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5th Edition

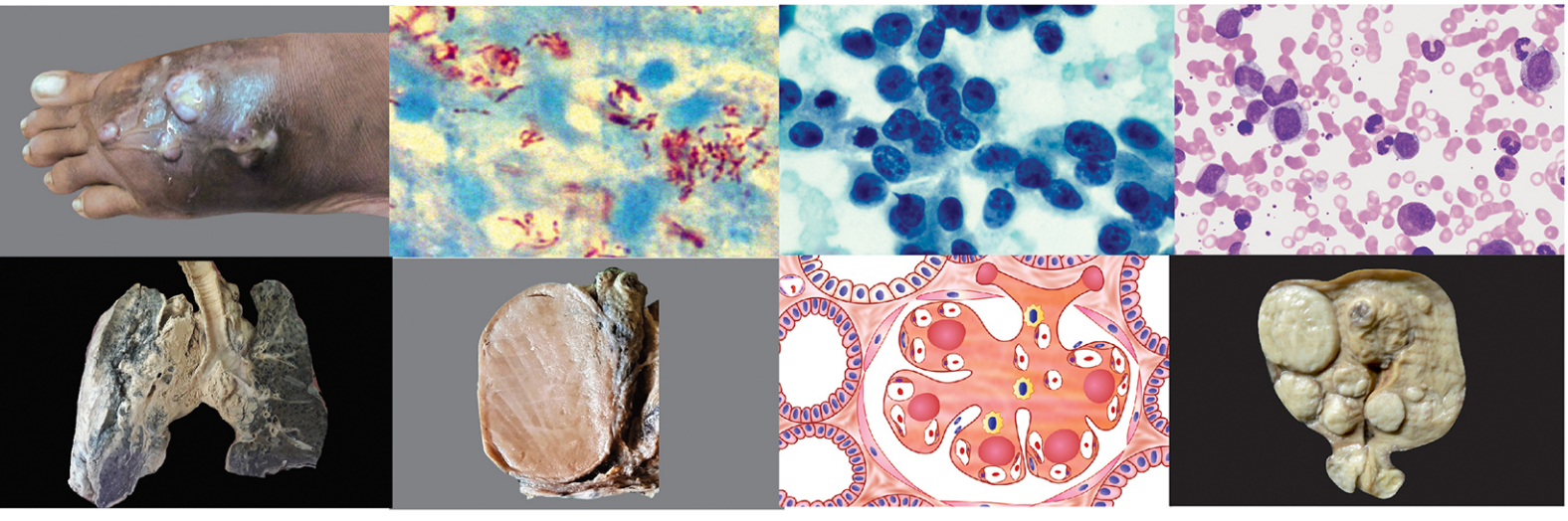
Exam Preparatory Manual for Undergraduates

Pathology

Online Additional Reading

HIGHLIGHTS

- **Recent Updates in Pathology:** Incorporates the latest advancements and updates in the field.
- **Assured Success:** High-scoring potential in theory, viva-voce, and practical examinations.
- **Complete Examination Preparation:** Covers everything an undergraduate student needs to know before the pathology examination, presented in a concise text with boxes, flowcharts, tables, figures, and illustrations, making it an ideal quick reference before examinations.
- **Highlighted Key Pointers:** Essential points are emphasized to aid in quick revision.
- **High-Yield Content:** Exclusive coverage of high-yield points to help answer essay questions, short notes, short answer questions, and MCQs effectively.
- **Scenario-Based Questions:** Includes scenario-based essays and MCQs, along with frequently asked questions in examinations.
- **Comprehensive Subject Coverage:** Essential and must-know subjects are thoroughly covered, while nice-to-know topics are provided online in supplementary boxes that help in scoring well in qualifying examinations. Online illustrations further aid in understanding the subject easily.



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CHAPTER 4

Infections and Infestations

Chapter Outline

MYCOBACTERIAL INFECTIONS

Mycobacteria are bacteria that appear as slender, aerobic rods. They grow in straight or branching chains. Mycobacteria have a characteristic waxy cell wall composed of unusual glycolipids and lipids including mycolic acid. This wall is responsible for its acid-fast nature on staining. Acid-fast means that they will retain stains, even on treatment with a mixture of acid and alcohol. They are weakly gram-positive. Two important mycobacteria that cause granulomatous disease are *Mycobacterium tuberculosis (tuberculosis)* and *Mycobacterium leprae (leprosy)*. Tuberculosis is discussed on pages 559-67 of Chapter 17. Nontuberculous mycobacteria (NTM) are mycobacteria other than *M. tuberculosis* and *M. leprae*. Of the 150 NTM species, the most frequent human pathogens are *Mycobacterium avium* complex (MAC).

Leprosy

PA 10.3 (CC): Define and describe the pathogenesis and pathology of leprosy.

Leprosy or **Hansen disease** (named after the discovery of the causative organism by Hansen), is a **chronic, granulomatous, slowly progressive, destructive infection** caused by ***Mycobacterium leprae***. Leprosy is one of the oldest human diseases and lepers were isolated from the community in the olden days.

Sites of involvement: *Mycobacterium leprae* mainly affects the **peripheral nerves, skin, and mucous membranes** (nasal) and results in disabling deformities.

***Mycobacterium leprae*:** The characteristic features of this mycobacteria are:

- **Slender, weakly acid-fast intracellular bacillus:** It closely resembles *Mycobacterium tuberculosis* but is less acid-fast.
- **Proliferates at low temperature of the human skin:** These bacilli prefer temperatures lower than those in internal organs. **Cannot be cultured** on artificial media or in cell culture. Lepra bacilli grow at sites where the temperature is below that of the internal organs. Examples: **Footpads of mice**, ear lobes of hamsters, rats, and other rodents. **Experimentally transmitted to nine branded armadillos** (they have low body temperature ranging from 32–34°C).
- **Antigen in lepra bacilli:** The bacterial cell wall contains mainly 2 antigens namely *M. leprae*-specific phenolic glycolipid (PGL-1) and lipoarabinomannan (LAM).

Mode of transmission: Leprosy has **comparatively low communicability**.

1. **Inoculation/inhalation:** Likely to be transmitted from person to person through **aerosols from** asymptomatic lesions in the **upper respiratory tract**. Inhaled *M. leprae*, is taken up by alveolar macrophages and disseminates through the blood, but replicates only in relatively cool tissues of the skin and extremities.
2. **Intimate contact:** It may be transmitted by intimate contact for many years with untreated leprosy patients. They shed many bacilli from damaged skin, nasal secretions, mucous membranes of the mouth, and hair follicles.

Source of infection: *M. leprae* is present in **nasal/respiratory secretions or ulcerated lesions of patients** suffering from leprosy.

Incubation period: Generally, 5–7 years.

Classification

Q. Classify leprosy.

A. Ridley and Jopling (1966) Classification (Table 4.1)

It **depends on the clinicopathological spectrum of the disease**, which is **determined by the immune resistance of the host (Flowchart 4.1)**. Leprosy is classified into five groups with two extreme or polar forms, namely—**tuberculoid and lepromatous types**.

Variants of leprosy: These include indeterminate and histoid leprosy.

Q. Write a short note on indeterminate leprosy.

- **Indeterminate leprosy:** It is an initial nonspecific stage of any type of leprosy. Pure neural leprosy with neurologic involvement is the main feature. The skin lesions of leprosy are not seen. Indeterminate leprosy and tuberculoid lesions are paucibacillary and their diagnosis is made together with clinical evidence (for microscopy *refer* page 110).
- **Histoid leprosy:** It is a **variant of lepromatous leprosy** in which the **skin lesions grossly resemble nodules of dermatofibroma** (a soft tissue tumor involving skin) and microscopically shows numerous lepra bacilli.

