2nd Edition

Textbook of Pathology and Genetics for Nurses

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Foreword
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JAYPEE

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SECOND EDITION

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SECTION 4: GENETICS

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CHAPTER

Infectious Diseases

CHAPTER OUTLINE

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INTRODUCTION

Infection is defined as the entry and development or multiplication of an infectious agent in the humans or animals. All infections do not always cause illness.

Infectious Diseases

Infectious diseases are clinically manifestation of disease in human resulting from an infection.

Causes of Infections

Infectious agents include:

- Bacteria
- Viruses
- Prions
- Eukaryotes (includes fungi, protozoa and helminths)

Routes of entry of microbes: Microbes can enter the host by:

- **Inhalation** (e.g. respiratory infections, tuberculosis)
- **Ingestion** (e.g. water, food)
- **Inoculation into skin/mucosa** (breaching epithelial surfaces, e.g. rabies)
- **Direct contact** (e.g. leprosy)
- **Sexual transmission** (sexually transmitted diseases/STD)
- **Transplacental** (e.g. TORCH infections).

Development of Disease

1. **Incubation period:** It is the **time interval between the infection** by an infectious agent **and the appearance** of the first sign or **symptoms** of the disease.
2. **Prodromal period:** Early, mild symptoms of disease.
3. **Illness period:** Disease is most acute. Clinically obvious signs and symptoms.
4. **Decline period:** Signs and symptoms subside.
5. **Convalescence period:** Recovery in which body returns to predisease state.

BACTERIAL INFECTIONS

Streptococcal Infections

Streptococci are Gram-positive cocci (bacteria that is spherical or ovoid) 1 μm in

diameter, non-motile and non-sporing. Many strains of streptococci are capsulated.

Examples of Diseases Produced by Streptococci

- **Streptococcal pharyngitis:** Characterized by sore throat, dysphagia (difficulty in swallowing), headache, malaise (sense of discomfort, weakness, fatigue), anorexia (loss of appetite), and fever.
- **Scarlet fever:** Characterized by the development of an **erythematous (pinkish) rash** on the second day of illness. The primary lesion is in the throat.
- **Erysipelas:** It is an **acute spreading infection** of the **skin and the subcutaneous tissue** by streptococci.
- **Streptococcal impetigo:** It is inflammation of the skin characterized by isolated pustules (a visible collection of pus within or beneath the epidermis) which become crusted (dried pus on the skin surface). Sites of predilection are around the mouth and nostrils.
- **Cellulitis:** This is spreading inflammation of the subcutaneous tissue due to entry of the organism through the abrasions scraping away of the skin.
- **Lymphangitis:** Acute lymphangitis (inflammation of lymphatics) may follow local trauma. This condition presents in the form of linear red streaks (lines) radiating from the site of entry to the draining lymph nodes.
- **Streptococcal bacteremia:** Irrespective of the focus of entry and primary lesion, streptococcal bacteremia gives rise to metastatic foci of infection such as suppurative arthritis, osteomyelitis, peritonitis, endocarditis, meningitis, or visceral abscesses.
- **Pneumonia and empyema:** Streptococcal pneumonia usually follows a viral infection, and it manifests as bronchopneumonia. In many cases empyema (collection of pus in the pleural space.) develops as a complication.
- **Streptococcal toxic shock syndrome:** Infection by group A streptococcus may lead to vascular collapse and organ failure.

Staphylococcal Infections

- Various diseases caused by Staphylococci are listed in Table 7.1.

Pyogenic Bacteria

- They **produce suppurative/purulent (with pus) inflammation.** Pyogenic inflammation is a type of inflammation characterized by increased vascular permeability and leukocytic infiltration, mainly of neutrophils. The neutrophils

Table 7.1: Diseases caused by staphylococci

Superficial lesions	*Deep lesions*
• Furuncle, carbuncle, impetigo, ecthyma, sycosis barbae	• Staphylococcal pneumonia
• Follicular Impetigo of Bockhart	• Osteomyelitis/septic arthritis
• The Scalded Skin Syndrome (Syn: pemphigus neonatorum, Ritter's disease, toxic epidermal necrolysis)	• Staphylococcal bacteremia
	• Staphylococcal food poisoning
	• Endocarditis
	• Toxic shock syndrome

accumulate at the site of infection due to release of chemoattractants from the "pyogenic" (pus-forming) bacteria. These bacteria are mostly extracellular Gram-positive cocci and Gram-negative rods.

- **Gross:** 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 lung usually spares alveolar walls and cause lobar pneumonia that resolves completely.
  - Staphylococci and *Klebsiella* infection of lung destroy alveolar walls and form abscesses that heal with scar formation.
  - Bacterial pharyngitis resolves without sequelae.
  - 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 into the bloodstream and form small aggregates (microemboli). They result in either pyemic abscesses or septic infarct in various organs.

Typhoid fever is discussed in Chapter 11 (pages 141–4).

VIRAL INFECTIONS

Poliomyelitis

Etiology

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

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

Incubation period: About 10 days.

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 forming cuffs surrounding blood vessels (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.

ACQUIRED IMMUNODEFICIENCY SYNDROME

Acquired immunodeficiency syndrome (AIDS) is caused by the retrovirus **human immunodeficiency virus** (HIV).

Characteristic Features

- Infection and depletion of CD4+ T lymphocytes.
- Severe immunosuppression leads to opportunistic infections, secondary neoplasms, and neurologic manifestations.

