Leprosy
Leprosy is caused by *M. leprae* and predominantly affects the skin and peripheral nerves.
Immunopathologic Spectrum

Leprosy
The sequence of disease pathogenesis is complex and very chronic and depends on host-parasite immunologic responses. The ... and few bacilli in tissues; at the opposite pole, lepromatous leprosy indicates an absent cellular immune response to M. leprae antigens, with no macrophage activation and abundant bacilli in tissues. The spectrum of leprosy is a continuum, and several patterns are recognized, including TT (tuberculoid), TB (tuberculoid borderline), 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.
Lepromatous leprosy = اﻠﺠذاﻤﻲ اﻠﺠذاﻢ
absence of treatment. The central point of the spectrum (BB) is the patient most unstable, with wide variability in clinical appearance. It is likely that in endemic areas, a high proportion of people are infected by M. leprae and no disease or have developed lepromatous leprosy. The term indeterminate leprosy describes patients presenting with very early lesions that cannot be categorized definitely along the immunopathologic spectrum (e.g., cannot be determined as BT or LL).
Staining of Mycobacterium leprae Bacilli
The classical method for demonstrating leprosy bacilli in lesions is a modified Ziehl-Neelsen stain, where

\[
\text{BI} = 0: \text{no bacilli observed}
\]
<table>
<thead>
<tr>
<th>BI</th>
<th>Bacillary Index</th>
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<tbody>
<tr>
<td>1:</td>
<td>1: 1 to 10 bacilli in 10 to 100 high-power fields (hpf, oil immersion)</td>
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<tr>
<td>2:</td>
<td>2: 1 to 10 bacilli in 1 to 10 hpf</td>
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<td>3:</td>
<td>3: 1 to 10 bacilli per hpf</td>
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<tr>
<td>4:</td>
<td>4: 10 to 100 bacilli per hpf</td>
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<tr>
<td>5:</td>
<td>5: 100 to 1,000 bacilli per hpf</td>
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<tr>
<td>6:</td>
<td>6: &gt;1,000 bacilli per hpf</td>
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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...
For general discussions of clinical leprosy and leprosy pathology, the reader is referred to Job (147) and
Early, Indeterminate Leprosy

Many patients present with obvious or advanced skin and peripheral nerve lesions (the latter are primarily nerve damage).
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 formation of large, firm, nodular lesions that resemble dermatofibromas. 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).
Lepromatous leprosy, in the usual macular or infiltrative-nodular lesions, exhibits an extensive cellular infiltrate that is composed of monocytes, lymphocytes, and plasma cells. The macrophages have abundant eosinophilic cytoplasm and contain a mixed population of solid and fragmented bacilli (Bl = 4 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 form epithelioid cell granulomas. Lymphocyte infiltration is not prominent, but there may be many plasma cells.

Histopathology.
Lepromatous leprosy = اﻠﺠذاﻤﻲ اﻠﺠذاﻢ

In time, and with anti mycobacterial chemotherapy, degenerate bacilli accumulate in the macrophages—the so-called lepra cells. Of the different forms of leprosy, these are seen most often in lepromatous leprosy. The 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

Histoid leprosy shows the highest loads of bacilli (frequently, the BI is 6), and the majority are solid staining.
Histopathology.

The important difference between LL and BL leprosy histology is that in BL, the lymphocytes are more prominent and there is less granuloma formation compared to LL. In BL, the Bl classification 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 macrophages 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

*Tuberculoid Leprosy*
The skin lesions of tuberculoid (TT) leprosy are scanty, dry, erythematous, hypopigmented papules or plaques with sharply defined margins. They tend to be distributed symmetrically and may involve the face, hands, and feet. The lesions heal rapidly on chemotherapy.

Histopathology
Primary TT leprosy has large epithelioid cells arranged in compact granulomas and neurovascular bundles.
Peripheral Nerves

In all of these patterns of leprosy, the major peripheral nerves are often undergoing parallel pathologies.
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 have fluctuations such as upgrading reactions, which are associated with edema that results in enlargement of lesions with more erythema. 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 well evaluated. The distinction between upgrading and downgrading reactions is difficult to make and may require serial examinations.
there is edema within and about the granulomas and proliferation of fibrocytes in the dermis. In upgrading reactions, who upgrade on therapy show old foamy macrophages and degenerate bacilli admixed with new epithelioid cell granulomas.
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 develop and 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 abundant and there is a marked dermal edema. The bacilli are few, if any, and lie free in the dermis. The epidermis may show extensive acanthosis. The permeation of the dermis by lymphocytes is enormous and there is a tendency for the epithelium to split into the dermis and to produce large numbers of epidermal pearls. The perivascular lymphocytes are often of the Peyer's patch variety.
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, rash, and arthralgia are not present. The most frequent manifestation is diffuse erythema and edema of the hands and feet. Edema may also occur on the face, upper arms, and legs. Pain, tenderness, and erythema of affected areas may be intense. Skin changes due to the reaction may be subtle, particularly on the legs, into ulcers. There may be repeated attacks or continuous appearance of new lesions for years.

**Histopathology.** In the Lucio reaction, vascular changes are critical. Endothelial proliferation leading to luminal obliteration is brought on by the vascular occlusion, leads to hemorrhagic infarcts and results in 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 mycolic acid 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 reactivity, patients with lepromatous leprosy have a defect in cell-mediated immune responses specifically to live bacilli and thus do not adequately activate macrophages to destroy phagocytosed bacilli. 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... 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 to the...
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In patients with either ENL or the Lucio reaction, deposits of IgG and the third component of complement...
Lepromatous leprosy = اﻠﺠذاﻤﻲ اﻠﺠذاﻢ

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...