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Material

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ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

ETIOLOGIC AGENT. AIDS is caused by an RNA retrovirus called human immunodeficiency virus (HIV) which is a type of human T cell leukaemia-lymphoma virus (HTLV). HIV resembles other HTLVs in shape and size and both have tropism for CD4 molecules present on subpopulation of T cells which are the particular targets of attack by HIV. However, HIV differs from HTLV in being cytolytic for T cells causing immunodeficiency (cytopathic virus) while HTLV may transform the target cells into T cell leukaemia (transforming virus) (Chapter 8). Two forms of HIV have been described, HIV1 being the etiologic agent for AIDS in the US and Central Africa, while HIV2 causes a similar disease in West Africa and parts of India. Both HIV1 and HIV2 are zoonotic infections and their origin can be traced to a species of chimpanzees who are natural reservoir of HIV and most likely source of original infection. HIV-I virion or virus particle is spherical in shape and 100140 nm in size (Fig. 4.4): It contains a core having core proteins, chiefly p24 and p18, two strands of genomic RNA and the enzyme, reverse transcriptase. The core is covered by a double layer of lipid membrane derived from the outer membrane of the infected host cell during budding process of virus. The membrane is studded with 2 envelope glycoproteins, gp120 and gp41, in the positions shown. Besides various other genes, three important genes code for the respective components of virion: i) gag (group antigen) for core proteins, ii) pol (polymerase) for reverse transcriptase, and iii) env (envelope) for the envelope proteins.

These genes and viral components act as markers for the laboratory diagnosis of HIV infection. Besides, there is tat (transcription activator) gene for viral functions such as amplification of viral genes, viral budding and replication. ROUTES OF TRANSMISSION. Transmission of HIV infection occurs by one of following three routes: 1. Sexual transmission. Sexual contact in the main mode of spread and constitutes 75% of all cases of HIV transmission. Most cases of AIDS in the industrialised world like in the US occur in homosexual or bisexual males while heterosexual promiscuity seems to be the dominant mode of HIV infection in Africa and Asia. Other sexually transmitted diseases (STDs) may act as cofactors for spread of HIV, in particular gonorrhoeal and chlamydial infection.

Transmission from male-to-male and male-to-female is more potent route than that from female-to-male.

Major Abnormalities in Immune System in AIDS. 1. T CELL ABNORMALITIES (i) Lymphopenia (ii) CD4+ T cell depletion (iii) CD8+ T cell lymphocytosis (iv) Reversal of CD4: CD8 cell ratio (v) Decreased production of cytokines by CD4+ T cells (vi) Decreased antibody-dependent cellular cytotoxicity (ADCC) by CD8+ T cells

2. B CELL ABNORMALITIES (i) No direct viral damage (ii) Decreased Ig production (iii) Polyclonal activation (iv) Hypergammaglobulinaemia (v) Circulating immune complexes

3. NK CELL ABNORMALITIES (i) No direct viral damage (ii) Depressed number (iii) Decreased cytotoxicity

4. MONOCYTE-MACROPHAGE CELL ABNORMALITIES (i) No destruction (ii) Decreased chemotaxis (iii) Decreased cytotoxicity.

Syphilis

Syphilis is a venereal (sexually-transmitted) disease caused by spirochaetes, Treponema pallidum. Other treponemal diseases are yaws, pinta and bejel. The word ‘syphilis’ is derived from the name of the mythological handsome boy, Syphilus, who was cursed by Greek god Apollo with the disease.

Causative Organism T. pallidum is a coiled spiral filament 10 µm long that moves actively in fresh preparations. The organism cannot be stained by the usual methods and can be demonstrated in the exudates and tissues by: 1. dark ground illumination (DGI) in fresh preparation; 2. fluorescent antibody technique; 3. silver impregnation techniques; and 4. PCR as a research method. The organism has not been cultivated in any culture media but experimental infection can be produced in rabbits and chimpanzees. The organism is rapidly destroyed by cold, heat, and antiseptics.

Immunology T. pallidum does not produce any endotoxin or exotoxin. The pathogenesis of the lesions appears to be due to host immune response. There are two types of serological tests for syphilis: treponemal and non-treponemal. A.