Route of Transmission

Transmission of HIV occurs when there is an exchange of blood or body fluids containing the virus or virus-infected cells. The three major routes of transmission are:

1. **Sexual transmission:** It is the **main route of infection** in more than 75% of cases of HIV.
   - **Homosexual or bisexual men** or **heterosexual contacts:** It may be male-to-male, or male-to-female or female-to-male transmission.
   - **HIV is present in genital fluids,** such as vaginal secretions and cervical cells (in women), and semen (in men).
2. **Parenteral transmission:** Three groups of individuals are at risk.
   - **Intravenous drug abusers:** Transmission occurs by **sharing of needles, and syringes contaminated** with HIV-containing blood.
   - **Hemophiliacs** (patients with hemophilia have deficiency of blood coagulation factor VIII/IX)**:** Mainly those who received large amount of factor VIII and factor IX concentrates before 1985. Now increasing use of recombinant (produced from genetic recombination) clotting factors have eliminated this mode of transmission.
   - **Transfusion of blood or blood components:** Recipients of blood transfusion of **HIV-infected whole blood or components** (e.g. platelets, plasma) was one of the modes of transmission.
3. **Perinatal transmission (mother-to-infant transmission):**
   - **Major mode of transmission of AIDS in children**.
   - Transmission of infection can occur by **three routes**:
     - **In utero:** It is transmitted by transplacental spread.
     - **Perinatal spread:** During normal vaginal delivery or child birth (intrapartum) **through an infected birth canal** and in the immediate period (peripartum).
     - **After birth:** It is transmitted by ingestion of breast milk or from the genital secretions.

Transmission of HIV infection to healthcare workers: There is an extremely small risk of transmission to healthcare professionals, after accidental needle-stick injury or exposure of nonintact skin to infected blood.

Etiology

Properties of HIV

AIDS is caused by HIV, which is a **nontransforming human retrovirus** belonging to the lentivirus family. Retroviruses are **RNA viruses having an enzyme called reverse transcriptase**, which **prepares a DNA copy of the RNA genome of the virus in host cell**.

Genetic forms: HIV occurs in two genetically different but related main forms, **HIV-1 and HIV-2**.

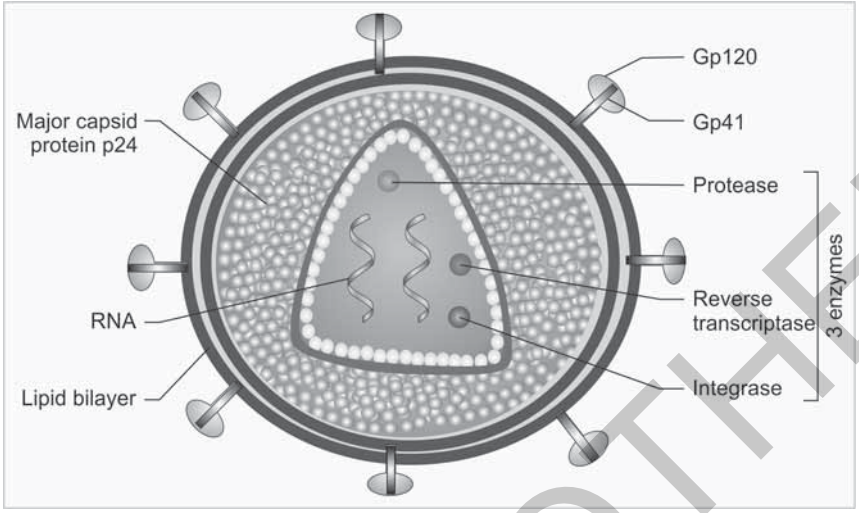


Fig. 7.1: Diagrammatic representation of structure of the human immune deficiency virus (HIV)–1 virion. The viral particle is covered by a lipid bilayer derived from the host cell and studded with viral glycoproteins gp41 and gp120

- **HIV-1** is most common in the United States, Europe, and Central Africa.
- **HIV-2 is common** in West Africa and India.

***Structure of HIV** (Fig. 7.1)*

- **HIV-1** is **spherical enveloped** virus which is about 90–120 nm in diameter.
- It consists of electron-dense, cone-shaped core surrounded by nucleocapsid cell which is covered by lipoprotein envelope.
  - **Viral core:** It contains
    - **Major capsid protein p24:** This viral antigen and the antibodies against this are **used for the diagnosis of HIV infection** in enzyme-linked immunosorbent assay (**ELISA**).
    - **Nucleocapsid protein p7/p9**.
    - **Two identical copies of single stranded RNA genome**.
    - **Three viral enzymes: (1) protease, (2) reverse transcriptase** (RNA-dependent DNA polymerase), and **(3) integrase**.
  - **Nucleocapsid:** The **viral core is surrounded by a matrix protein p24 and p17**, which **lies underneath the lipid envelope** of the virion.
  - **Lipid envelope:** The virus contains a lipoprotein envelope, which **consist of lipid derived from the host cell and two viral glycoproteins**. These glycoproteins are: **(1) gp120** which project as a knob-like spikes on the surface and **(2) gp41** anchoring transmembrane pedicle. These **glycoproteins are essential for HIV infection of cells**.

Pathogenesis of HIV Infection and AIDS

Infection is transmitted when the virus enters the blood or tissues of an individual.

