Leprosy
Leprosy is caused by *M. leprae* and predominantly affects the skin and peripheral nerves.
Lepromatous leprosy = اﻠﺠذاﻤﻲ اﻠﺠذاﻢ

**Immunopathologic Spectrum**

**Leprosy**
The sequence of disease pathogenesis is complex, very chronic, and depends on host-parasite immunologic responses. Lepra, or Mycobacterium leprae, acts as a slow-growing intracellular parasite and eliminates host cellular immune responses. Depending on the balance of host and parasite interaction, there are five disease categories: TT (tuberculoid), TB (tuberculoid lepromatous), BT (borderline tuberculoid), BB (midborderline), BL (borderline lepromatous), and LL (lepromatous). The term "borderline" is used to denote patterns that share some features of both tuberculoid and lepromatous leprosy.
TT and LL patients are stable, the former often self-healing and the latter remaining heavily infected unless given appropriate chemotherapy.
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It is likely that in endemic zones, a high proportion of people are infected by M. leprae but either have full immunity and no disease or have developed one or a few lesions that have self-healed without significant morbidity. Patients with determined leprosy are most numerous at the BT and LL points of the spectrum.
Staining of Mycobacterium leprae Bacilli
The classical method for demonstrating leprosy bacilli in lesions is a modified Ziehl-Neelsen stain, where the degree of bacterial index (BI) follows Ridley's logarithmic scale (which applies to both skin biopsies and slit skin smears).

\[ BI = 0: \text{no bacilli observed} \]
Lepromatous leprosy = اﻠﺠذاﻤﻲ اﻠﺠذاﻢ

- BI = 1: 1 to 10 bacilli in 10 to 100 hpf (oil immersion)
- BI = 2: 1 to 10 bacilli in 1 to 10 hpf
- BI = 3: 1 to 10 bacilli per hpf
- BI = 4: 10 to 100 bacilli per hpf
- BI = 5: 100 to 1,000 bacilli per hpf
- BI = 6: >1,000 bacilli per hpf
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Solid-staining bacilli indicate that the organisms are capable of multiplication. Fragmented (beaded) and granular acid-fast bacilli indicate that they are dead. Patients with no bacilli detectable in lesions are termed paucibacillary; those with some or many bacilli are multibacillary (this distinction is important in determining the duration of chemotherapy).

Immunocytochemical methods for demonstrating mycobacterial antigens have a limited role. The most frequently used is a method that uses a monoclonal antibody to lysozyme to detect lysozyme in the bacilli. The lysozyme has been shown to be lost from the cell walls of bacilli that have fragmented, been partly digested by macrophage enzymes, and lost their acid-fast staining quality.
For general discussions of clinical leprosy and leprosy pathology, the reader is referred to Job (147) and...
Many patients present with obvious or advanced skin and peripheral nerve lesions (the latter are primarily nerve loss).
Histopathology

There is mild lymphocytic and macrophage accumulation around neurovascular bundles, the superficial and deep dermal vessels, sweat glands, and erector pili muscle; focal lymphocytic invasion into the epidermis, or in a macrophage about a vessel. Without demonstrating bacilli, the diagnosis can only be presumptive.
A distinctive variant of lepromatous leprosy, the histoid type, first described in 1963 (149), is characterized by the presence of dermal nodules that may coalesce to form larger masses or lesions. It frequently follows incomplete chemotherapy or acquired drug resistance, leading to bacterial relapse.

Rarely, lepromatous leprosy can present as a single lesion rather than as multiple lesions (150).
*Histopathology.*

Lepromatous leprosy, in the usual macular or infiltrative-nodular lesions, exhibits an extensive cellular infiltrate that ... the macrophages have abundant eosinophilic cytoplasm and contain a mixed population of solid and fragmented bacilli (B. lepromatosis = 3 or 5) (Figs. 21-33). The bacilli, on Wade-Fite staining, can be seen to measure about 5.0 by 0.5 μm and if solid may ... to form epithelioid cell granulomas. Lymphocyte infiltration is not prominent, but there may be many plasma cells.
In time, and with anti mycobacterial chemotherapy, degenerate bacilli accumulate in the macrophages—the so-called lepra ... bacilli are fragmented or granular and, especially in very chronic lesions, disposed in large basophilic clumps called globi. In lepromatous leprosy, in contrast to tuberculoid leprosy, the nerves in the skin may contain considerable numbers of leprosy bacilli but remain well preserved for a long time and slowly become fibrotic.
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Histoid leprosy shows the highest loads of bacilli (frequently, the BI is 6), and the majority are solid staining, ... pattern, similar to those of a fibrohistiocytoma. The epidermis may be stretched over such dermal expansile nodules.
The important difference between LL and BL leprosy histology is that in BL, the lymphocytes are more prominent and there is less fibrosis. Foamy cells are not prominent, and globi do not usually accumulate; the Bl ranges from 4 to 5.
**Midborderline Leprosy**

In midborderline (BB) leprosy, the skin lesions are irregularly dispersed and shaped erythematous plaques.
**Histopathology.** In BB leprosy, the macro phages are uniformly activated to epithelioid cells but are not focalized into distinct granulomas. There are no Langhans giant cells. The Bl ranges from 3 to 4. Dermal edema is prominent between the inflammatory cells.

