville, sandal but the upper is made of Plastizote material and rises to just below the gastroc muscle belly. This device adds support for moderate to severely deformed feet, such as resolved Charcot fractures for in-house and shower or bath use.
    - Heel ulcers are common in those with an insensitive foot and who need long-term bedrest or positioning during surgery. These ulcers can be located on the medial, lateral, or posterior aspect with a plantar component. A boot is cut to appropriately relieve the area. The boot is to be worn at all times, especially when the involved foot is in contact with any surface (eg, bed, recliner, foot stool, sofa). When the wound closes, permanent footwear and orthotics are fitted to prevent reulceration.
    - All options used for the wound-healing phase and initial ambulation after wound closure must include use of an assistive device for partial weight bearing (PWB), preferably with crutches or a walker.
- Consult a psychologist to deal with the social aspects of the disease.

Activity

Restrict potentially damaging activities in patients with sensation loss.

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MEDICATION

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The goal of pharmacotherapy is to reduce morbidity. Eradication of organisms may ensure a cure in mild cases, and reduce the reservoir and chances of spread of infection in the community. In view of the immune mechanisms involved, eradication

of bacteria is only one aspect of treatment.

Drug Category: *Antileprosy medications*

These agents are bacteriostatic or bactericidal against *M leprae.* These drugs are usually used in combination, since monotherapy may lead to the emergence of resistant organisms.

Drug Name	Dapsone (diamino diaphenylsulfone; Avlosulfon, DDS)
Description	Bacteriostatic; resistant organisms may emerge with monotherapy. Inhibits incorporation of PABA into folic acid. Slowly and almost completely absorbed from GI tract. Peak plasma concentrations in 1-3 h; half-life 10-50 h, mean 28 h. Distributed throughout body water to all tissues and tends to be retained in skin, liver, kidney, and muscle. Acetylated in liver, which is genetically defined.
Adult Dose	100 mg PO qd in combination with other drugs
Pediatric Dose	2 mg/kg PO qd
Contraindications	Documented hypersensitivity; G-6-PD deficiency; porphyria; severe anemia
Interactions	No hazardous interactions reported; may inhibit anti-inflammatory activity of clofazimine; folic-acid antagonists (eg, pyrimethamine) increase likelihood of hematologic reactions; probenecid increases plasma concentrations; due to increased renal clearance, rifampin may significantly decrease levels; concurrent trimethoprim may increase levels of both drugs
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Adverse effects include hematologic (monitor for agranulocytosis during months 2-3 of therapy, hemolysis usually occurs with 200-300 mg/d or with G-6-PD deficiency or methemoglobinemia), GI (anorexia, nausea, vomiting), neurologic (headache, nervousness, insomnia, blurred vision, paresthesia, reversible peripheral neuropathy thought to be due to axonal degeneration), and miscellaneous (drug fever, hematuria, pruritus, psychosis, skin rashes), effects; infectious mononucleosis-like syndrome, which may be fatal, occurs occasionally; exacerbation of LL thought to be analogous to Jarisch-Herxheimer reaction (this sulfone syndrome may develop 5-6 wk after start of treatment in malnourished people, characterized by fever, malaise, exfoliative dermatitis, jaundice with hepatic necrosis, lymphadenopathy, methemoglobinemia, and anemia)

Drug Name	Clofazimine (Lamprene)
Description	Phenazine dye that inhibits template function of DNA by binding to it. Weakly bactericidal and has anti-inflammatory effects. Absorbed orally, accumulates in tissues; half-life >70 d. In addition to daily dose, loading dose of 300 mg once a month (under supervision) given in leprosy-control programs. This approach maintains optimal amount of drug in body tissue, even if patient occasionally misses daily dose.
Adult Dose	50 mg PO qd self-administered, and 300 mg once a month under supervision (per WHO regimen)
Pediatric Dose	1 mg/kg/d PO self-administered, and 6 mg/kg PO once a month under supervision
Contraindications	Documented hypersensitivity; pregnancy; persistent GI symptoms
Interactions	Dapsone may inhibit anti-inflammatory activity

Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Adverse effects include GI toxicity (dose related), resulting in diarrhea, cramping, and abdominal pain; GI symptoms may be progressive and potentially life threatening; severe abdominal symptoms may mimic surgical emergencies, resulting in exploratory laparotomies; caution in patients with GI problems (eg, abdominal pain, diarrhea); skin discoloration due to drug may be distressing to light-skinned individuals and may result in depression leading to suicide; for skin dryness, itching, and ichthyosis, apply oil to the skin; acneform eruption and photosensitivity possible

Drug Category: *Antimycobacterial agents*

This agent is highly bactericidal against *M leprae.* It can kill intracellular organisms as well as semidormant or persistent ones. It inhibits DNA-dependent RNA polymerase of mycobacteria and other microorganisms, suppressing the initiation of chain formation in RNA synthesis.