Major targets: HIV can infect many tissues, but two major targets of HIV infection are the:

- **Immune system.**
- **Central nervous system (CNS)**.

Life Cycle of HIV

Consists of four main steps namely: (1) infection of cells by HIV, (2) integration of the provirus into the host cell genome, (3) activation of viral replication, and (4) production and release of infectious virus (Fig. 7.2).

- **Infection of cells by HIV:**
  - **Cell tropism:** HIV has **selective affinity** for host cells with **CD4 molecule receptor**. The cells with such receptors include **CD4+ T cells** and other CD4+ cells such as **monocytes/macrophages** and **dendritic cells**. The HIV envelope contains two glycoproteins, surface gp120 noncovalently attached to a transmembrane protein, gp41.
  - **Gp120 of HIV binding to CD4 molecule receptor** on the host cell is the first step in HIV infection. Binding alone is not enough for infection and **requires participation of a coreceptor molecule**.
  - **Conformational change:** Binding to CD4 leads to a conformational (shape) change **in the HIV, that results in the formation of a new recognition site on gp120 for the coreceptors CCR5 or CXCR4**.
  - **Gp120 binding to chemokine receptor:** New recognition site on gp120 of HIV bind to **chemokine receptors,** i.e. CCR5 and CXCR4.
  - **Penetration of host cell membrane by gp41**.
  - **Membrane fusion: HIV penetrate the cell membrane of the target cells** (e.g. CD4+ T cells or macrophages), **leading to fusion of the virus with the host cell**.
  - **Entry of viral genome into cytoplasm of host cell**.
- **Integration of the proviral DNA into the genome of the host cell.**
  - After the internalization of the virus core, the **RNA genome of the virus undergoes reverse transcription** leading to the **synthesis of double-stranded complementary DNA (cDNA/proviral DNA)**.
  - **Episomal form: In quiescent T cells, HIV cDNA** may remain as a linear **episomal form in the cytoplasm of infected cell**.
  - **Integration of cDNA: In dividing T cells**, HIV **cDNA enters the nucleus**, and **becomes integrated into the genome** of the host cell using a viral integrase protein.
- **Viral replication:** After the integration of proviral DNA it can either be latent or productive infection.

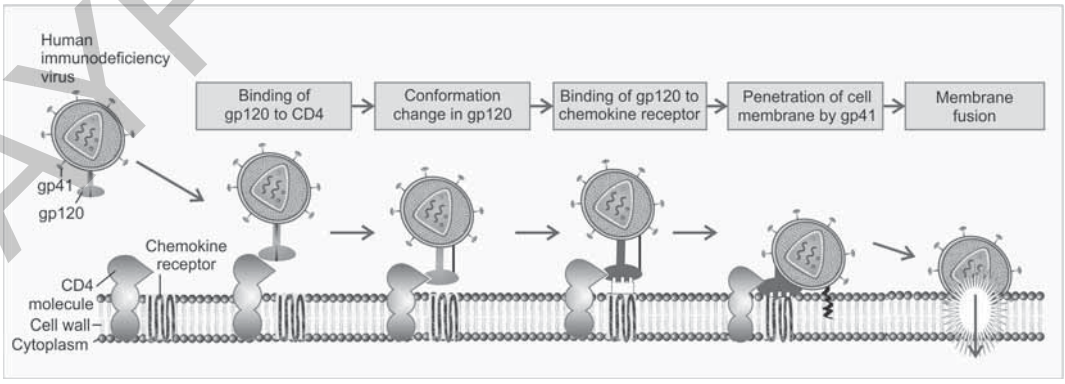


Fig. 7.2: Various molecular steps involved in the life cycle of HIV

  - **Latent infection:** During this, the **provirus remains silent** for months or years.
  - **Productive infection:** In this the **proviral DNA is transcribed** leading to **viral replication** and formation of **complete viral particles**.
- **Production and release of infectious virus:** The complete **virus particle** formed, **buds from the cell membrane** and **release new infectious virus**. This productive infection when extensive, leads to death of infected host cells.

The virus **infection remains latent for long periods in lymphoid tissues**. **Active viral replication is associated with more infection of cells and progression to AIDS**.

Dissemination: Virus disseminates to other target cells. This occurs either by fusion of an infected cell with an uninfected one or by the budding of virions from the membrane of the infected cell.

Natural History of HIV Infection

Virus usually enters the body through mucosal epithelia and clinical course can be divided into three main phases:

- **Early acute phase:** It may present as an acute, usually **self-limited nonspecific illness**. These symptoms include **sore throat, myalgias, fever, weight loss, and fatigue**. **Other features, such as rash, cervical adenopathy**, diarrhea, and vomiting, may also occur.
- **Middle chronic phase:** It may have **few or no clinical manifestations**, and is called the clinical latency period. The **symptoms may be due to minor opportunistic infections**, such as oral candidiasis (thrush), vaginal candidiasis, herpes zoster, and perhaps mycobacterial tuberculosis.
- **Final crisis phase:** It is **final phase of HIV with progression to AIDS**. It presents with **fever, weight loss, diarrhea, generalized lymphadenopathy, multiple opportunistic infections, neurologic disease, and secondary neoplasms**. Most of untreated (but not all) patients with HIV infection **progress to AIDS after a chronic phase lasting from 7 to 10 years**.

The opportunistic infections and neoplasms found in patients with HIV infection are presented in Table 7.2.