Treponemal serological tests: These tests measure antibody to T. pallidum antigen and are as under: i) Fluorescent treponemal antibody-absorbed (FTA-ABS) test.ii) Agglutinin assays e.g. microhaemagglutination assay for T. pallidum (MHA-TP), and Serodia TP-PA which is more sensitive. iii) T. pallidum passive haemagglutination (TPHA) test. B. Non-treponemal serological tests. These tests measure non-specific reaginic antibodies IgM and IgG immunoglobulins directed against cardiolipin-lecithin-cholesterol complex and are more commonly used. These tests are as under: i) Reiter protein complement fixation (RPCF) test: test of choice for rapid diagnosis. ii) Venereal Disease Research Laboratory (VDRL) test: Wassermann described a complement fixing antibody against antigen of human syphilitic tissue. This antigen is used in the Standard Test for Syphilis (STS) in Wassermann complement fixing test and Venereal Disease Research Laboratory (VDRL) test.Stages of Acquired Syphilis Acquired syphilis is divided into 3 stages depending upon the period after which the lesions appear and the type of lesions. These are: primary, secondary and tertiary syphilis.

1. PRIMARY SYPHILIS. Typical lesion of primary syphilis is chancre which appears on genitals or at extra-genital sites in 2-4 weeks after exposure to infection (Fig. 6.34,A). Initially, the lesion is a painless papule which ulcerates in the centre so that the fully-developed chancre is an indurated lesion with central ulceration accompanied by regional lymphadenitis. The chancre heals without scarring, even in the absence of treatment. Histologically, the chancre has following features: i) Dense infiltrate of mainly plasma cells, some lymphocytes and a few macrophages. ii) Perivascular aggregation of mononuclear cells, particularly plasma cells (periarteritis and endarteritis). iii) Proliferation of vascular endothelium. Antibody tests are positive in 1-3 weeks after the appearance of chancre. Spirochaetes can be demonstrated in the exudates by DGI. 2. SECONDARY SYPHILIS. Inadequately treated patients of primary syphilis develop mucocutaneous lesions and painless lymphadenopathy in 2-3 months after the exposure (Fig. 6.34,B). Mucocutaneous lesions may be in the form of the mucous patches on mouth, pharynx and vagina; and generalised skin eruptions and condyloma lata in anogenital region. Antibody tests are always positive at this stage. Secondary syphilis is highly infective stage and spirochaetes can be easily demonstrated in the mucocutaneous lesions. 3. TERTIARY SYPHILIS. After a latent period of appearance of secondary lesions and about 2-3 years following first

exposure, tertiary lesions of syphilis appear. Lesions of tertiary syphilis are much less infective than the other two stages and spirochaetes can be demonstrated with great difficulty. These lesions are of 2 main typesi) Syphilitic gumma. It is a solitary, localised, rubbery lesion with central necrosis, seen in organs like liver, testis, bone and brain. In liver, the gumma is associated with scarring of hepatic parenchyma (hepar lobatum).

Histologically, the structure of gumma shows the following features (Fig. 6.35): a) Central coagulative necrosis resembling caseation but is less destructive so that outlines of necrosed cells can still be faintly seen. b) Surrounding zone of palisaded macrophages with many plasma cells, some lymphocytes, giant cells and fibroblasts.

ii) Diffuse lesions of tertiary syphilis. The lesions appear following widespread dissemination of spirochaetes in the body. The diffuse lesions are predominantly seen in cardiovascular and nervous systems which are described in detail later in the relevant chapters. Briefly, these lesions are as under: a) Cardiovascular syphilis mainly involves thoracic aorta. The wall of aorta is weakened and dilated due to syphilitic aortitis and results in aortic aneurysm, incompetence of aortic valve and narrowing of mouths of coronary ostia (Chapter 15). b) Neurosyphilis may manifest as: meningovascular syphilis affecting chiefly the meninges; tabes dorsalis affecting the spinal cord; and general paresis affecting the brain.

CONGENITAL SYPHILIS. Congenital syphilis may develop in a foetus of more than 16 weeks gestation who is exposed to maternal spirochaetaemia. The major morphologic features as under: i) Saddle-shaped nose deformity due to destruction of bridge of the nose.

ii) The characteristic ‘Hutchinson’s teeth’ which are small, widely spaced, peg-shaped permanent teeth. iii) Mucocutaneous lesions of acquired secondary syphilis. iv) Bony lesions like epiphysitis and periostitis. v) Interstitial keratitis with corneal opacity. vi) Diffuse fibrosis in the liver. vii)Interstitial fibrosis of lungs. viii) If the foetus with congenital syphilis is born dead, it is premature, with macerated skin, enlarged spleen and liver, and with syphilitic epiphysitis.

Histologically, the basic morphology of lesions in syphilis is seen in all the affected organs: perivascular plasma cell rich inflammatory infiltrate and endothelial cell proliferation. Many spirochaetes can be demonstrated in involved tissues.