Drug Name	Rifampicin, rifampin (Rifadin, Rimactane)
Description	Single 600-mg dose can kill 99.9% or more of viable *M leprae,* probably because of slow doubling time of bacilli or possible delayed effect of drug. Subsequent doses do not proportionately enhance rate of killing. High bactericidal activity makes once-a-month dosing feasible and cost-effective for leprosy-control programs. Oral administration produces peak plasma concentrations in 2-4 h; drug eliminated in bile. Even deacetylated metabolite retains full antibacterial activity. Induction of enzymes leads to progressive shortening of half-life during first 14 d of therapy. Dose adjustment not necessary in impaired renal function.
Adult Dose	600 mg PO qmo
Pediatric Dose	10 mg/kg PO qmo
Contraindications	Documented hypersensitivity; liver disease; jaundice; pregnancy and lactation
Interactions	Enzyme inducer, decreases half-life of prednisolone, digoxin, quinidine, ketoconazole, propranolol, clofibrate, and sulfonylureas; decreases efficacy of oral anticoagulants and oral contraceptives; may interfere with laboratory assays of folate and vitamin B-12 and calorimetric tests; food delays absorption of drug
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Obtain CBC count before and throughout therapy; obtain blood for baseline clinical chemistry studies before dosing; adverse effects include GI (nausea, vomiting, diarrhea, hepatic toxicity), hematologic (hemolytic anemia, thrombocytopenia), orange-red discoloration of body fluids (sweat, urine, other), discoloration of soft contact lenses Rifampicin-resistant *M leprae* reported, mainly in rifampicin monotherapy, in combination with dapsone to dapsone-resistant patients, or in patients with selective noncompliance to dapsone or clofazimine Patients with liver disease may have an increased risk (weigh benefits against risk of further liver damage); closely monitor patients receiving intermittent therapy for compliance, and caution against intentional or accidental interruption, which may increase risk of serious adverse reactions; high-dose intermittent therapy and resumption of interrupted therapy associated with high incidence of thrombocytopenia, which is rare during well-supervised daily therapy (effect reversible if drug discontinued as soon as purpura occurs); death may

	occur when continued or resumed after appearance of purpuric cerebral hemorrhage

Drug Category: *Antibiotics*

Empiric antimicrobial therapy must cover all likely pathogens in the context of the clinical setting.

Drug Name	Minocycline (Dynacin, Minocin)
Description	Inhibits protein synthesis by binding to 30S ribosomal subunit at a site that blocks binding of amino acid–charged tRNA to acceptor site of ribosomal mRNA complex. Susceptible organisms accumulate drug intracellularly by energy-dependent mechanism, undergo enterohepatic circulation, and excreted primarily in the urine.
Adult Dose	100 mg PO qd under guidance of leprologist
Pediatric Dose	<8 years: Not recommended >8 years: 4 mg/kg PO initially, then 2 mg/kg q12h
Contraindications	Documented hypersensitivity; severe hepatic or renal dysfunction, systemic lupus erythematosus, hypersensitivity to tetracyclines
Interactions	Bioavailability decreases with antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate; can decrease effects of oral contraceptives, causing breakthrough bleeding and increased risk of pregnancy; tetracyclines can increase hypoprothrombinemic effects of anticoagulants
Pregnancy	D - Unsafe in pregnancy
Precautions	Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment; reduce dose in renal impairment; consider determinations of drug serum level in prolonged therapy; tetracycline use during tooth development (last half of pregnancy through age 8 y) can permanently discolor teeth; Fanconi-like syndrome may occur with outdated tetracyclines; hepatitis or lupus-like syndromes may occur