Diagnosis of HIV Infection or AIDS

- **ELISA:** Detects antibodies against viral proteins. It is the **most sensitive** and best screening test for the diagnosis of AIDS.
- **Western blot:** Most specific or the confirmatory test for HIV.
- **Direct detection of viral infection:**
  - p24 antigen capture assay
  - Reverse transcriptase polymerase chain reaction (RT-PCR)
  - DNA-PCR
  - Culture of virus from the monocytes and CD4+T cells.

Prognosis: The prognosis of AIDS is poor.

AMEBIASIS

Amebiasis is an **infection caused by protozoan *Entamoeba histolytica*** (named so because of its lytic actions on involved tissue).

Etiology

Entamoeba histolytica has three distinct stages:

1. **Trophozoite stage** (Fig. 7.3A)
2. **Precyst stage**
3. **Cyst stage** (Fig. 7.3B)**: Amebic cysts are the infecting stage** and are found only in stools.

Source of infection: Humans are the only known reservoir for *E. histolytica*. It is reproduced in the colon of infected individual and passes in the feces.

Table 7.2: AIDS-defining opportunistic infections and neoplasms found in patients with HIV infection

Opportunistic Infections	
Protozoal and helminthic infections	**Organ or site involved or type of damage**
• Cryptosporidiosis or isosporidiosis	• Enteritis
• Toxoplasmosis	• Pneumonia or CNS infection
Fungal Infections	
• Pneumocystosis	• Pneumonia or disseminated infection
• Candidiasis	• Esophageal, tracheal, or pulmonary
• Cryptococcosis	• Infection of central nervous system
• Coccidioidomycosis	• Disseminated
• Histoplasmosis	• Disseminated
Bacterial Infections	
• Mycobacteriosis	• Disseminated or extrapulmonary
• Atypical, e.g. *Mycobacterium avium*-intracellulare *M. tuberculosis*	• Pulmonary or extrapulmonary • Pneumonia, meningitis, disseminated
• Nocardiosis	• Disseminated
• *Salmonella* infections	
Viral Infections	
• Cytomegalovirus	• Pulmonary, intestinal, retinitis, or CNS infections
• Herpes simplex virus	• Localized or disseminated
• Varicella-zoster virus	• Localized or disseminated
• Progressive multifocal leukoencephalopathy	• Central nervous system
Neoplasms	*Cause*
Kaposi sarcoma (KS)	Kaposi sarcoma herpes virus
Non-Hodgkin B-cell lymphoma—Primary lymphoma of the brain	Epstein-Barr Virus (EBV)
Cervical cancer in women	Human papilloma virus (HPV)
Anal carcinoma	HPV

Mode of infection: It is **acquired by fecal-oral route** through ingestion of materials contaminated with human feces containing *E. histolytica*.

Incubation period: About 8–10 days.

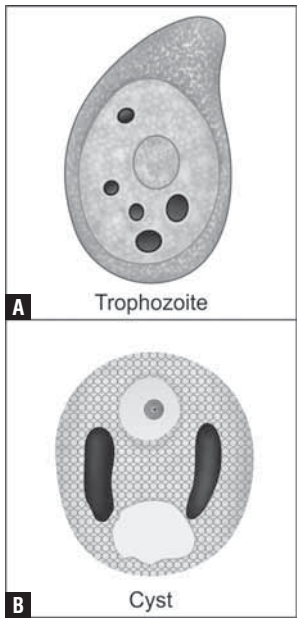
Pathogenesis

The amebic cysts are passed in the stool and the **cysts can contaminate water, food, or fingers**.

- On ingestion, *E. histolytica* cysts traverse the stomach. They are **resistant to the action of gastric acid** and they pass to the colon.
- **Amebic cysts then colonize the epithelial surface of the colon and release trophozoites**. They may colonize any part of the large intestine, but **most frequently in the cecum and ascending colon causing amebic colitis**. These patients pass both cysts and trophozoites in the stool.
- **Trophozoite attaches the colonic epithelial cell** and **invades crypts, and burrow laterally into the lamina propria**. It creates a **flask-shaped ulcer** with a narrow neck and broad base.
- **Trophozoite may penetrate blood vessels and reach the liver** to produce **abscesses** in about 40% of patients with amebic dysentery.

Morphology

Entamoeba histolytica can produce intestinal or extraintestinal disease.