Tuberculosis

TUBERCULOSIS Tissue response in tuberculosis represents classical example of chronic granulomatous inflammation in humans. CAUSATIVE ORGANISM. Tubercle bacillus or Koch's bacillus (named after discovery of the organism by Robert Koch in 1882) called Mycobacterium tuberculosis causes tuberculosis in the lungs and other tissues of the human body. The organism is a strict aerobe and thrives best in tissues with high oxygen tension such as in the apex of the lung. Out of various pathogenic strains for human disease included in Mycobacterium tuberculosis complex, currently most common is M. tuberculosis hominis (human strain), while M. tuberculosis bovis (bovine strain) used to be common pathogen to human beings during the era of consumption of unpasteurised milk but presently constitutes a small number of human cases. Other less common strains included in the complex are M. africanum (isolated from patients from parts of Africa), M. microti, M. pinnipedii and M. canettii. A nonpathogenic strain, M. smegmatis, is found in the smegma and as contaminant in the urine of both men and women. M. tuberculosis hominis is a slender rod-like bacillus, 0.5 µm by 3 µm, is neutral on Gram staining, and can be demonstrated by the following methods: 1. Acid fast (Ziehl-Neelsen) staining. The acid fastness of the tubercle bacilli is due to mycolic acids, cross-linked fatty acids and other lipids in the cell wall of the organism making it impermeable to the usual stains. It takes up stain by heated carbol fuchsin and resists decolourisation by acids and alcohols (acid fast and alcohol fast) and can be decolourised by 20% sulphuric acid (compared to 5% sulphuric acid for declourisation for M. leprae which are less acid fast) (Fig. 6.20). False positive AFB staining is seen due to Nocardia, Rhodococcus, Legionella, and some protozoa such as Isospora and Cryptosporidium. 2. Fluorescent dye methods. 3. Culture of the organism from sputum in LowensteinJensen (L.J.) medium for 6 weeks. 4. Guinea pig inoculation method by subcutaneous injection of the organisms. 5. Molecular methods such as PCR are the most recent methods. ATYPICAL MYCOBACTERIA (NON-

TUBERCULOUS MYCOBACTERIA). The term atypical mycobacteria or nontuberculous mycobacteria is used for mycobacterial speciesother than M. tuberculosis complex and M. leprae. Nontuberculous mycobacteria are widely distributed in the environment and are, therefore, also called as environmental mycobacteria. They too are acid fast. Occasionally, human tuberculosis may be caused by atypical mycobacteria which are non-pathogenic to guinea pigs and resistant to usual antitubercular drugs.

Conventionally, atypical mycobacteria are classified on the basis of colour of colony produced in culture and the speed of growth in media: Rapid growers. These organisms grow fast on solid media (within 7 days) but are less pathogenic than others. Examples include M. abscessus, M.fortuitum, M. chelonae.

SPREAD OF TUBERCULOSIS. The disease spreads in the body by various routes: 1. Local spread. This takes place by macrophages carrying the bacilli into the surrounding tissues. 2. Lymphatic spread. Tuberculosis is primarily an infection of lymphoid tissues. The bacilli may pass into lymphoid follicles of pharynx, bronchi, intestines or regional lymph nodes resulting in regional tuberculous lymphadenitis which is typical of childhood infections. Primary complex is primary focus with lymphangitis and lymphadenitis. 3. Haematogenous spread. This occurs either as a result of tuberculous bacillaemia because of the drainage of lymphatics into the venous system or due to caseous material escaping through ulcerated wall of a vein. This produces millet seed-sized lesions in different organs of the body like lungs, liver, kidneys, bones and other tissues and is known as miliary tuberculosis. 4. By the natural passages. Infection may spread from: i) lung lesions into pleura (tuberculous pleurisy); ii) transbronchial spread into the adjacent lung segments;iii) tuberculous salpingitis into peritoneal cavity (tuberculous peritonitis); iv) infected sputum into larynx (tuberculous laryngitis); v) swallowing of infected sputum (ileocaecal tuberculosis); and vi) renal lesions into ureter and down to trigone of bladder.