Drug Name	Ofloxacin (Floxin)
Description	Interferes with DNA synthesis by binding to topoisomerases II and IV and thus bacterial lysis. Eliminated through kidneys by active tubular secretion, which probenecid can block.
Adult Dose	400 mg PO qd; must be reduced in renal failure in proportion to creatinine clearance
Pediatric Dose	<18 years: Not recommended
Contraindications	Documented hypersensitivity; lactation
Interactions	Antacids, iron salts, and zinc salts may reduce serum levels; administer antacids 2-4 h before or after fluoroquinolones; cimetidine may interfere with metabolism of fluoroquinolones; ciprofloxacin reduces therapeutic effects of phenytoin; probenecid may increase ciprofloxacin serum concentrations; may increase toxicity of theophylline, caffeine, cyclosporine, and digoxin (monitor digoxin levels); may increase effects of anticoagulants (monitor PT)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Adverse effects include nausea, vomiting, abdominal pain and diarrhea, headache, dizziness, (rare) seizures, hallucinations, pseudomembranous colitis, skin rash, bone marrow depression, abnormal liver function, tendonitis, and photosensitivity; in prolonged therapy, periodically evaluate organ (eg, renal, hepatic, hematopoietic) function; adjust dose

	in renal function impairment; superinfections may occur with prolonged or repeated antibiotic therapy

Drug Name	Clarithromycin (Biaxin)
Description	Binds to 50S ribosomal subunit of bacteria. Inhibits protein synthesis by interfering with tRNA translocation and inhibiting formation of the initiation complex. Well absorbed when given orally and excreted after hepatic metabolism and as intact drug in urine; 14-hydroxy metabolite has antimicrobial activity.
Adult Dose	500 mg PO qd
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; coadministration of pimozide
Interactions	Toxicity increases with coadministration of fluconazole and pimozide; effects decrease and GI adverse effects may increase with coadministration of rifabutin or rifampin; may increase toxicity of anticoagulants, cyclosporine, tacrolimus, digoxin, carbamazepine, ergot alkaloids, triazolam, HMG-CoA reductase inhibitors; plasma levels of certain benzodiazepines may increase, prolonging CNS depression; arrhythmias and increased QTc intervals occur with disopyramide; coadministration with omeprazole may increase plasma levels of both; decreases metabolism of repaglinide, increasing serum levels and effects
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Adverse effects include nausea, diarrhea, glossitis, stomatitis, skin rashes, pruritus, urticaria, anaphylaxis, Steven-Johnson syndrome, eosinophilia, headache, transient CNS symptoms (eg, anxiety, dizziness, insomnia, confusion, bad dreams); coadministration with ranitidine or bismuth citrate not recommended when CrCl <25 mL/min; give half dose or increase dosing interval if CrCl <30 mL/min; diarrhea may indicate pseudomembranous colitis; superinfections may occur with prolonged or repeated antibiotic therapy

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FOLLOW-UP

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Deterrence/Prevention

- Periodically examine contacts of persons with MB leprosy. This is essential to detect and treat disease in its early stages.
- Several studies of 1 or more antileprosy drugs (eg, dapsone, long-acting injectable dapsone [acedapsone], rifampicin) as chemoprophylaxis failed to demonstrate any significant protection against leprosy. Therefore, at present, the only practical method of prevention is early detection and MDT in all patients with leprosy.
- BCG or other antileprosy vaccines may increase immunity to the disease and help in prevention.
- Isolation or leprosarium is not indicated. Viability of bacteria in skin biopsy samples decreases sharply within 3 weeks of the start of therapy with dapsone and rifampicin. Family members have already had prolonged exposure to the

patient before diagnosis.

Complications

- Deformities and trophic changes may occur.
    - Deformities may be due to direct effects of proliferation of *M leprae* (eg, collapse of nasal septum and rarely, direct invasion of phalanges with pathologic finger fractures).
    - Deformities are usually due to neuropathy. These include crippling deformities of the hand, contractures due to paralysis, and recurrent injuries to the hands, feet, and eyes due to insensitivity. This leads to progressive absorption of extremities and/or blindness.
    - Common problems include ulcerations on plantar surfaces, sides of feet and toes, and hands. Lacerations, burns, abrasions, and hematomas are common on the hands. Shortening of digits on feet and hands may occur through destructive osteomyelitis, and fragments of bone may be discharged through ulcerated areas. Amputations may occur traumatically.
    - Impairment grading is as follows (WHO, 1982):
        - Grade 0 - Normal, no impairments
        - Grade 1 - Peripheral anesthesia over hands and/or feet
        - Grade 2 - Trophic ulcers over hands and/or feet; mobile clawing of fingers or toes; minimal absorption of fingers and/or toes and wrist and/or foot drop
        - Grade 3 - Fixed deformities of fingers and/or toes; more than minimal absorption of fingers and/or toes and nasal collapse
- Lucio phenomenon is seen in certain Latin American patients with diffuse infiltrative LL leprosy. It is characterized by thrombosis of deeper subcutaneous arteries, resulting in necrosis of the skin and subcutaneous fat. Underlying tendons and muscles may be exposed. The outcome is often fatal.
- Secondary amyloidosis is a complication of severe LL disease, often related to the severity and frequency of ENL reactions.