Figs 7.3A and B: A. Trophozoite and B. Cyst of *E. histolytica*

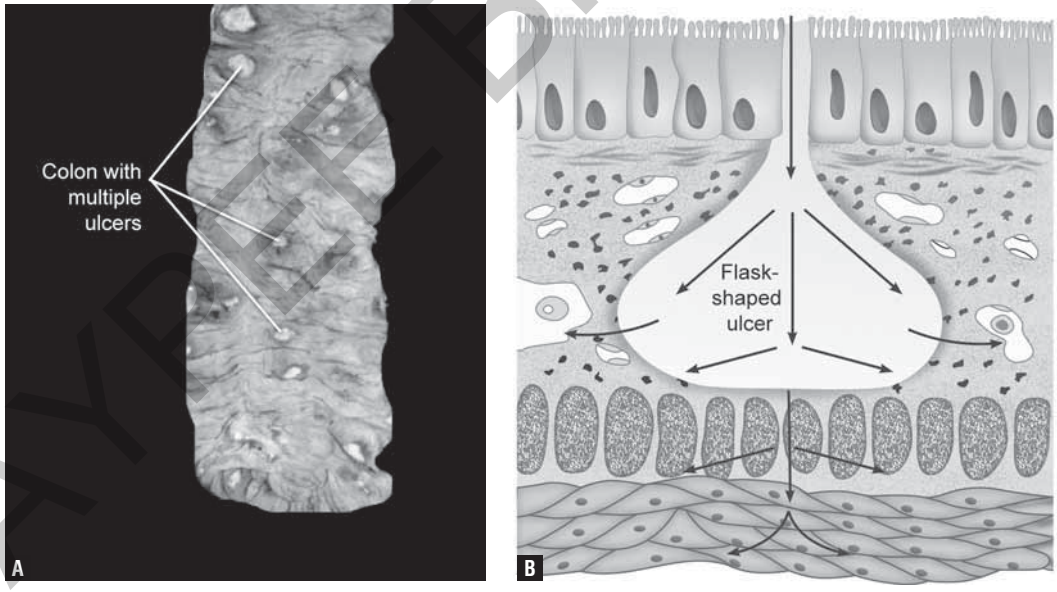
- **Intestinal disease:** It mainly involves the **colon** causing bloody dysentery.
- **Extraintestinal disease:** It can produce **amebic liver abscesses**.

Colon

- Amebic lesions start as small **foci of necrosis,** which progress to **ulcers**. The **chronic amebic ulcers** described as **flask-shaped ulcer** with a narrow/bottle neck and broad base resembling a **flask** (Figs 7.4A and B).

Clinical Features

Intestinal amebiasis: It may be asymptomatic or to produce dysentery (diarrhea with mucous and blood in feces) of varying severity. Amebic dysentery may present with **abdominal pain, bloody diarrhea, or weight loss**. Liquid stools (up to 25 a day) contain blood and mucus.



Figs 7.4A and B: A. Gross appearance of multiple amebic ulcers in the colon; B. Microscopically appear as flask-shaped amebic ulcer (diagrammatic)

Amebic Liver Abscess *(Fig. 7.5)*

It is a **major complication of intestinal amebiasis**.

- *E. histolytica* trophozoites **from the colon** may reach liver **through the portal circulation**.
- **Trophozoites kill hepatocytes** and produce **abscess**.
- Abscess cavity is filled with a dark brown, odorless, semisolid necrotic material, which resembles **anchovy paste (sauce) in color and consistency**. The size of amebic liver abscess may vary and can exceed 10 cm in diameter.
- **Spread of amebic liver abscess**.
  - **Local spread:** It may expand and rupture through the capsule of the liver. It may directly **spread into the peritoneum, diaphragm, pleural cavity, lungs, or pericardium**.
  - **Hematogenous spread:** Rare and may spread to the **brain** and kidneys and produce necrotic lesions.

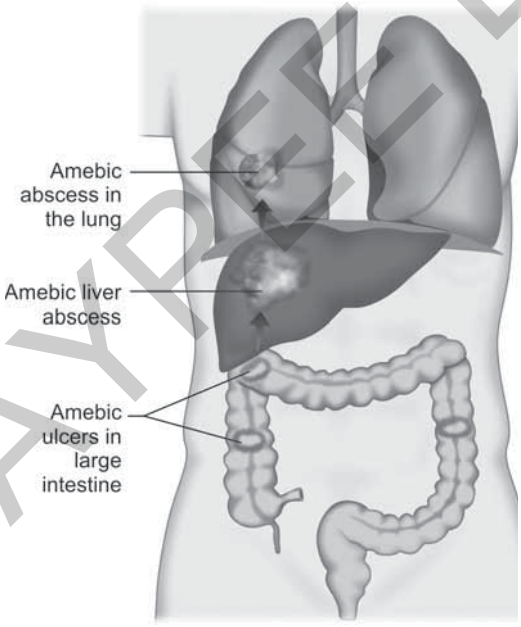


Fig. 7.5: Complications of amebiasis (diagrammatic)

Clinical features of amebic liver abscess: It may present with severe right upper quadrant pain, low-grade fever, and weight loss. The diagnosis is usually made by radiologic or ultrasound demonstration of the abscess, in conjunction with serologic testing for antibodies to *E. histolytica*.

MYCOBACTERIAL DISEASES

Mycobacterium is bacteria, which appear as slender aerobic rods that grow in straight or branching chains. Mycobacteria have a waxy cell wall composed of mycolic acid, which is responsible for their **acid-fast nature**. Mycobacteria are weakly Gram-positive.

Tuberculosis is discussed in Chapter 10.

LEPROSY

Leprosy (Hansen disease), is a **chronic**, **granulomatous**, slowly progressive, destructive infection caused by ***Mycobacterium leprae.***

Sites of involvement: Mainly involves the **peripheral nerves**, **skin and mucous membranes** (nasal) and results in disabling deformities.

Leprosy is one of the oldest human diseases and lepers were isolated from the community in the olden days.

Mycobacterium Leprae

- Slender, **weakly acid-fast** intracellular bacillus.
- **Proliferates at low temperature** of the human skin.

Mode of transmission: *Mycobacterium leprae* 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 of leprosy patients. Inhaled *M. leprae*, is taken up by alveolar macrophages and disseminates through the blood, but

replicates (multiply) only in relatively cool tissues of the skin and extremities.