TABLE 4.1 Ridley and Jopling (1966) classification and associated immune response.

Group	*Immune response*
Tuberculoid leprosy (TT)	Polar form that has maximal immune response
Borderline tuberculoid (BT)	Immune response falls between BB and TT
Borderline leprosy (BB)	Immune response exactly falls between two polar forms of leprosy
Borderline lepromatous (BL)	Immune response that falls between BB and LL
Lepromatous leprosy (LL)	Polar form with the least immune response

B. WHO Classification

- **Paucibacillary:** All cases of tuberculoid leprosy and some cases of borderline type are paucibacillary. They do not show lepra bacilli on microscopic examination.
- **Multibacillary:** All cases of lepromatous leprosy and some cases of borderline type are multibacillary.

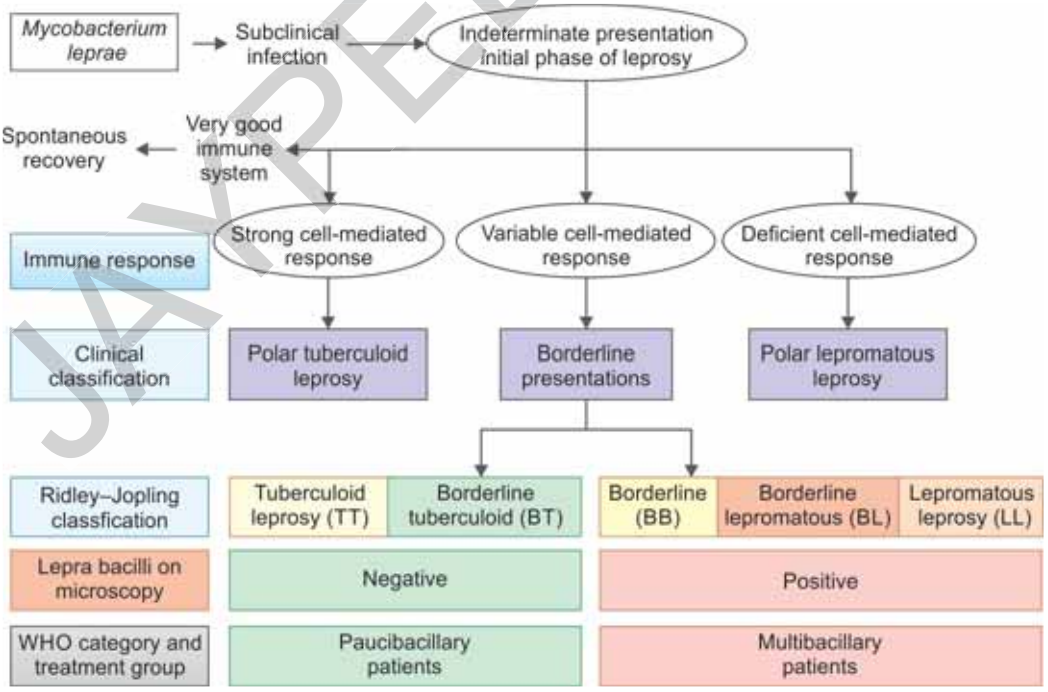
Pathogenesis

Ingestion of mycobacteria by macrophages and proliferation: After the inoculation, *M. leprae* is taken up by macrophages and disseminates in the blood. However, the mycobacteria **replicate mainly in relatively cool tissues** of the skin and extremities. Its proliferation occurs at 32–34°C, the temperature of the human skin.

Virulence depends on the properties of the mycobacterial cell wall: *Mycobacterium leprae* does not secrete any toxins. Its virulence depends on the properties of its cell wall (like that of *M. tuberculosis*) and immunization with BCG may provide some protection against *M. leprae* infection.

Cell-mediated immunity: An infected individual develops delayed-type hypersensitivity reactions (cell-mediated/type IV hypersensitivity reaction) to dermal

Flowchart 4.1: Ridley–Jopling classification of leprosy.



Classification of leprosy:
1. Ridley and Jopling classification.
2. WHO classification: Paucibacillary and multibacillary.

Lepromatous leprosy (LL): Polar form with the least immune response.
Tuberculoid leprosy (TT): Polar form with maximal immune response.

Fite-Faraco stain: Modified Ziehl-Neelsen stain used for demonstration of lepra bacilli in tissue.

injections of **lepromin.** Lepromin is a bacterial extract obtained from lepra bacillus.

Different T-cell responses: *M. leprae* causes two different patterns of disease namely tuberculoid and lepromatous. They have different types of helper T-lymphocyte response to *M. leprae*. The **T-helper (Th1) lymphocyte response** to *M. leprae*, determines whether an individual develops a tuberculoid or lepromatous type of leprosy.

- **Tuberculoid leprosy:** These patients **have a Th1 response**. This is associated with the secretion of IL-2 and IFN-γ as well as a Th17 response. The IFN-γ is essential for an effective host macrophage response.
- **Lepromatous leprosy:** These patients have **a weak Th1 response** and, some have a **relative increase in the Th2 response.** This causes poor cell-mediated immunity and proliferation of lepra bacilli. Sometimes, antibodies may be produced against *M. leprae* antigens, but they are usually not protective. These antibodies may combine with free antigens leading to the formation of immune complexes. These can lead to the development of erythema nodosum, vasculitis, and glomerulonephritis.

MORPHOLOGY

Two extremes or polar forms of the diseases are the tuberculoid and lepromatous types. **M. leprae multiplies at temperatures** below the core human body temperature. Hence, the **lesions tend to occur in cooler parts of the body** (e.g., hands and face). Lesions show marked variations. It may vary from small, insignificant, and self-healing macules of tuberculoid leprosy to the diffuse, and disfiguring lesions of lepromatous leprosy. This marked variation in disease presentation is due to differences in immune reactivity.

Q. Write a short note on the morphology of tuberculoid leprosy.

1. Tuberculoid Leprosy

It is the **less severe form** of leprosy. The lesions of tuberculoid leprosy cause **minimal disfigurement** and are **not infectious**. It is **very slow in its course** and most patients die with leprosy.

Lesion in skin

- **Number of lesions: Single or very few lesions**.
- **Common sites:** Usually on the **face, extremities, or trunk**
- **Type: Localized, well-demarcated, flat, red or hypopigmented, dry, scaly, elevated, skin patches (Fig. 4.1)** having raised outer edges and depressed pale centers (central healing). As they progress they develop irregular shapes with induration.

Nerve involvement

- **The dominating feature of tuberculoid leprosy is nerve involvement**. They often show **asymmetric** involvement of large peripheral nerves.
- **Loss of sensation:** Nerve involvement causes **loss of sensation in the skin** and atrophy of skin and muscle. These affected parts are liable to trauma and lead to the development of **chronic skin ulcers**.
- **Consequences:** It may lead to **contractures, paralyses, and autoamputation of fingers or toes**. Involvement of facial nerve can lead to paralysis of the eyelids, with keratitis and corneal ulcerations.

Fig. 4.1: Localized, well-demarcated, red or hypopigmented skin patches on the face (arrow).