Prognosis

- Progression of tissue and nerve damage can be limited, but recovery of lost sensory and motor function is variable and generally incomplete.
- Hyperpigmentation, hypopigmentation, and loss of skin organs persist.
- Intercurrent reactional states, poor compliance, and emergence of dapsone resistance can lead to clinical exacerbations or relapses that necessitate close follow-up.
- Much chronic debility results from repeated trauma to anesthetic digits and limbs. Careful counseling and consultations with physical and occupational therapy services are essential for optimal outcome.
- Rejection and isolation by community and family members leads to social and economic dislocation. Even when the disease is fully controlled, its stigma and social isolation persist.

Patient Education

- Educate the patient about the disease, its bacterial origin, low communicability, and possibilities for successful treatment. This knowledge improves their self-esteem and motivation to complete medical treatment.
- Educate the patients about the condition, the consequences of neuropathy and the proper self-care techniques. Periodic screening is recommended to detect signs and symptoms of neuropathic feet. Any change in status may require a change in the treatment protocol (possibly a different style of shoe or orthotic). The patient must realize the importance of taking responsibility for self-care to ensure healthy feet. All of the following activities should be explained and monitored on follow-up visits.

- A person with insensitive feet must always wear shoes (no barefoot walking), but the shape and size of the shoe must be appropriate. The shoe must match the shape of the foot. Always have the feet measured when one buys shoes. Allow for a 0.5-in. space between the length of the longest toe and the shoe. One should be able to pinch a small area at the widest part of the shoe to determine sufficient width. The toe box (end of the shoe) should be roomy enough to accommodate the toes. Leather uppers are preferred because the leather conforms to the shape of the foot over time. Purchase shoes with a wedge and soft rubber sole. Wear shoes with a closure system; clogs, slip-ons, or loose-fitting shoes may easily come off the foot or rub red areas.

- Gradually break in new shoes. Begin wearing new shoes no more than 2 hours the first time, and gradually prolong the time if no problems occur.

- Always wear socks with shoes and inspect them daily. White cotton socks are preferred because they are more absorbent than socks made of other materials and because white easily shows evidence of skin breakdown and drainage.

- Inspect shoes before and after wear to ensure that no objects have accidentally fallen into the shoe and that no sharp items have penetrated the sole. Do not wear high-heeled shoes, as they tend to put pressure on the forefoot.

- Inspect the feet daily for redness, warmth, swelling, or new injury. Use a mirror to check the bottom of the feet. If any new injury or redness, swelling, or change in temperature is noted, it should be brought to the attention of a healthcare professional.

- Cut toenails straight across. If nails are large and irregular in shape, professional care may be necessary. Do not cut calluses or corns or use corn removers. These are problems that a healthcare professional should address.

- For dry skin, use a lotion that does not contain alcohol.

- Never use heating pads or hot water bottles or stand too close to a heater or fireplace. Insensitive feet and lower legs may not detect when temperatures have reached dangerous, burning level.

- To enable acceptance, educate the patient's family, friends, and employers about leprosy.

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MISCELLANEOUS

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Medical/Legal Pitfalls

- Treatment progress and decreasing prevalence make differential diagnosis difficult, and neurologic expertise is required. Silent nerve lesions may be present long before symptomatic neuropathy appears. Detection of asymptomatic leprous neuropathy by means of careful clinical examination and electrophysiologic studies in persons at risk can aid early detection and treatment.

- Inexperience with the disease may delay diagnosis and treatment.

- Epidemiologic studies reveal that many cases occur within families. This pattern may lead to misdiagnosis of a hereditary neuropathy.