2. **Intimate contact:** For many years of intimate contact with leprosy patients.

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

Incubation period: Generally 5 to 7 years.

Classification

- **Ridley–Jopling (1966) classification:** It depends on the clinicopathological spectrum of the disease, which is **determined by the immune resistance of the host** (Fig. 7.6). They are classified into five groups with two extremes or polar forms, namely tuberculoid and lepromatous types.
  - **Tuberculoid leprosy (TT):** It is the polar form that has maximal immune response.
  - **Borderline tuberculoid (BT):** In this type, the immune response falls between BB and TT.
  - **Borderline leprosy (BB):** It exactly falls between two polar forms of leprosy.
  - **Borderline lepromatous (BL):** It has the immune response that falls between BB and LL.
  - **Lepromatous leprosy (LL):** It is the other polar form with least immune response.
- **WHO classification:**
  - **Paucibacillary:** All cases of tuberculoid leprosy and some cases of borderline type.
  - **Multibacillary:** All cases of lepromatous leprosy and some cases of borderline type.

Lepromin Test

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

- **Procedure:** An antigen extract of *M. leprae* called lepromin is intradermally injected.
- **Reaction:**
  - An **early positive reaction** appears as an indurated area in 24 to 48 hours is called **Fernandez reaction**.
  - A **delayed granulomatous reaction** appearing after 3 to 4 weeks is known as **Mitsuda reaction**.
- **Interpretation:**
  - **Lepromatous leprosy**—shows **negative lepromin test**.
  - **Tuberculoid leprosy—**show **positive lepromin test**.

Differences between lepromatous and tuberculoid leprosy are presented in Table 7.3.

Diagnosis of Leprosy

- **Clinical examination:**
  - **Sensory testing**.
  - Examination of peripheral nerve.
- **Demonstration of acid-fast bacilli**.
  - Skin smears prepared by **slit and scrape method**.
  - **Nasal swabs stained by Ziehl–Neelsen method**.
- **Skin biopsy.**
- **Nerve biopsy.**
- **Molecular method: PCR.**

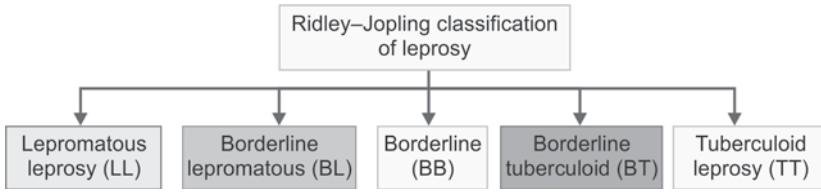


Fig. 7.6: Ridley–Jopling classification of leprosy

Table 7.3: Differences between lepromatous and tuberculoid leprosy

Opportunistic infections	*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 ear lobes, 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 dermis	Noncaseating granulomas composed of epithelioid cells and 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

Morphology

Two extremes or polar forms of the diseases are the tuberculoid and lepromatous types.

- **Tuberculoid leprosy**.
  - **Lesion in skin:**
    - **Site:** Usually on the **face, extremities, or trunk**.
    - **Type: Localized, well-demarcated, red or hypopigmented, dry, elevated**, skin **patches** having raised outer edges and depressed pale centers (central healing).
  - **Nerve involvement:**
    - **Dominating feature** in tuberculoid leprosy.
    - Nerve involvement causes **loss of sensation** in the skin and results in 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.
  - **Microscopy** (Fig. 7.7)**:**
    - **Granuloma:** These are well-formed, circumscribed and **non-caseating** (no caseation). Termed tuberculoid leprosy because the granulomas resemble those found in tuberculosis. Granulomas are composed of epithelioid cells (modified macrophages), Langhans giant cells, and lymphocytes.
    - **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.

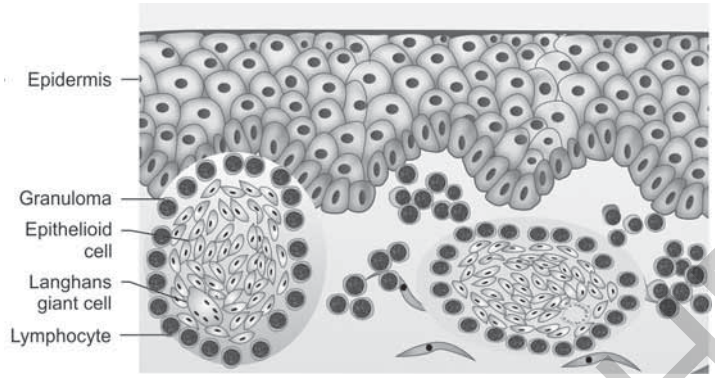


Fig. 7.7: Microscopy of tuberculoid leprosy with circumscribed noncaseating granulomas (diagrammatic)

- **Lepromatous leprosy:** It is the **more severe form**.
  - **Lesion in skin:**
    - **Thickening of skin** and **multiple, symmetric, macular, papular, or nodular lesions**. The nodular skin lesions may ulcerate. Most skin lesions are **hypoesthetic or anesthetic**.
    - More severe involvement of the **cooler areas of skin** (e.g. earlobes, wrists, elbows, and knees, and feet).
    - With progression, the nodular lesions produce a lion-like appearance known as **leonine facies** (Fig. 7.8).
  - **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.
  - **Microscopy of skin lesion** (Fig. 7.9)**:**
    - **Flattened epidermis**.
    - **Grenz (**clear) **zone:** It is a characteristic **narrow, uninvolved dermis** (normal collagen) which separates the epidermis from nodular accumulations of macrophages.
    - **Lepra cells:** The nodular lesions contain large aggregates of lipid-laden foamy macrophages (lepra cells, Virchow cells), filled with aggregates ("globi") of acid-fast lepra bacilli (*M. leprae*).
    - **Fite-Faraco (acid-fast) stain:** It shows **numerous lepra bacilli**