Microscopy (Figs. 4.2A and B)

- **Granuloma:** These are well-formed, circumscribed, and **non-caseating** (no caseation). The term "tuberculoid leprosy" is used because the granulomas resemble those found in tuberculosis, It is seen in all involved sites and the dermis of skin. Granulomas are composed of **epithelioid cells** (modified macrophages), **Langhans giant cells, and lymphocytes.** though they **lack necrosis**.
- **Absence of Grenz zone:** Granulomas in the dermis extend to the basal layer of the epidermis (without a clear/Grenz zone).
- **Fite-Faraco** (modified Z-N stain for demonstration of lepra bacillus) stain generally **does not show lepra bacillus**, hence the name "**paucibacillary**" leprosy.
- **Perineural (surrounding nerve fibers) inflammation**: Nerve fibers are usually swollen and infiltrated with **lymphocytes (Fig. 4.2B).**
- **Strong T-cell immunity:** It is responsible for granuloma formation, without lepra bacilli.
- **Peripheral nerves:** They are surrounded by **granulomatous inflammatory reactions**. The destruction of small dermal nerve twigs may occur and is **responsible for the sensory deficit** associated with tuberculoid leprosy.

2. Lepromatous Leprosy

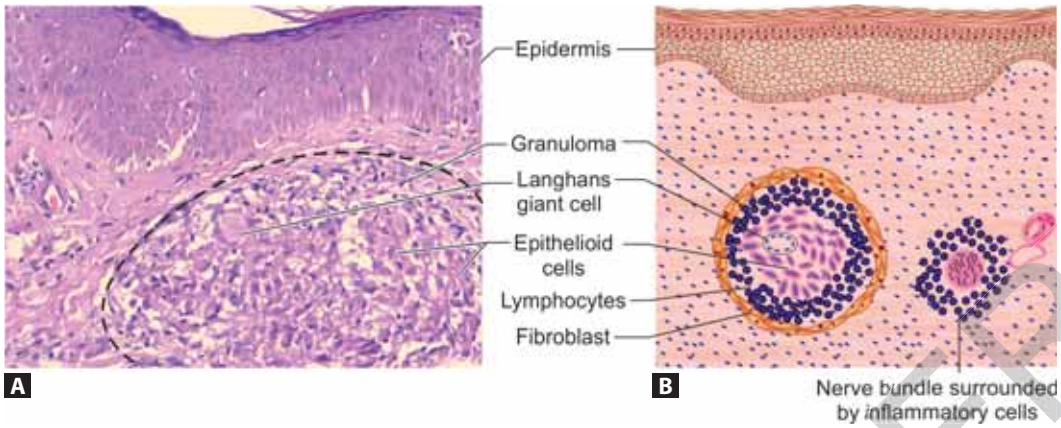
It is the **more severe form** and is also called **anergic leprosy**, because of the unresponsiveness (anergy) of the host immune system.

Q. Write a short note on the morphology of lepromatous leprosy.

Sites involved: These include **skin, peripheral nerves, anterior eye chamber, upper airways** (down to the larynx), **testes, hands, and feet**.

Lesion in skin

- **Symmetric thickening of skin.**
- **Nodules. Multiple, symmetric, macular, papular, or nodular lesions:** The nodular skin lesions may ulcerate. Most skin lesions are **hypoesthetic or anesthetic**.



Figs. 4.2A and B: Microscopy of tuberculoid leprosy with circumscribed noncaseating granulomas (dotted line): (A) Photomicrograph; (B) Diagrammatic.

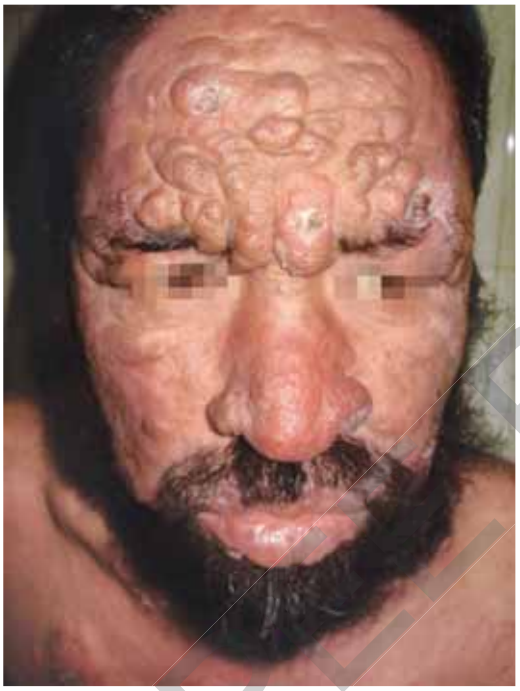


Fig. 4.3: Leonine facies of lepromatous leprosy.

- **Sites of lesions:** More severe involvement of the **cooler areas of skin** (e.g., earlobes, wrists, elbows, knees, and feet), than warmer areas (e.g., axilla and groin). Other sites include eyes, testes, nerves, lymph nodes, and spleen.
- **Leonine facies:** With progression, the **nodular lesions in the face and earlobes may coalesce** to produce a lion-like appearance known as **leonine facies (Fig. 4.3)**. This may be accompanied by loss of eyebrows and eyelashes.

Peripheral nerves

- Particularly the **ulnar and peroneal nerves** are **symmetrically invaded** with mycobacteria.
- **Loss of sensation and trophic changes** in the hands and feet may follow the damage to the nerves.

Other sites

Testes: Usually, severely involved, leading to the destruction of the seminiferous tubules leading to **sterility**.

The anterior chamber of the eye: It may lead to **blindness**.
Upper airways: Chronic nasal discharge and voice change.

Microscopy of skin lesion (Figs. 4.4 and 4.5)

It shows **nodular or diffuse infiltrates of foamy macrophages containing numerous lepra bacilli.**

- **Flattened epidermis:** Epidermis is thinned and flattened (loss of rete ridges) over the nodules.
- **Grenz** (clear) **zone:** Beneath the epidermis, there is a **narrow, uninvolved "clear zone" of the dermis** (normal collagen) **called the Grenz zone (Figs. 4.4A and B).** It separates the epidermis from nodular accumulations of macrophages.

Q. Write a short note on the lepra cell.

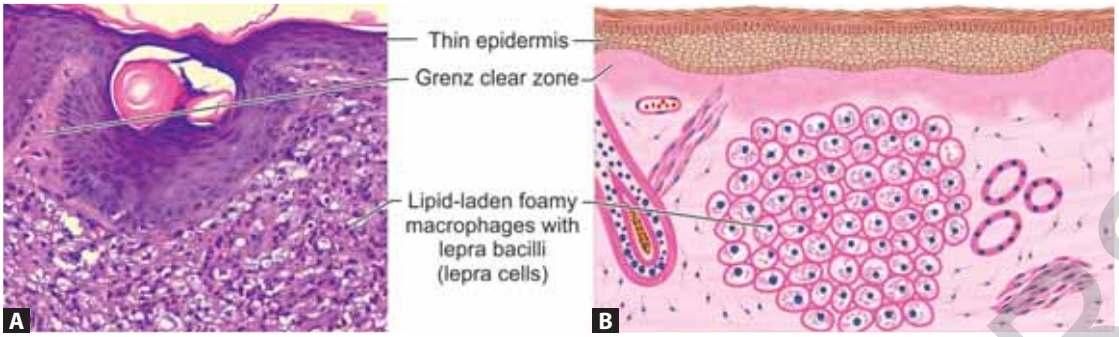
- **Lepra cells (Fig. 4.5A):** The nodular lesions contain large aggregates of **lipid-laden foamy macrophages**. These are called lepra cells, or **Virchow cells**. These are filled with aggregates of acid-fast lepra bacilli (*M. leprae*). The aggregates or masses of acid-fast material inside the macrophage are called **"globi."**
- **Fite-Faraco (acid-fast) stain (Fig. 4.5B):** It shows **numerous lepra bacilli** ("red snappers") **within the foamy macrophages.** They may be arranged in a parallel fashion like **cigarettes in a pack**. Due to the presence of numerous mycobacteria, lepromatous leprosy is also referred to as **"multibacillary"**.
- **Damage to peripheral nerves:** Widespread symmetrical invasion of the mycobacteria into Schwann cells and endoneural and perineural macrophages damages the peripheral nervous system. It **particularly involves the ulnar and peroneal nerves** where they approach the skin surface. Loss of sensation and trophic changes in the hands and feet develop following nerve involvement.
- *M. leprae* in sputum and blood. This may be observed **in advanced cases** of lepromatous leprosy,