- Neuropathies, especially those involving small fibers of the peripheral nerve, may closely mimic leprosy.
- Differentiating leprous neuropathy from hereditary sensory neuropathy may be difficult. Both may involve family members, the clinical pictures may be similar, and the diagnosis may be missed unless skin smears or skin and/or nerve biopsy is done.
- Neuritic leprosy produces no obvious skin lesions, and skin smears are negative for AFB. Suspect this diagnosis when persons from areas of endemic disease present with nerve thickening and associated nerve deficit. In some studies, neuritic leprosy was reported in 5-15% of patients with leprosy. Some cases may have been treated partially; others may subsequently evolve to classic leprosy. Nerve biopsy is essential for diagnosis.
- In areas where the disease is not endemic, confirm the diagnosis by performing smears or biopsy and, if possible, by obtaining cultures in a mouse footpad. Consult local health authorities regarding treatment policies. Seek the help of referral centers performing and interpreting the results of nerve biopsy and in difficult cases, such as those in pregnant women, in patients who cannot tolerate standard drugs, and in patients with associated hepatic and/or renal disease or HIV infection.
- Pay special attention to prevent deformities, blindness, and damage to insensitive areas.
- Even in areas of endemic disease, not all persons with thickened nerves have leprosy; other neuropathies must be excluded.
- The involvement of the median nerve at the wrist, ulnar nerve at the elbow, and common peroneal nerve at the fibular head are common in leprosy and may lead to difficulty in distinguishing this condition from idiopathic entrapment neuropathy involving these nerves. A history of previous residence or travel to an area of endemic disease, a careful search for skin lesions, and a careful search for nerve enlargement, combined with an appropriate diagnostic workup for leprosy, may confirm the diagnosis. In leprosy, the nerve is often thickened and involves areas proximal to the entrapment site. Motor weakness and wasting are often more severe in leprosy than in a carpal tunnel syndrome. Idiopathic entrapment neuropathy must not be misdiagnosed as neuritic leprosy (ie, leprosy without skin lesions).

Special Concerns

- Nerve destruction in leprosy reactions
  - Significant nerve destruction occurs during the reactive phase of both the ENL and reversal reactions.
  - Acute granulomatous inflammation can destroy nerves to the extent of causing caseation necrosis of nerve tissue and irreversible paralysis. Swelling of nerves due to sudden increase in inflammatory cells and edema within an unyielding perineurium produces ischemia and paralysis.
  - High-risk patients may require corticosteroids for 6 months with MDT as a preventive measure. Nerve damage can occur even after clinical cure and release from treatment.
- Social rehabilitation
  - Social rehabilitation should focus on suitable vocational evaluation and placement of persons with deformities or insensitivity.
  - Many patients are in low socioeconomic groups. This disease may pose insurmountable problems for the patient.
  - Social service is helpful in achieving sources of financial support, home and community health services, and adequate housing.
- Intolerance, adverse effects, and contraindications related to MDT
  - After adverse events are conclusively established to be due to antileprosy drugs, other new antileprosy drugs can be used under direct supervision in a referral center. For patients who refuse clofazimine, educate the patient about the advantages of the drug, particularly the reversible nature of the discoloration produced by the drug; this information should be sufficient to encourage the patient to continue with clofazimine therapy. In exceptional cases, ofloxacin 400 mg or minocycline 100 mg daily may be used under supervision in place of clofazimine.
  - As an alternative, such patients may be treated with the monthly administration of 600 mg rifampin, 400 mg ofloxacin, and 100 mg minocycline (ie, ROM therapy) for 24 months. The following is recommended for adults

with MB leprosy who do not tolerate rifampin: clofazimine 50 mg/d with ofloxacin 400 mg, and minocycline 100 mg for 6 months, followed by clofazimine 50 mg/d with minocycline 100 mg or ofloxacin 400 mg for at least an additional 18 months.

- If the toxic effects of dapsone are severe in patients with PB disease, clofazimine may be substituted for dapsone at the same dosage as that used for patients with MB but for 6 months. In patients with MB, dapsone should be stopped, and treatment should be continued with rifampin and clofazimine at the standard dosages.