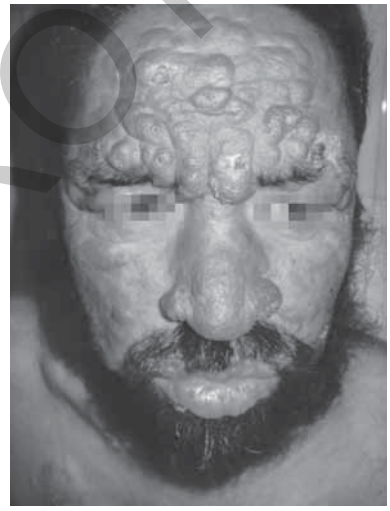
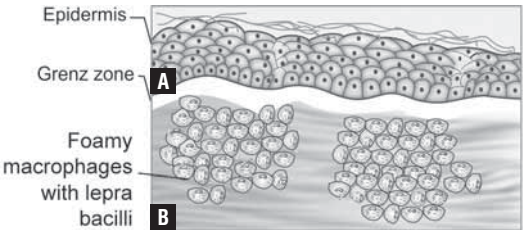


Fig. 7.8: Leonine facies of lepromatous leprosy



Figs 7.9A and B: Microscopic appearance of lepromatous leprosy. 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

("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 bacteria, lepromatous leprosy is also referred to as **"multibacillary"**.

SYPHILIS

Syphilis (lues) is a **chronic, sexually transmitted** disease **caused by spirochete** ***Treponema pallidum***.

Etiology

- ***Treponema pallidum*** *(Fig. 7.10)***:**
  - It is a **thin, delicate, corkscrew-shaped spirochete**, with tapering ends.
  - Actively motile.
  - **Staining:** It can be visualized by **silver stains, dark-field examination and immunofluorescence techniques**.
- **Source of infection:** An open lesion of **primary or secondary syphilis**. These lesions include those in the mucous membranes or skin of the genital organs, rectum, mouth, fingers, or nipples.
- **Mode of transmission:**
  - **Sexual contact:** It is the usual mode of spread.
  - **Transplacental transmission:** From mother with active disease to the fetus (during pregnancy) results in congenital syphilis.
  - **Blood transfusion**.
  - **Direct contact:** with the open lesion of syphilitic patients is rare mode of transmission.

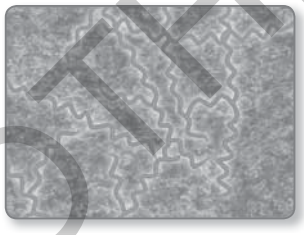


Fig. 7.10: Appearance of *Treponema pallidum* under dark-field examination

Stages of Syphilis (Fig. 7.11)

Treponema pallidum passes from the site of inoculation to regional lymph nodes. From here it enters to the systemic circulation, and disseminate throughout the body. Syphilis can be **(1) congenital or (2) acquired**. The course of acquired syphilis is divided into three stages:

1. Primary syphilis.
2. Secondary syphilis.
3. Tertiary syphilis.

Primary Syphilis

Develops about **3 weeks after contact** with an infected individual and the lesion is primary chancre.

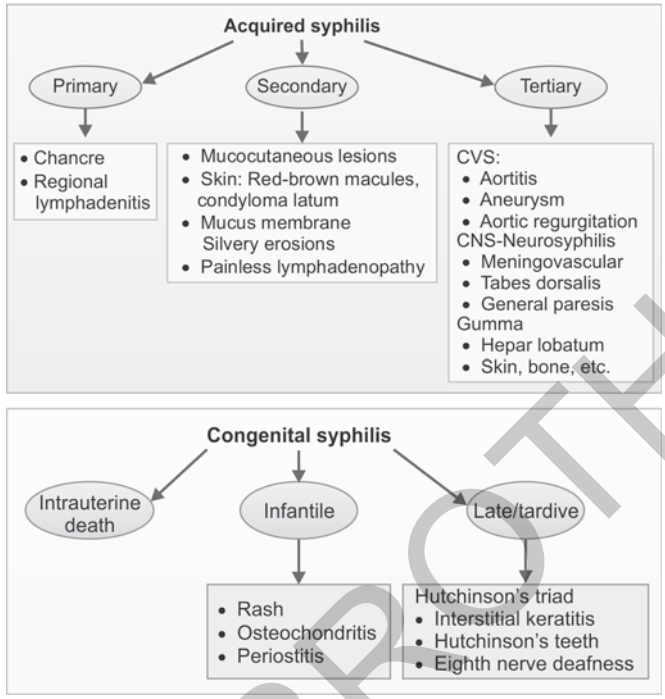


Fig. 7.11: Various manifestations of syphilis

Primary chancre: It is the classical lesion of primary syphilis.