3. Borderline Leprosy

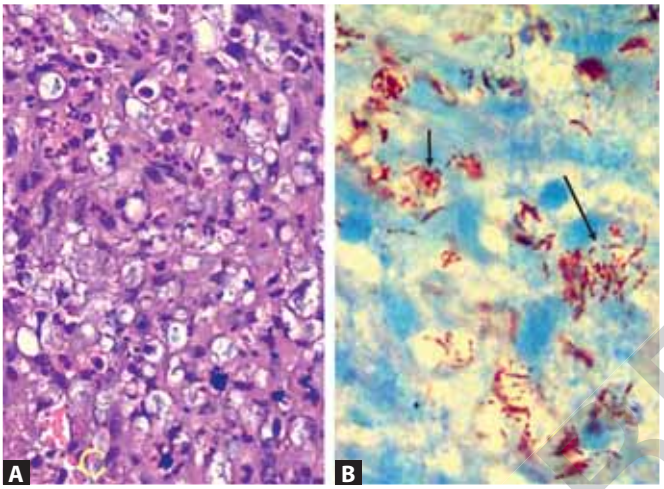
Some individuals may have with intermediate form of disease, called **borderline leprosy.**

Borderline tuberculoid (BT) shows epithelioid cells and numerous lymphocytes with a narrow clear subepidermal zone. Lepra bacilli are few and found in nerves.

Borderline lepromatous (BL) shows predominantly histiocytes, few epithelioid cells, and lymphocytes. Numerous lepra bacilli are found.



Figs. 4.4A and B: Microscopic appearance of lepromatous leprosy: (A) Photomicrograph; (B) Diagrammatic. The epidermis is thinned and the dermis shows dense collections of lepra cells. The epidermis is separated from the collections of lepra cells by an uninvolved Grenz zone.



Figs. 4.5A and B: Lepromatous leprosy: (A) High power view showing foamy macrophages; (B) Acid-fast lepra bacilli within macrophages (Fite–Faraco stain) (arrows).

Mid-borderline (BB) or dimorphic form shows sheets of epithelioid cells without any giant cells. Few lymphocytes are found in the perineurium. Lepra bacilli are seen mostly in nerves.

4. Indeterminate Leprosy

Microscopically, features are nonspecific and few findings help in suspecting leprosy. These include (1) local infiltration of lymphocytes or mononuclear cells surrounding the skin adnexa (e.g., hair follicles and sweat glands) or around blood vessels, (2) involvement of nerve (if seen strongly favors the diagnosis), and (3) finding of lepra bacilli (which confirms the diagnosis).

Lepromin Test

It is **not a diagnostic test** for leprosy. It is **used for classifying leprosy** based on the immune response.

Procedure: An antigen extract of *M. leprae* called lepromin is intradermally injected.

Q. Write a short note on the lepromin test/Mitsuda reaction.

Reaction: (1) An **early positive reaction** appearing as an indurated area in 24–48 hours is called the **Fernandez reaction,** and (2) a **delayed granulomatous reaction** appearing after 3–4 weeks is known as the **Mitsuda reaction.**

Interpretation: (1) **Lepromatous leprosy shows** a **negative lepromin test** due to suppression of cell-mediated immunity. (2) **Tuberculoid leprosy** shows a **positive lepromin test** because of delayed hypersensitivity reaction.

Reactions in Leprosy

The immunity in leprosy may change spontaneously or following treatment.

Type I reaction: Borderline leprosy is the most unstable form of leprosy where immune status may shift up or down.

These are called type I reactions, which may be of **two types:**

1. **Upgrading reactions:** If immunity improves, the disease may shift towards tuberculoid leprosy.
2. **Downgrading reaction:** If the immunity decreases, the disease moves towards lepromatous leprosy.

Type II reaction or erythema nodosum leprosum: It **occurs mostly in lepromatous leprosy**, particularly when on treatment. Clinically, it presents with (1) tender red plaque or nodules and (2) fever, malaise, and arthralgia. Microscopically, it shows **necrotizing vasculitis and lepra bacilli in the foamy macrophages.**

Differences between lepromatous and tuberculoid leprosy are presented in **Table 4.2.**

Diagnosis of Leprosy

1. **Clinical examination:**
   - **Sensory testing**
   - Examination of peripheral nerve
2. **Demonstration of acid-fast bacilli: Skin smears prepared by slit** (split skin smears by splitting the skin) **and scrape method** (scrapings from cut edges of the dermis). *Mycobacterium leprae* can be demonstrated in split skin smears by splitting the skin, and in nasal smears by the following techniques:
   - **Acid-fast (Ziehl–Neelsen) staining.** The staining procedure is similar to that procedure employed for *M. tuberculosis* but can be decolorized by lower concentration (5%) of sulphuric acid (less acid-fast).

TABLE 4.2 Differences between lepromatous and tuberculoid leprosy.

Characteristics	*Lepromatous leprosy*	*Tuberculoid leprosy*
Clinical features		
Skin lesions	Symmetrical, multiple, ill-defined, macular, nodular	Asymmetrical, hypopigmented, well-defined macular
Disfigurement	Leonine facies, loss of eyebrows, pendulous earlobes, claw hands, saddle nose	Minimal disfigurement
Nerve involvement	Seen but with less severe sensory loss than tuberculoid	Common with sensory disturbances
Microscopy of skin lesions		
Type of lesion	Nodular or diffuse collections of lepra cells within the dermis	Noncaseating granulomas are composed of epithelioid cells and Langhans giant cells
Grenz/clear zone between inflammatory cells and epidermis	Present	Absent
Lepra bacilli	Plenty within the lepra cells as globular masses (globi)	Rare if any
Bacillary index	4 or 5	0
Other features		
Immunity	Suppressed-low resistance	Good immunity-high resistance
Lepromin test	Negative	Positive
Infectivity	High	Low
Complications	Erythema nodosum leprosum (ENL) may cause vasculitis, glomerulonephritis, and nerve damage	Nerve damage can lead to sensory disturbance, paralysis

3. **Skin biopsy:** Fite–Faraco staining procedure is a modified ZN procedure and is better for tissue sections **(Fig. 4.5B)**. Gomori methenamine silver (GMS) staining can also be used.
4. **Nerve biopsy**
5. **Molecular method: Polymerase chain reaction (PCR).**
6. *IgM antibodies to PGL-1 antigen*. Detected in 95% of cases of lepromatous leprosy but only in 60% of cases of tuberculoid leprosy.

SPIROCHETE INFECTIONS

Spirochetes are long, slender, corkscrew-shaped bacteria covered by a specialized cell envelope (membrane) called an outer sheath. This envelope may mask its antigens from the host's immune response. It also permits them to move by flexion and rotation.

Identification: Spirochetes have the basic cell wall structure of gram-negative bacteria. But, they stain poorly with the Gram stain. They cannot be detected by routine light microscopy. Specialized techniques, such as **darkfield microscopy or silver impregnation,** are required for their detection.

Diseases caused by spirochetes: They generally cause chronic and relapsing disease. Three spirochetes that cause disease are *Treponema*, *Borrelia*, and *Leptospira*.