**Borderline Tuberculoid Leprosy**
In borderline tuberculoid (BT) leprosy, the lesions are asymmetrical and may be scanty. They are dry, hairless plaques with central hypopigmentation. Nerve enlargement is usually found, and the lesions are usually anesthetic.

*Histopathology.* Granulomas with peripheral lymphocytes follow the neurovascular bundles and infiltrate sweat glands and erector pili muscles. Langhans giant cells are variable in number.
and are not large in size. Granulomas along the superficial vascular plexus are frequent, but they do not infiltrate up to the nerves. Immunocytochemical staining for 8-100 protein often demonstrates the perineural and intraneural granuloma well.

_Tuberculoid Leprosy_
The skin lesions of tuberculoid (TT) leprosy are scanty, dry, erythematous, hypopigmented papules or plaques with sharply demarcated borders. These lesions range in size from a few millimeters to a few centimeters. Thickening of peripheral nerves may be present. The lesions heal rapidly on chemotherapy.

Histopathology
Primary TT leprosy has large epithelioid cells arranged in compact granulomas and...
In all of these patterns of leprosy, the major peripheral nerves are often undergoing parallel pathologies.
Lepromatous leprosy

Leprosy Reactions

Leprosy reactions are classified into two main types (1 and 2). A third reaction is specific to Lucio multibacillary leprosy.
Type 1 Reactions
Because the immunopathologic spectrum of leprosy is a continuum, patients may move along it in both directions. Shifts toward the tuberculoid pole are called upgrading or reversal reactions; shifts toward the lepromatous pole are termed downgrading reactions. Both are aspects of delayed hypersensitivity, or type 1, leprosy reactions. TT patients are stable. BT patients may suffer from type 2 reactions, which are damaging. At worst, there is caseous necrosis of large peripheral nerves resulting from upgrading reactions.
Histopathology. The histopathology of type 1 reactions has still not been...
there is edema within and about the granulomas and proliferation of fibrocytes in the dermis. In upgrading
type 2 Reaction: Erythema Nodosum Leprosum

Erythema nodosum leprosum (ENL) occurs most commonly in LL leprosy and less frequently in BL leprosy.
On the skin, tender, red plaques and nodules together with areas of erythema, and occasionally also purpura and vesicles, may occur. This skin involvement may last for weeks and even years in others. This is the only type of reactional leprosy that responds to treatment with thalidomide.

**Histopathology.** In ENL, the lesions are foci of acute inflammation superimposed on chronic multibacillary leprosy. Polymorph neutrophils are prominent, and mononuclear cells are also often a component of these ENL foci. In the context of ENL, there are no bacilli present. However, macrophages have a granular pink hue on the Wade-Fite staining, indicating mycobacterial debris.
anti mycobacterial immunocytochemical stain (e.g., anti-BCG) will indicate abundant antigen. A necrotizing vasculitis affecting arterioles, venules, and capillaries occurs in some cases of ENL; these patients may have superficial ulceration.

Lucio Reaction
The Lucio reaction occurs exclusively in diffuse lepromatous leprosy, in which it is a fairly common complication. It usually occurs in patients who have received either no treatment or inadequate treatment. In contrast to ENL, fever, tender nodules, and edema are less pronounced, and the eruption is typically pruritic.

**Histopathology.** In the Lucio reaction, vascular changes are critical. Endothelial proliferation leads to luminal obliteration, resulting in hemorrhagic infarcts and crusted erosions or frank ulcers.
Electron Microscopy of Leprosy
Under electron microscopy, *M. leprae* can be seen to consist of an electron-dense cytoplasm lined by a trilaminal plasma membrane. Outside of this membrane is a single unit membrane with a thick homogeneous coating typical of mycobacteria. Lepra bacilli are found in the skin, predominantly in macrophages and in Schwann cells.

Pathogenesis of Leprosy
With respect to immunologic activity, patients with lepromatous leprosy have a defect in cell-mediated immune responses. This defect is specific for M. leprae, because patients with lepromatous leprosy show normal immunologic responses to antigens other than lepromin in both in vivo and in vitro testing.
The specific inability of T lymphocytes obtained from patients with lepromatous leprosy to react against lepromin is an increase in the lymphocyte response to lepromin during the reaction and a decrease during the postreaction phase.
Analysis of T-cell subsets in lesions has shown that in tuberculoid leprosy, with its high degree of resistance...
In patients with either ENL or the Lucio reaction, deposits of IgG and the third component of complement...
The lepromin skin test, or Mitsuda test, consists of the intradermal injection of a preparation of *M. leprae* derived from autoclaved infected human tissue. A positive reaction consists of the formation of a nodule measuring 45/45.