- **Sites: Penis or scrotum** in men and **cervix, vulva** and **vaginal** wall in women. It may also be seen in the anus or mouth.
- **Gross features:** It is single, firm, **nontender (painless)**, slightly raised, **red papule** small circumscribed, superficial, solid elevation of the skin-(chancre). It erodes to create a clean-based shallow ulcer. Because of the induration surrounding the ulcer, it is designated as **hard chancre.**
- **Demonstration of treponema:** Plenty of treponemes can be demonstrated in the chancre.

Regional Lymphadenitis: It is due to nonspecific acute or chronic inflammation.

Symptoms: Usually painless and often unnoticed.

Fate: It heals in 3 to 6 weeks with or without therapy.

Secondary Syphilis

It develops 2–10 weeks after the primary chancre in approximately 75% of untreated patients.

Lesions of secondary syphilis

Mucocutaneous lesions

These are painless, and contain spirochetes and are infectious.

- **Skin lesions:**
  - **Skin rashes:** Consist of **discrete red-brown macules** (discolored skin lesion that is not elevated above the surface). They are more frequent on the **palms** of the hands, or **soles** of the feet.
  - **Condylomata lata:** These are **broad-based, elevated plaques** (superficial, solid, skin lesion) 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 **oral cavity or vagina as silvery-gray superficial erosions Rarely, they may coalesce to produce characteristic "snail track"ulcers in the mouth.** These are **highly infectious**.

Painless lymphadenopathy: Especially involves **epitrochlear nodes** and shows plenty of spirochetes.

Tertiary Syphilis

- After the lesions of secondary syphilis have subsided patients enters 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.

Manifestations: Three main manifestations of tertiary syphilis are: **cardiovascular syphilis, neurosyphilis, and so-called benign tertiary syphilis.** These may occur alone or in combination.

Cardiovascular syphilis: Most **frequently involves the aorta** and known as syphilitic aortitis.

- **Syphilitic aortitis:** affects the **proximal aorta**.
- **Saccular aneurysm and aortic valve insufficiency:** On gross examination, the aortic intima appears rough and pitted (**tree-bark appearance**).
- **Myocardial ischemia:** Due to narrowing of the coronary artery ostia (at the origin from aorta).

Neurosyphilis: It may be asymptomatic or symptomatic.

Asymptomatic neurosyphilis: 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 base of the brain, cerebral convexities and spinal leptomeninges.
- **Tabes dorsalis:** It is characterized by **demyelination of posterior column, dorsal root and dorsal root ganglia**.
- **General paresis of insane:** Shows generalized brain parenchymal disease with **dementia**; hence called as general paresis of insane.

Benign tertiary syphilis: It is characterized by the formation of nodular lesions called **gumma**s in any organ or tissue.

Syphilitic gummas

- May be single or multiple.
- **White-gray and rubbery**.
- Vary in size from microscopic lesions to large tumor-like masses.
- **Site:** They occur in most organs but mainly involve the following:
  - **Skin, subcutaneous tissue** and the mucous membranes of the upper airway and mouth.
  - **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:** Center of the gammas show **coagulative necrosis** surrounded by plump, **palisading macrophages**, fibroblasts and plenty of **plasma cells**. Treponemes are scant in gummas.

Congenital Syphilis

Transplacental Transmission

- *T. pallidum* can cross placenta and spread from infected **mother to the fetus** (during pregnancy).
- Transmission occurs, when **mother is suffering from primary or secondary syphilis** (when the spirochetes are abundant). Because of routine serologic testing for syphilis in done in all pregnancies congenital syphilis is rare.

Manifestations of congenital syphilis can be divided into.

- **Intrauterine death and perinatal death.**
- **Early (infantile) syphilis:** It occurs in the **first 2 years of life** and often manifested by **nasal discharge** and congestion (**snuffles**).
  - A **desquamating or bullous eruption/rash**, mainly in the hands, feet, around the mouth and anus.
  - **Skeletal abnormalities:**
    - **Syphilitic osteochondritis:** Inflammation of bone and cartilage is more distinctive in the nose produces characteristic **saddle nose deformity**.
    - **Syphilitic periostitis:** Leads to anterior bowing, or **saber shin**.
  - **Liver: Diffuse fibrosis** in the liver.
  - **Lungs:** Diffuse interstitial fibrosis causes lungs to appear pale and airless (**pneumonia alba**).
- **Late (tardive) syphilis:** Manifests **2 years after birth** and about 50% of untreated children with neonatal syphilis will develop late manifestations.
  - **Manifestations:** Distinctive manifestation is **Hutchinson's triad** and consists of:
    - **Interstitial keratitis**.
    - **Hutchinson's teeth:** They are like small screwdrivers or peg-shaped incisors, with notches in the enamel.
    - **Eighth-nerve deafness.**

Laboratory Diagnosis

- **Immunofluorescence of exudate**.
- Microscopy and PCR are also useful.
- **Serological tests:**
  - **Nontreponemal antibody tests:** These tests measure antibody 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**.
  - **Antitreponemal antibody tests:** These measure antibodies, which react with *T. pallidum*.

SELF-ASSESSMENT EXERCISES

I. Short Notes

1. Poliomyelitis
2. Opportunistic infections associated with AIDS
3. Modes/routes of transmission of AIDS
4. Etiopathogenesis of AIDS
5. HIV virus
6. Amebic ulcer of intestine
7. Amebiasis
8. Classify leprosy
9. Tuberculoid leprosy
10. Lepromatous leprosy
11. Congenital syphilis
12. Gumma.

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