Syphilis

Syphilis (lues) is a **chronic, sexually transmitted infection (STI)** caused **by spirochete *Treponema pallidum***. It manifests with multiple clinical and pathologic presentations.

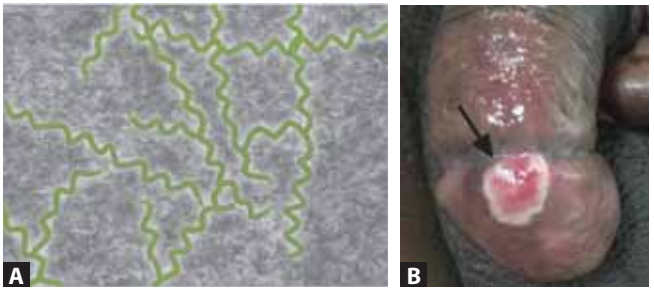
Etiology: Syphilis is caused by a spirochete Treponema pallidum (Fig. 4.6A). *Treponema pallidum* has the following characteristics.

- *T. pallidum* is a **thin, delicate, corkscrew-shaped spirochete**, that measures about 10 µm long with tapering ends and has about 10 regular spirals. It is very fragile and is killed by soap, antiseptics, drying, and cold.
- **Actively motile**, showing rotation around the long axis, backward and forward motion.
- **Cannot be grown in artificial media**.
- **Staining:** It does not stain with ordinary bacterial stains and *Treponema pallidum* is too slender to be seen in Gram stain. It can be visualized by **silver stains, dark-field examination, and immunofluorescence techniques**.

Source of infection: An **open lesion of primary or secondary syphilis.** Lesions in the mucous membranes or skin of the genital organs, rectum, mouth, fingers, or nipples.

Mode of transmission: These are through the following routes:

- **Sexual contact:** It is the **usual mode of spread**.



Figs. 4.6A and B: (A) Diagrammatic appearance of *Treponema pallidum* under Dark-field examination; (B) Primary chancre on glans penis (arrow).

- **Transplacental transmission**: It can also be transmitted by the mother suffering from active disease to the fetus (during pregnancy) or during delivery. It results in congenital syphilis.
- **Blood transfusion.**
- **Direct contact with the open lesion** is a rare mode of transmission.

Pathogenesis

Basic microscopic lesion: Irrespective of stage, the basic microscopic lesion of syphilis consists of:

- **Proliferative endarteritis:** It is a characteristic obstructive vascular lesion in which mononuclear infiltrates surround small vessels (arteries and arterioles) and is termed **periarteritis**. Much of the pathologic changes of syphilis can be due to the ischemia produced by these vascular lesions. The pathogenesis of endarteritis is unknown.
- **Mononuclear inflammatory infiltrate:** It consists predominantly of **plasma cells** (plasma cell–rich infiltrate) accompanied by **lymphocytes**.

Stages of Syphilis (Fig. 4.7)

Q. Write a short note on the stages of syphilis.

Treponema pallidum passes from the site of inoculation to regional lymph nodes, enters the systemic circulation, and disseminates throughout the body. Syphilis can be **(1) congenital or (2) acquired**. The course of acquired syphilis is divided into three stages: (i) primary syphilis, (ii) secondary syphilis, and (iii) tertiary syphilis. These **stages have distinct clinical and pathologic manifestations.**

Acquired Syphilis

Primary syphilis

Q. Write a short note on primary chancre.

Treponemes may spread throughout the body by blood and lymphatics even before the appearance of the primary chancre.

Primary chancre: It is the **classical lesion of primary syphilis**. Primary chancre develops about **3 weeks after contact** with an infected individual. It is **usually, painless** and often unnoticed.

MORPHOLOGY

Gross

Sites: Primary chancre occurs at sites of entry of *T. pallidum*. The primary chancre is located at the site of treponemal invasion.

- **Men:** It is on the **penis (Fig. 4.6B) or scrotum of 70% of men.**
- **Women:** It is on the **cervix, vulva,** and **vaginal wall of 50% of women.**

It may also be seen in the anus or mouth.

Hard chancre: It is a **single, firm, nontender (painless), slightly raised, red papule** (chancre) up to several centimeters in diameter. It erodes to create a **clean-based shallow ulcer**. Because of the induration surrounding the ulcer (creates a buttonlike mass), it is designated as a **hard chancre (Fig. 4.6B).**

Microscopy

Mononuclear infiltration: Primary chancre consists of a clean-based shallow ulcer with mononuclear infiltrate. This consists of **plasma cells,** with scattered macrophages and lymphocytes. These mononuclear cells are also seen surrounding the blood vessels (periarteritis).

Blood vessels with proliferative endarteritis (luetic vasculitis): It is characterized by endothelial cell proliferation which progresses to intimal fibrosis.

Demonstration of treponema: Plenty of treponemes can be demonstrated in the chancre by: (1) silver stains (e.g., Warthin-Starry stain) or (2) immunofluorescence techniques or (3) Dark-field examination.

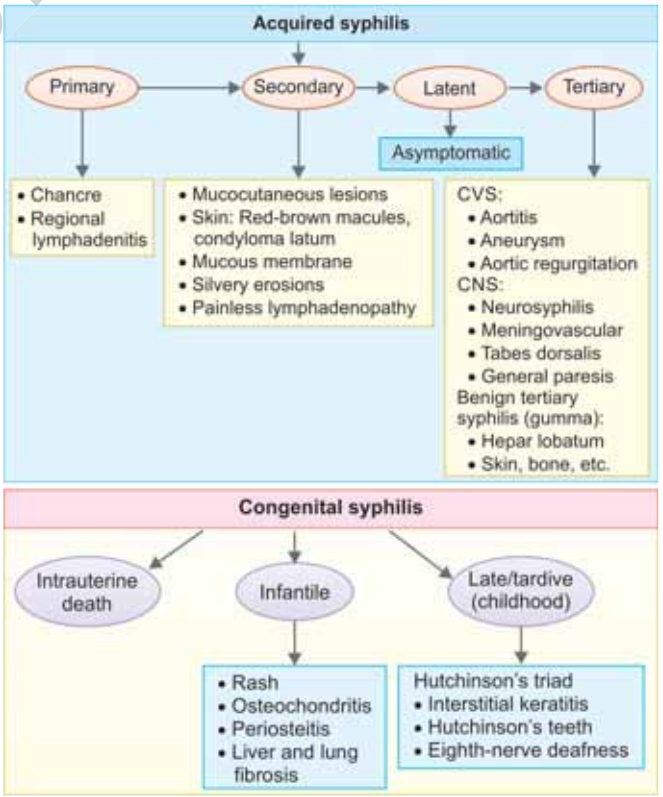


Fig. 4.7: Various manifestations of syphilis.
(CVS: cardiovascular system; CNS: central nervous system)

Regional lymphadenitis: It is due to nonspecific acute or chronic inflammation, plasma cell-rich infiltrates, or granulomas.
Fate: Primary chancre **heals in 3–6 weeks with/without therapy**.

Secondary Syphilis

Q. Write a short note on secondary syphilis.
This stage develops **2–10 weeks after the primary chancre** in approximately 75% of untreated patients. Its manifestations are due to systemic spread and proliferation of the spirochetes within the skin and mucocutaneous tissues.