HYPERSENSITIVITY AND IMMUNITY IN TUBERCULOSIS. Hypersensitivity or allergy, and immunity or resistance, play a major role in the development of lesions in tuberculosis. Tubercle bacilli as such do not produce any toxins. Tissue changes seen in tuberculosis are not the result of any exotoxin or endotoxin but are instead the result of host response to the organism which is in the form of

development of cell-mediated hypersensitivity (or type IV hypersensitivity) and immunity. Both these host responses develop as a consequence of several lipids present in the microorganism which include the following: 1. mycosides such as 'cord factor' which are essential for growth and virulence of the organism in the animals; and 2. glycolipids present in the mycobacterial cell wall like 'Wax-D' which acts as an adjuvant acting along with tuberculoprotein. It has been known since the time of Robert Koch that the tissue reaction to tubercle bacilli is different in healthy animal not previously infected (primary infection) from an animal who is previously infected (secondary infection). 1. In the primary infection, intradermal injection of tubercle bacilli into the skin of a healthy guinea pig evokes no visible reaction for 10-14 days. After this period, a nodule develops at the inoculation site which subsequently ulcerates and heals poorly as the guinea pig, unlike human beings, does not possess any natural resistance. The regional lymph nodes also develop tubercles. This process is a manifestation of delayed type of hypersensitivity (type IV reaction) and is comparable to primary tuberculosis in children although healing invariably occurs in children. 2. In the secondary infection, the sequence of changes is different. The tubercle bacilli are injected into the skin of the guinea pig who has been infected with tuberculosis 4-6 weeks earlier. In 1-2 days, the site of inoculation is indurated and dark, attaining a diameter of about 1 cm. The skin lesion ulcerates which heals quickly and the regional lymph nodes are not affected. This is called Koch's phenomenon and is indicative of hypersensitivity and immunity in the host. Similar type of changes can be produced if injection of live tubercle bacilli is replaced with old tuberculin (OT). Hypersensitivity and immunity are closely related and are initiated through CD4+ T lymphocytes sensitised against specific antigens in tuberculin. As a result of this sensitisation, lymphokines are released from T cells which induce increased microbicidal activity of the macrophages. Tuberculin (Mantoux) skin test. This test is done by intradermal injection of 0.1 ml of tuberculoprotein, purified protein derivative (PPD). Delayed type of hypersensitivity develops in individuals who are having or have been previously infected with tuberculous infection which is identified as an indurated area of more than 15 mm in 72

hours. However, patients having disseminated tuberculosis may show negative test due to release of large amount of tuberculoproteins from the endogenous lesions masking the hypersensitivity test. A positive test is indicative of

cellmediated hypersensitivity to tubercular antigens but does not distinguish between infection and disease. The test may be false positive in atypical mycobacterial infection and false negative in sarcoidosis, some viral infections, Hodgkin's disease and fulminant tuberculosis. Immunisation against tuberculosis. Protective immunisation against tuberculosis is induced by injection of attenuated strains of bovine type of tubercle bacilli, Bacille Calmette-Guérin (BCG). Cell-mediated immunity with consequent delayed hypersensitivity reaction develops with healing of the lesion, but the cell-mediated immunity persists, rendering the host tuberculin-positive and hence immune.TYPES OF TUBERCULOSIS Lung is the main organ affected in tuberculosis. Depending upon the type of tissue response and age, the infection with tubercle bacilli is of 2 main types: A. Primary tuberculosis; and B. Secondary tuberculosis.

A. Primary Tuberculosis The infection of an individual who has not been previously infected or immunised is called primary tuberculosis or Ghon's complex or childhood tuberculosis. Primary complex or Ghon's complex is the lesion produced in the tissue of portal of entry with foci in the draining lymphatic vessels and lymph nodes. The most commonly involved tissues for primary complex are lungs and hilar lymph nodes. Other tissues which may show primary complex are tonsils and cervical lymph nodes, and in the case of ingested bacilli the lesions may be found in small intestine and mesenteric lymph nodes. The incidence of disseminated form of progressive primary tuberculosis is particularly high in immunocompromised host e.g. in patients of AIDS. Primary complex or Ghon's complex in lungs consists of 3 components (Fig. 6.22): 1. Pulmonary component. Lesion in the lung is the primary focus or Ghon's focus. It is 1-2 cm solitary area of tuberculouspneumonia located peripherally under a patch of pleurisy, in any part of the lung but more often in subpleural focus in the upper part of lower lobe. Microscopically, the lung lesion consists of tuberculous granulomas with caseation necrosis. 2. Lymphatic vessel component. The lymphatics draining the lung lesion contain phagocytes containing bacilli and may develop beaded, miliary tubercles along the path of hilar lymph nodes. 3. Lymph node component. This consists of enlarged hilar and tracheo-bronchial lymph nodes in the area drained. The affected lymph nodes are matted and show caseation necrosis (Fig. 6.23, A). Microscopically, the lesions are characterised by extensive caseation, tuberculous granulomas and fibrosis.

