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, is very chronic, and depends on host-parasite immunologic responses. The ... 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 ... 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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absence of treatment. The central point of the spectrum (BB) is the most unstable, with most patients progressing to LL if not treated. The term indeterminate leprosy is used to describe patients presenting with very early lesions that cannot be categorized definitely along the immunopathologic spectrum (e.g., cannot be determined as BT or LL). It is likely that in endemic zones, a high proportion of people are infected by M. leprae, a high proportion have full immunity and no disease or have developed indeterminate leprosy.
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).

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

Many patients present with obvious or advanced skin and peripheral nerve lesions (the latter are primarily nerve...
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 in
A distinctive variant of lepromatous leprosy, the histoid type, first described in 1963 (149), is characterized by the presence of numerous, small, subcutaneous nodules that may be confused with 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).
Histopathology.

Lepromatous leprosy, in the usual macular or infiltrative-nodular lesions, exhibits an extensive cellular infiltrate that...
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**

Histoid leprosy shows the highest loads of bacilli (frequently, the BI is 6), and the majority are solid staining.
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 with punched-out centers. There may be small satellite lesions. Edema is prominent in the lesions.
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 borders. Over time, they become skin-colored. Local lymph nodes may also be involved. Thickened local peripheral nerves may be found. The lesions heal rapidly on chemotherapy.

Histopathology
Primary TT leprosy has large epithelioid cells arranged in compact granulomas and...
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.
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 develop type 2 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.
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. Typically,
there is edema within and about the granulomas and proliferation of fibrocytes in the dermis. In upgrading reactions, the...
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, develop over 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.
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, edema, and pain usually occur simultaneously, and the pain is more pronounced. It typically resolves within one to three weeks. Lesions may appear on the face, arms, legs, and other body areas and may form crusted erosions or frank ulcers.

**Histopathology.** In the Lucio reaction, vascular changes are critical. Endothelial proliferation leads to luminal obliteration, resulting in hemorrhagic infarcts and crusted erosions or 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 the typical of mycobacteria (81). 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 that 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...