MORPHOLOGY

Mucocutaneous Lesions

These are painless, superficial lesions that contain spirochetes and are infectious.
Skin lesions: These consist of the following:

- **Skin rashes:** They consist of **discrete red-brown macules** less than 5 mm in diameter, **but they may be maculopapular, follicular, scaly, pustular, or annular**. They are **more frequent on the palms of the hands** (*refer* **online Fig. 4.8A**), or **soles** of the feet.
- **Condylomata lata** (*refer* **online Fig. 4.8B**)**:** These are **broad-based, elevated plaques** with numerous spirochetes. They are seen in moist areas of the skin, such as the **anogenital region (perineum, vulva, and scrotum), inner thighs, and axillae**.

Mucosal lesions: Usually occurs in the mucous membranes of the **oral cavity, pharynx, or genital region** (e.g., **vagina**). They appear as **silvery-gray superficial erosions**. These lesions contain numerous *T. pallidum* and are **highly infectious**.
Microscopy of lesions of secondary syphilis is similar to primary chancre, i.e., infiltration by plasma cells and endarteritis obliterans.

Painless Lymphadenopathy

Lymphadenopathy especially involves **epitrochlear nodes** and shows plenty of spirochetes.

Symptoms: Secondary syphilis may manifest with mild fever, malaise, and weight loss which may last for several weeks. Secondary syphilis lasts several weeks. The lesions subside even without treatment, and the patient enters the latent stage of the disease.
Asymptomatic neurosyphilis: It occurs in 8–40% of patients. Asymptomatic neurosyphilis with meningitis, visual changes, or hearing changes occurs in 1–2% of patients.

Tertiary Syphilis

Q. Write a short note on tertiary syphilis and its manifestations.
Asymptomatic latent phase: After the lesions of secondary syphilis have subsided patients enter an asymptomatic latent phase of the disease. The latent period may last for 5 years or more (even decades), but spirochetes continue to multiply. This stage is rare if the patient gets adequate treatment, but can occur in about one-third of untreated patients. Focal ischemic necrosis due to obliterative endarteritis is responsible for many of the processes associated with tertiary syphilis.
Manifestations: Three main manifestations of tertiary syphilis are: **(i) cardiovascular syphilis, (ii) neurosyphilis, and (iii) so-called benign tertiary syphilis.** These may develop alone or in combination.

Cardiovascular syphilis

PA 27.10 (NC): Describe the etiology, pathophysiology, pathology features, and complications of syphilis in the cardiovascular system.

Cardiovascular syphilis accounts for more than 80% of cases of tertiary syphilis. Probably immune response may be involved in its pathogenesis. It most **frequently involves the aorta** and is known as syphilitic aortitis.

MORPHOLOGY

Syphilitic aortitis: Accounts for more than 80% of cases of tertiary disease, and affects the **proximal aorta**.
Saccular aneurysm (*refer* **pages 490-1**) **and aortic valve insufficiency: Occlusion of the vasa vasorum** due to endarteritis leads to **necrosis and scarring of the aortic media** causing loss of elasticity, strength, and resilience. Gradual weakening and slow progressive **dilation of the aortic root and arch** causes **aortic valve insufficiency** and **aneurysms of the proximal aorta**. Syphilitic aneurysms are saccular and seen in the ascending aorta, which is an unusual site for the more common atherosclerotic aneurysms. On gross examination, the aortic intima appears rough and pitted (**tree-bark appearance**).
Myocardial ischemia: Narrowing of the coronary artery ostia (at the origin of the aorta) caused by subintimal scarring may lead to myocardial ischemia/infarction.

Neurosyphilis

It may be asymptomatic or symptomatic.

- **Asymptomatic neurosyphilis:** It accounts for about one-third of neurosyphilis cases. It is detected by **CSF examination**, which shows **pleocytosis (increased numbers of inflammatory cells), elevated protein levels**, or **decreased glucose**. Antibodies can also be detected in the CSF, which is the most specific test for neurosyphilis.
- **Symptomatic disease:** Takes one of several forms
  - **Chronic meningovascular disease:** Chronic meningitis involves the base of the brain, cerebral convexities, and spinal leptomeninges.
  - **Tabes dorsalis:** It is characterized by **demyelination of the posterior column, dorsal root, and dorsal root ganglia**.
  - **General paresis of insane:** Shows generalized brain parenchymal disease with **dementia**; hence called general paresis of insane.

Benign tertiary syphilis

It is characterized by the formation of nodular lesions called **gummas** in any organ or tissue. Gummas reflect the

development of delayed hypersensitivity to the spirochete. Gummas are very rare and may be found in patients with acquired immune deficiency syndrome (AIDS).

MORPHOLOGY

Gumma

May be **single or multiple, white-gray, and rubbery**. They **vary in size** from microscopic lesions to large tumor-like masses.

Site: They occur in most organs but mainly involve:

- **Skin, subcutaneous tissue,** and the **mucous membranes of the upper airway and mouth**. They may produce nodular lesions or, rarely, destructive, ulcerative lesions.
- **Bone and joints:** It causes local pain, tenderness, swelling, and sometimes pathologic fractures.
- In the **liver,** scarring due to gummas may cause a distinctive hepatic lesion known as **hepar lobatum**.

Microscopy: The center of the gumma shows **coagulative necrosis,** surrounded by **plump, palisading macrophages, fibroblasts, and plenty of plasma cells**. Treponemes are scant in gummas.

Congenital Syphilis

Q. Write a short note on congenital syphilis.

Transplacental transmission: *T. pallidum* can cross the placenta and spread from the infected **mother to the fetus** (during pregnancy). Transmission occurs when the **mother is suffering from primary or secondary syphilis** (when the spirochetes are abundant). It can also be transmitted by a mother suffering from primary syphilis to a child during delivery. Because routine serologic testing for syphilis in done in all pregnancies, congenital syphilis is rare.

Manifestations: It can be divided into:

1. **Intrauterine death and perinatal death:** Congenital syphilis may result in intrauterine and perinatal death.
2. **Early (infantile) syphilis:** It manifests in the **first 2 years of life** and is often manifested by **nasal discharge** and congestion **(snuffles)**. Other features are:
   - A **desquamating or bullous eruption/rash** can lead to epidermal sloughing of the skin, mainly in the hands, feet, around the mouth, and anus.
   - **Skeletal abnormalities.** These include:
     - **Syphilitic osteochondritis:** Inflammation of bone and cartilage is more distinctive in the nose. Destruction of the vomer causes the collapse of the nasal bridge. This produces characteristic **saddle nose deformity**.
     - **Syphilitic periostitis:** It involves the tibia and causes excessive new bone formation on the anterior surfaces and leads to **anterior bowing** or **saber shin**.
   - **Liver: Diffuse fibrosis** in the liver can develop and is called **hepar lobatum**.
   - **Lungs: Diffuse interstitial fibrosis** in the lungs can occur and the **lungs appear pale and airless** (**pneumonia alba**).
3. **Late (tardive) syphilis:** It **manifests 2 years after birth, and about 50% of untreated children with neonatal syphilis will develop late manifestations.** Its distinctive manifestations is **Hutchinson's triad**. It consists of (i) **interstitial keratitis**. (2) **Hutchinson's teeth** (they are like small screwdrivers or peg-shaped incisors, with notches in the enamel) and **eighth nerve deafness.**

Laboratory Diagnosis

Immunofluorescence of exudate from the chancre is important for the diagnosis of primary syphilis. Microscopy and polymerase chain reaction (PCR) are also useful.

Serological Tests

- **Nontreponemal antibody tests:** These tests measure antibodies to cardiolipin, a phospholipid present in both host tissues and *T. pallidum*. These antibodies are detected by the rapid plasma reagin and venereal disease research laboratory (VDRL) tests. False-positive VDRL test is found in certain acute infections, collagen vascular diseases (e.g., systemic lupus erythematosus), drug addiction, pregnancy, hypergammaglobulinemia of any cause, and lepromatous leprosy.
- **Antitreponemal antibody tests:** These measure antibodies, which react with *T. pallidum*. These include: (i) fluorescent treponemal antibody absorption test (FTA), and (ii) microhemagglutination assay for *T. pallidum* antibodies.

