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

The sequence of disease pathogenesis is complex and very chronic and depends on host-parasite immunologic responses. The spectrum of leprosy is a continuum, and it can range from a very strongly cellular immune response with few bacilli to an absent cellular immune response with abundant bacilli in tissues. The spectrum includes the following subtypes: TT (tuberculoid), BT (borderline tuberculoid), BB (midborderline), BL (borderline lepromatous), and LL (lepromatous). The term \textit{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 treated.
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absence of treatment. The central point of the spectrum (BB) is the patient presenting with widespread disease.

It is likely that in endemic countries, a high proportion of people are infected by M. leprae, have full immunity and no disease or have developed some disease (e.g., few lesions with rapid self-healing). Indeterminate leprosy is defined as patients presenting with skin 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 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>Bacilli per hpf</th>
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<tbody>
<tr>
<td>1</td>
<td>1: 1 to 10 bacilli in 10 to 100 hpf (oil immersion)</td>
</tr>
<tr>
<td>2</td>
<td>2: 1 to 10 bacilli in 1 to 10 hpf</td>
</tr>
<tr>
<td>3</td>
<td>3: 1 to 10 bacilli per hpf</td>
</tr>
<tr>
<td>4</td>
<td>4: 10 to 100 bacilli per hpf</td>
</tr>
<tr>
<td>5</td>
<td>5: 100 to 1,000 bacilli per hpf</td>
</tr>
<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 method is a form of immunofluorescence.
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 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.

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

Lepromatous leprosy, in the usual macular or infiltrative-nodular lesions, exhibits an extensive cellular infiltrate that consists of lymphocytes, histiocytes, and scavenger macrophages. 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 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.
In time, and with anti mycobacterial chemotherapy, degenerate bacilli accumulate in the macrophages—the so-called lepra 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 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. 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.
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 react adversely 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 fully evaluated.
there is edema within and about the granulomas and proliferation of fibrocytes in the dermis. In upgrading reactions, the...
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, are seen. These lesions are present for a few 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 found in large numbers. Despite these changes, no bacilli remain and macrophages have a granular pink hue on 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, skin lesions, and other symptoms may appear suddenly and quickly subside. The lesions typically begin on the fingers, toes, face, and neck, and spread from there. The skin thickens and hardens into calluses that may progress into painful 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 leads to luminal obliteration, endarteritis, and intimal thickening. These changes result in vascular occlusion, which 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, leprosy 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 (delayed-type hypersensitivity) that is specific for M. leprae, because patients with lepromatous leprosy show normal immunologic responses to antigens other than lepromin in both \textit{in vivo} and \textit{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...
Leprosy
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 4-6 mm in diameter. The test is positive in a high proportion of infected individuals who lack overt clinical disease, and it is used to detect infection and monitor response to treatment.