Nodal lesions are potential source of re-infection later (Fig. 6.23, B). In the case of primary tuberculosis of the alimentary tract due to ingestion of tubercle bacilli, a small primary focus is seen in the intestine with enlarged mesenteric lymph nodes producing tabes mesenterica. The enlarged and caseous mesenteric lymph nodes may rupture into peritoneal cavity and cause tuberculous peritonitis.B. Secondary Tuberculosis The infection of an individual who has been previously infected or sensitised is called secondary, or post-primary or reinfection, or chronic tuberculosis. The infection may be acquired from (Fig. 6.25): endogenous source such as reactivation of dormant primary complex; or exogenous source such as fresh dose of reinfection by the tubercle bacilli. Secondary tuberculosis occurs most commonly in lungs in the region of apex. Other sites and tissues which can be involved are tonsils, pharynx, larynx, small intestine and skin. Secondary tuberculosis of other organs and tissues is described in relevant chapters later while that of lungs is discussed here.

Secondary Pulmonary Tuberculosis The lesions in secondary pulmonary tuberculosis usually begin as 1-2 cm apical area of consolidation of the lung, which may in time develop a small area of central caseation necrosis and peripheral fibrosis. It occurs by haematogenous spread of infection from primary complex to the apex of the affected lung where the oxygen tension is high and favourable for growth of aerobic tubercle bacilli. Microscopically, the appear

ance is typical of tuberculous granulomas with caseation necrosis. Patients with HIV infection previously exposed to tuberculous infection have particularly high incidence of reactivation of primary tuberculosis and the pattern of lesions in such cases is similar to that of primary tuberculosis i.e. with involvement of hilar lymph nodes rather than cavitary and apical lesions in the lung. In addition, infection with M. avium-intracellulare occurs more frequently in cases of AIDS. FATE OF SECONDARY PULMONARY TUBERCULOSIS. The subapical lesions in lungs can have the following courses: 1. The lesions may heal with fibrous scarring and calcification. 2. The lesions may coalesce together to form larger area of tuberculous pneumonia and produce progressive secondary pulmonary tuberculosis with the following pulmonary and extrapulmonary involvements: i) Fibrocaseous tuberculosis ii) Tuberculous caseous pneumonia iii) Miliary tuberculosis.

Leprosy

Leprosy or Hansen's disease (after discovery of the causative organism by Hansen in 1874), was first described in ancient Indian text going back to 6th Century BC, is a chronic non-fatal infectious disease affecting mainly the cooler parts of the body such as the skin, mouth, respiratory tract, eyes, peripheral nerves, superficial lymph nodes and testis. Though the earliest and main involvement in leprosy is of the skin and nerves but in bacteraemia from endothelial colonisation or by bacilli filtered from blood by reticuloendothelial system, other organs such as the liver, spleen, bone marrow and regional lymph nodes are also involved. Advanced cases may develop secondary amyloidosis and renal disease, both of which are of immunologic origin.

Causative Organism The disease is caused by Mycobacterium leprae which closely resembles Mycobacterium tuberculosis but is less acid-fast. The organisms in tissues appear as compact rounded masses (globi) or are arranged in parallel fashion like cigarettes-inpack. M. leprae can be demonstrated in tissue sections, in split skin smears by splitting the skin, scrapings from cut edges of dermis, and in nasal smears by the following techniques: 1. Acid-fast (Ziehl-Neelsen) staining. The staining procedure is similar as for demonstration of M. tuberculosis but can be decolourised by lower concentration (5%) of sulphuric acid (less acid-fast) (Fig. 6.31). 2. Fite-Faraco staining procedure is a modification of Z.N. procedure and is considered better for more adequate staining of tissue sections. 3. Gomori methenamine silver (GMS) staining can also be employed. 4. Molecular methods by PCR. 5. IgM antibodies to PGL-1 antigen seen in 95% cases of lepromatous leprosy but only in 60% cases of tuberculoid leprosy.

Mode of Transmission Leprosy is a slow communicable disease and the incubation period between first exposure and appearance of signs of disease varies from 2 to 20 years (average about 3 years). The infectivity may be from the following sources: 1. Direct contact with untreated leprosy patients who shed numerous bacilli from damaged skin, nasal secretions, mucous membrane of mouth and hair follicles. 2. Materno-foetal transmission across the placenta. 3. Transmission from milk of leprosy patient to infant.