Jarisch–Herxheimer reaction: Treatment of syphilitic patients having a high bacterial load, by antibiotics can cause a massive release of endotoxins, and cytokine that may manifest with high fever, rigors, hypotension, and leukopenia. This **syndrome** is called the Jarisch–Herxheimer reaction, which **can develop not only in syphilis but also in other spirochetal diseases**, such as Lyme disease.

BACTERIAL DISEASES

PA 10.4 (NC): Define and describe the pathogenesis and pathology of common bacterial, viral, protozoal, and helminthic diseases.

Pyogenic Bacteria

They produce suppurative/purulent inflammation: Pyogenic inflammation is a type of inflammation characterized by increased vascular permeability and leukocytic infiltration, mainly of neutrophils. The neutrophils accumulate at the site of infection due to the release of chemoattractants from the "pyogenic" (pus-forming) bacteria. These bacteria are mostly extracellular gram-positive cocci and gram-negative rods.

MORPHOLOGY

Gross: The size of the lesion depends on the location of the lesion and the organism involved. The size of purulent lesions may range from tiny microabscesses to diffuse involvement of the involved organ or tissue.

Microscopy: It consists of pus, which is formed by masses of dying and dead neutrophils and liquefactive necrosis of the involved tissue.

Consequences: Depends on the site and causative organism. Examples include: Pneumococcal infection of the lung usually spares alveolar walls and causes lobar pneumonia that resolves completely; Staphylococci and *Klebsiella* infection of the lung destroys alveolar walls and form abscesses that heal with scar formation; bacterial pharyngitis resolves without sequelae, and untreated acute bacterial infection of a joint destroys the joint.

Bacteremia: It is an invasion of the bloodstream by bacteria and occurs when bacteria enter the blood. It occurs commonly as an integral part of some infections.

Pyemia: Septicemia is the presence of infective agents in the bloodstream. Pyemia is **septicemia due to pyogenic organisms**. Pyemia occurs when pathogenic organisms enter the bloodstream and form small aggregates (microemboli). They result in either pyemic abscesses or septic infarct in various organs.

Diphtheria

Diphtheria is caused by *Corynebacterium diphtheria*. *Corynebacterium diphtheria* is a slender gram-positive rod with clubbed ends.

Mode of spread: From person to person in respiratory droplets (respiratory diphtheria) or skin exudate (cutaneous diphtheria).

Incubation period: Commonly 3–4 days.

Types: Common types include:

1. **Respiratory diphtheria:** It causes pharyngeal infection. Inhaled *C. diphtheria* is carried in respiratory droplets that proliferate at the site of attachment on the mucosa. It produces exotoxin which causes necrosis of the epithelium and formation of a dense fibrinosuppurative exudate. The coagulation of this exudate on the ulcerated necrotic surface creates a tough, dirty gray to black, superficial membrane known as **pseudomembrane** (because it is not formed by viable tissue). When the membrane sloughs off, there is bleeding which may lead to asphyxia. With control of the infection, the pseudomembrane is either coughed-up or dissolved by enzymatic digestion. The toxin also damages the heart, nerves, and other organs.
2. **Cutaneous diphtheria:** It causes chronic ulcers with a dirty gray membrane without any systemic damage.

Immunization with diphtheria toxoid (formalin-fixed toxin): It stimulates the production of toxin-neutralizing antibodies which protect persons from the lethal effects of the toxin.

Gram-negative Bacterial Infections

Whooping Cough or Pertussis

Pertussis or whooping cough is a highly communicable acute bacterial disease of childhood, caused by the gram-negative coccobacillus ***Bordetella pertussis***. The wide use of the DPT (**D**iphtheria, **P**ertussis, and **T**etanus) vaccine has reduced the prevalence of whooping cough.

Incubation period: About 1–2 weeks.

Pathogenesis: *Bordetella pertussis* has a strong affinity for the bronchial epithelium and invades macrophages. *B. pertussis* proliferates and stimulates the bronchial epithelium to produce abundant tenacious mucus causing laryngotracheobronchitis. In severe cases, it causes bronchial mucosal erosion, hyperemia, and copious mucopurulent exudate. The toxin produced by the organism inhibits neutrophils and macrophages and paralyzes cilia. Within 7–10 days after exposure, the catarrhal stage of whooping cough begins and is the most infectious stage. Peripheral blood shows marked lymphocytosis (up to 90%) and enlargement of lymphoid follicles in the bronchial mucosa and peribronchial region.

Clinical features: It is characterized by **paroxysms of violent coughing** followed by a characteristic **loud inspiratory "whoop."** Other features include low-grade fever, rhinorrhea, conjunctivitis, and excess tear production. The condition is self-limiting but may cause death due to asphyxia in infants.

Bacillary dysentery (*refer* pages 616-7).

VIRAL DISEASES

Poliovirus Infection

Poliovirus causes an acute systemic viral infection. It can produce a wide range of clinical manifestations ranging from mild, self-limited infections to paralysis of limb muscles and respiratory muscles. Poliovirus is a spherical, unencapsulated **RNA virus** belonging to the enterovirus genus.

Mode of infection: Poliovirus infects only humans and is transmitted by the **fecal-oral route**.

Incubation period: About 10 days.

The vaccines [Salk formalin-fixed (killed) vaccine and the Sabin oral, attenuated (live) vaccine] have eradicated polio in India.

Pathogenesis: The polio virus is ingested and replicates in the mucosa of the pharynx, tonsils, and gut (Peyer patches in the ileum). From the mucosa, it spreads through

lymphatics to lymph nodes and eventually the blood. Most poliovirus infections are asymptomatic. In nonimmunized patients, poliovirus infection causes a subclinical or mild gastroenteritis. In about 1% of infected patients, poliovirus secondarily invades the CNS and replicates in motor neurons of the spinal cord (spinal poliomyelitis) or brain stem (bulbar poliomyelitis).

MORPHOLOGY

Acute cases show mononuclear cell perivascular cuffs in the **anterior horn motor neurons of the spinal cord**.

Clinical Features

- **Spinal cord involvement:** When polio affects the motor neurons of the spinal cord, it destroys motor neurons and leads to paralysis.
- **CNS infection:** It causes meningeal irritation and shows features of aseptic meningitis.

Herpes Virus Infections

Herpes viruses are large encapsulated viruses with double-stranded DNA genomes. Herpes viruses cause acute infection followed by latent infection. During latent infection, the viruses persist in a noninfectious form with periodic reactivation and shedding of infectious viruses. Reactivation of the virus causes dissemination of the infection and tissue injury. There are eight types of human herpes viruses, belonging to three subgroups: the α-group (e.g., HSV-1, HSV-2); β-group (e.g., CMV, human herpesvirus-6), and the γ-group (EBV and KSHV/HHV-8).