- Nonresponse to therapy
  - Nonresponse may be due to poor drug compliance or other concomitant, debilitating, intercurrent infections, including HIV infection.
  - When the patient's condition shows no improvement despite supervised drug administration, health education, and thorough investigation and management of intercurrent infections, an expert opinion may be necessary.
- Relapse
  - In MB leprosy, relapse is defined as the multiplication of *M leprae,* suggested by the marked increase (at least 2+ over the previous value) in the bacillary index at any single site, usually with evidence of clinical deterioration (new skin patches or nodules and/or new nerve damage). In most cases, this condition can be confirmed by the growth of *M leprae* in the mouse footpad system.
  - Recognition of relapse in PB leprosy is somewhat difficult because it is hard to distinguish it from reversal reaction. In theory, a therapeutic test with corticosteroids may be able to distinguish between the phenomena: Definite improvement within 4 weeks of corticosteroid therapy indicates a reversal reaction, and no response to corticosteroids during the same period suggests clinical relapse.
- Steroid therapy and leprosy
  - Indications for steroid therapy in persons with leprosy include neuritis, impending nerve palsies, iridocyclitis, epididymoorchitis, severe reversal reaction, ENL reaction, or systemic involvement.
  - No evidence suggests that immunosuppressive drugs, such as corticosteroids, accelerate multiplication of organisms located in dormant foci and cause reactivation of leprosy.
  - Whenever the duration of steroid therapy (for late reversal reaction or other medical conditions) is expected to exceed 4 months, clofazimine 50 mg/d can be started as a prophylactic measure. This treatment should be continued until the course of steroids is complete.
- HIV Infections and leprosy
  - Unlike the situation with tuberculosis and atypical mycobacteriosis, case-controlled studies have not revealed any significant association between HIV and leprosy.
  - HIV serodiagnostic tests based on ELISA and/or western blot may show significantly higher rates of false-positive results among patients with LL.
  - Care of patients with leprosy who also are infected with HIV is the same as that of any other patient, including treatment of reactions.
  - HIV-associated neuropathy might be confused with or exacerbate leprosy neuritis.
  - Neuropathy due to antiretroviral chemotherapy might be confused with leprosy.
  - Nonleprosy mycobacterioses in HIV-positive people might be confused diagnostically with leprosy.
  - National policies on BCG vaccination might be amended because of endemic HIV infection.
  - Slit-skin smear taking could spread HIV infection if proper precautions are not taken.
  - Leprosy workers in countries of endemic infection may become increasingly involved with problems of HIV counseling.
- Women, pregnancy, and leprosy
  - Hormonal changes in puberty and pregnancy cause nonspecific suppression of cell-mediated immunity with

worsening of leprosy. Pregnancy also can be associated with reactions. Deterioration usually occurs in the second half of pregnancy or first 3 months after delivery. Late nerve damage associated with childbirth has been recorded, even in women in whom MDT is stopped. Therefore, the WHO recommends that MDT be continued during pregnancy.

- Dapsone is not known to have any adverse effects on mother or fetus. Clofazimine, prednisolone, and thalidomide may affect both mother and fetus. Rifampicin is not recommended in the first trimester. Small quantities of antileprosy drugs are excreted through breast milk, but no adverse reactions have been reported as a result of this except for mild discoloration of infants due to clofazimine. Infants of mothers suffering from leprosy have lower birth weights and higher risk of contracting the disease.

- Tuberculosis and leprosy
  - MDT for leprosy is not adequate for treatment of tuberculosis. Therefore, an appropriate antitubercular regimen should be given, in addition to antileprosy MDT, to patients who have both leprosy and tuberculosis.
  - Except where daily rifampicin is part of antituberculosis treatment, monthly rifampicin is not needed as part of leprosy MDT.
  - If a patient with leprosy and tuberculosis is treated with a rifampicin-containing antitubercular regimen, the patient may run the risk of developing rifampicin-resistant leprosy. Hence, both diseases need to be treated simultaneously.

- Leprosy and human rights
  - Patients on MDT and those cured of disease should not have restrictions in terms of employment, education, and travel.
  - Any special legal measures that might increase prejudice against patients with leprosy or prevent patients with early cases from presenting themselves for diagnosis and treatment should be abolished.