Herpes Simplex Viruses

There are two types of herpes simplex viruses (HSV) namely—**HSV-1 and HSV-2. They differ serologically but are closely related genetically and cause a similar set of primary and recurrent infections.**

1. **Mucocutaneous lesions:**
   - HSV-1 and HSV-2 cause self-limited cold sores and gingivostomatitis.
   - **Blisters or cold sores:** Both viruses replicate at the site of entry of the virus (namely—the skin and the mucous membranes usually the oropharynx or genitals). They cause vesicular lesions of the epidermis. Fever **blisters or cold sores** are observed in the facial skin around mucosal orifices (lips and nose).
   - **Gingivostomatitis:** It is usually observed in children and is caused by HSV-1. The viruses spread to sensory neurons and are transported along axons to the neuronal cell bodies, where they establish latent infection.
   - **Genital herpes** is more often caused by HSV-2 than by HSV-1.
   - In immunocompetent individuals, primary HSV infection resolves, although the virus remains latent in nerve cells. During the latency period, the viral DNA remains within the nucleus of the neuron. Reactivation of HSV-1 and HSV-2 may occur with or without symptoms, and this reactivation causes the spread of the virus from the neurons to the skin or mucous membranes.
2. **Ophthalmic lesions:** Two forms of **corneal lesions may be produced: (1) herpes epithelial keratitis and (2) herpes stromal keratitis** (which can lead to corneal blindness).
3. **Nervous system:** HSV-1 can also produce encephalitis.

MORPHOLOGY

HSV-infected cells contain large, pink to purple **intranuclear inclusions** (Cowdry type A). HSV also produces inclusion-bearing multinucleated syncytia.

Rabies

Rabies is a viral disease causing **severe encephalitis** and transmitted to humans by the **bite of a rabid animal (usually a dog)**. Rabies virus is sensitive to and killed by ethanol, iodine preparations, and soap detergents.

MORPHOLOGY

Gross: External examination of the brain shows edema and vascular congestion.

Microscopy: It shows widespread neuronal degeneration and an inflammatory reaction which is most severe in the brainstem.

Negri bodies: These are the **pathognomonic** microscopic features. They are cytoplasmic, round to oval, eosinophilic inclusions that can be found in pyramidal neurons of the hippocampus and Purkinje cells of the cerebellum. Rabies virus can be identified within the Negri bodies by ultrastructural and immunohistochemical methods.

Clinical features: Rabies virus enters the CNS by ascending along the peripheral nerves from the wound site (bite of a rabid animal).

The incubation period usually ranges from **1 to 3 months** and it depends on the distance between the wound and the brain.

Symptoms

- **Nonspecific symptoms:** Rabies presents with nonspecific symptoms such as malaise, headache, and fever. **Local paresthesia around the wound** along with the above symptoms is diagnostic.
- **CNS excitability:** As the infection progresses, the patient develops severe CNS excitability. The slightest touch is painful and causes violent motor responses or even convulsions. Signs of meningeal irritation and flaccid paralysis may develop as the disease progresses.

- **Hydrophobia:** Contracture of the pharyngeal muscles on swallowing produces foaming at the mouth. This causes aversion/fear to swallow even water (hydrophobia).
- Produces coma and death from respiratory failure.

Measles (Rubeola)

Q. Write a short note on measles.

Measles is an **acute viral infection** caused by the measles (rubeola) virus. It **affects multiple organs** and causes a wide range of diseases ranging from mild, self-limited infections to severe systemic manifestations. It can produce severe disease in patients with defects in cellular immunity (e.g., with HIV or hematologic malignancy). Measles can be prevented by vaccines. Epidemics of measles occur among unvaccinated individuals. Diagnosis is by clinical features, by serology, or by detection of viral antigens in nasal exudates or urinary sediments.

Mode of transmission: Measles virus is transmitted by respiratory droplets.

Incubation period: 9–11 days.

Pathogenesis: The measles virus is a single-stranded RNA virus of the paramyxovirus family. Measles can replicate in many cell types such as epithelial cells and leukocytes. Initially, the virus multiplies within the respiratory tract and then spreads to local lymphoid tissues. Replication of the virus in lymphoid tissue is followed by viremia and systemic dissemination to many tissues. The tissues involved are conjunctiva, skin, respiratory tract, urinary tract, small blood vessels, lymphatic system, and CNS. Most children develop T-cell–mediated immunity to the virus which controls the viral infection and produces the measles rash. Hence, the measles rash is less common in patients with deficiencies in cell-mediated immunity. In malnourished, it may cause croup, pneumonia, diarrhea and protein-losing enteropathy, keratitis (producing scarring and blindness), encephalitis, and hemorrhagic rashes ("black measles"). Measles can cause transient immunosuppression, resulting in secondary bacterial and viral infections. Antibody-mediated immunity to measles virus protects against reinfection.

MORPHOLOGY

Measles rash: It is blotchy, reddish-brown and observed on the face, trunk, and proximal extremities. It is produced by dilated skin vessels, edema, and a mononuclear perivascular infiltrate.

Koplik spots: These are pathognomonic of measles and consist of ulcerated mucosal lesions in the oral cavity near the opening of the Stensen (parotid) ducts. They appear as small, irregular, bluish-white dots measuring 1 mm in diameter surrounded by erythema.

Lymphoid organs—Warthin–Finkeldey giant cells: Lymphoid organs show marked follicular hyperplasia, enlarged germinal centers, and randomly distributed multinucleate giant cells, called **Warthin–Finkeldey giant cells** (pathognomonic of measles). These giant cells have eosinophilic nuclear and cytoplasmic inclusion bodies. These are also found in the lungs and sputum.

RICKETTSIAL INFECTIONS

Rickettsiales are vector-borne obligate intracellular bacteria. These organisms have the structure of gram-negative, rod-shaped bacteria. However, they stain poorly with Gram stain.

Diseases produced: They cause epidemic and scrub typhus, spotted fevers (*Rickettsia rickettsia*), ehrlichiosis, and anaplasmosis.

- **Epidemic typhus:** Caused by *Rickettsia prowazekii.*
  - **Mode of transmission.** Transmitted from person to person by body lice.
  - **Clinical features:** Includes macular rash that progresses to a petechial, maculopapular rash on the entire body except the face, palms, and soles.
- **Scrub typhus:** Caused by *Orientia tsutsugamushi*.
  - **Mode of transmission.** By chiggers.
  - **Clinical features:** Include fever, headache, myalgia and cough, and associated lymphadenopathy from the chigger bite.
- **Rocky Mountain spotted fever:** Caused by *Rickettsia rickettsia*.
  - **Mode of transmission:** By dog ticks.
  - **Clinical features:** Begins as a nonspecific severe illness with fever, myalgias, and gastrointestinal distress. As the disease progresses widespread macular then petechial rash involving the palms and soles develop.

Pathogenesis: The manifestations of rickettsial infections are mainly due to infection of endothelial cells (especially those in the lungs and brain) which results in endothelial dysfunction and injury. Widespread endothelial dysfunction/injury can cause shock, peripheral and pulmonary edema, and disseminated intravascular coagulation, renal failure, and CNS manifestations (e.g., coma).

MORPHOLOGY

Characterized by small vessel lesions and focal areas of hemorrhage and inflammation in many organs and tissues.

Diagnosis: Rickettsial diseases are usually diagnosed clinically. Diagnosis is confirmed by serology or immunostaining of the organisms.

CHLAMYDIAL INFECTIONS

Chlamydia Trachomatis

It is a small gram-negative bacterium and exists in two forms during its unique life cycle.

- **Elementary body:** It is an infectious, metabolically inactive form and has a spore-like structure. Host cells take up the elementary body by endocytosis and form endosomes. The bacteria prevent the fusion of the endosome and lysosome.
- **Reticulate body:** Inside the endosome of the host cell, the elementary body differentiates into a metabolically

Salient Features

- **Competency-Based Undergraduate Curriculum:** This book aligns with the National Medical Commission (NMC) guidelines for Indian Medical Students, incorporating both Core Competencies (CC) and Non-Core Competencies.
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This book serves as a reliable resource, ensuring students are well-prepared and confident for their examinations.

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