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MULTIMEDIA

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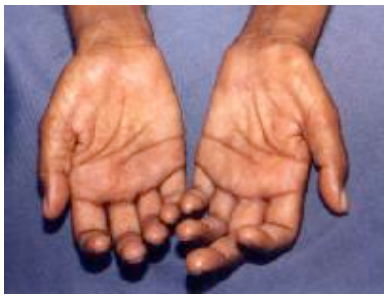
Media file 1: **Claw-hand deformities of both hands in a patient with neural leprosy.**



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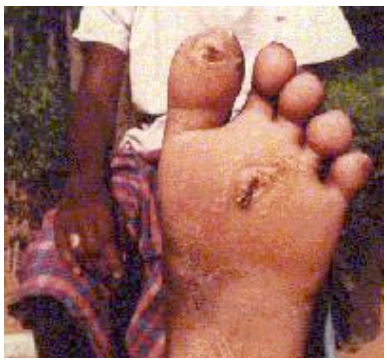
Media type: Photo

Media file 2: **Plantar trophic ulcers in a patient with leprous neuropathy.**



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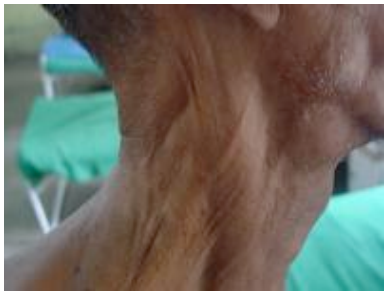
Media type: Photo

Media file 3: **Peripheral nerve thickening in leprosy.**



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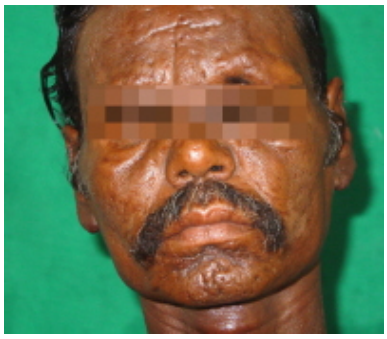
Media file 4: **Infiltration and thickening of skin in the face in lepromatous leprosy (leonine facies).**



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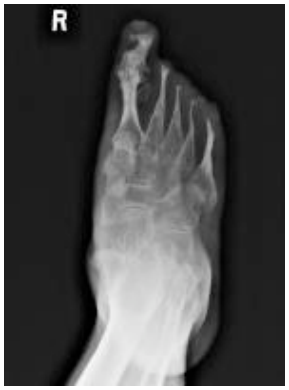
Media type: Photo

Media file 5: **Anteroposterior (AP) radiograph shows absence of toes 2-5 and distal tapering of the metatarsals secondary to neuropathy, ie, the licked–candy-stick appearance. Phalanges of the great toe show destruction secondary to osteomyelitis.**



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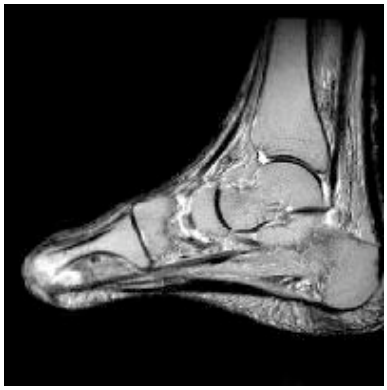
Media type: X-RAY

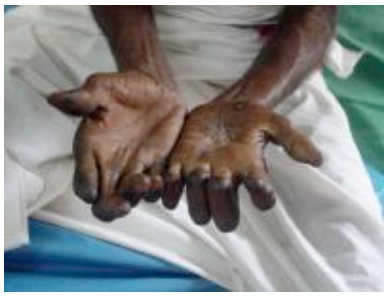
Media file 6: **Sagittal fat-saturated T2-weighted image shows amputation of the great toe with increased signal intensity in the head of the first metatarsal indicating osteomyelitis. Small abscess is noted beneath the first metatarsal head.**



View Full Size Image

Media type: MRI

Media file 7: **Bilateral total claw hand.**



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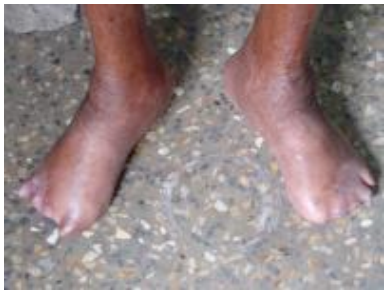
Media type: Photo

Media file 8: **Advanced lepromatous leprosy with amputation of toes and trophic ulceration.**



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Media type: Photo

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Neuropathy of Leprosy excerpt

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