Immunology of Leprosy Like in tuberculosis, the immune response in leprosy is also T cell-mediated delayed hypersensitivity (type IV reaction) but the two diseases are quite dissimilar as regards immune reactions and lesions. M. leprae do not produce any toxins but instead the damage to tissues is immune-mediated. This is due to following peculiar aspects in immunology of leprosy: 1. Antigens of leprosy bacilli. Lepra bacilli have several antigens. The bacterial cell wall contains large amount of M. leprae-specific phenolic glycolipid (PGL-1) and another surface antigen, lipo-arabinomannan (LAMN). These antigens of the bacilli determine the immune reaction of host lymphocytes and macrophages. Another unique feature of leprosy bacilli is invasion in peripheral nerves which is due to binding of trisaccharide of M. leprae to basal lamina of Schwann cells. 2. Genotype of the host. Genetic composition of the host as known by MHC class (or HLA type) determines whichantigen of leprosy bacilli shall interact with host immune cells. Accordingly, the host response to the leprosy bacilli in different individuals is variable. 3. T cell response. There is variation in T cell response in different individuals infected with leprosy bacilli: i) Unlike tubercle bacilli, there is not only activation of CD4+ T cells but also of CD8+ T cells. ii) CD4+ T cells in lepra bacilli infected persons act not only as helper and promoter cells but also assume the role of cytotoxicity. iii) The two subpopulations of CD4+ T cells (or T helper cells)—TH 1 cells and TH 2 cells, elaborate different types of cytokines in response to stimuli from the lepra bacilli and macrophages. iv) In tuberculoid leprosy, the response is largely by CD4+ T cells, while in lepromatous leprosy although there is excess of CD8+ T cells (suppressor T) but the macrophages and suppressor T cells fail to destroy the bacilli due to CD8+ T cell defect. 4. Humoral response. Though the patients of lepromatous leprosy have humoral components like high levels of immunoglobulins (IgG, IgA, IgM) and antibodies to mycobacterial antigens but these antibodies do not have any protective role against lepra bacilli. Based on above unique immunologic features in leprosy, lesions in leprosy are classified into 5 distinct clinicopathologic types and three forms of reactional leprosy which are described below), and an intradermal immunologic test, lepromin test. LEPROMIN TEST. It is not a diagnostic test but is used for classifying leprosy on the basis of immune response. Intradermal injection of lepromin, an antigenic extract of M. leprae, reveals delayed hypersensitivity reaction in patients of tuberculoid leprosy: An early positive reaction appearing as an indurated area in 24-48 hours

is called Fernandez reaction. A delayed granulomatous lesion appearing after 3-4 weeks is called Mitsuda reaction. Patients of lepromatous leprosy are negative by the lepromin test.Classification Leprosy is broadly classified into 2 main types: Lepromatous type representing low resistance; and Tuberculoid type representing high resistance. Salient differences between the two main forms of leprosy are summarised in Table 6.5. Since both these types of leprosy represent two opposite poles of host immune response, these are also called polar forms of leprosy. Cases not falling into either of the two poles are classified as borderline and indeterminate types. Leprosy is classified into 5 clinico-pathologic groups (modified Ridley and Jopling's classification) as under: TT—Tuberculoid Polar (High resistance) BT—Borderline Tuberculoid BB—Mid Borderline (dimorphic) BL—Borderline Lepromatous LL—Lepromatous Polar (Low resistance) In addition, not included in Ridley-Jopling's classification are cases of indeterminate leprosy, pure neural leprosy, and histoid leprosy resembling a nodule of dermatofibroma and positive for lepra bacilli.

Typhoid(enteric fever)

Enteric Fever The term enteric fever is used to describe acute infection caused by Salmonella typhi (typhoid fever) or Salmonella paratyphi (paratyphoid fever). Besides these 2 salmonellae, Salmonella typhimurium causes food poisoning. PATHOGENESIS. The typhoid bacilli are ingested through contaminated food or water. During the initial asymptomatic incubation period of about 2 weeks, the bacilli invade the lymphoid follicles and Peyer's patches of the small intestine and proliferate. Following this, the bacilli invade the bloodstream causing bacteraemia, and the characteristic clinical features of the disease like continuous rise in temperature and 'rose spots' on the skin are observed. Immunological reactions (Widal's test) begin after about 10 days and peak titres are seen by the end of the third week. Eventually, the bacilli are localised in the intestinal lymphoid tissue (producing typhoid intestinal lesions), in the mesenteric lymph nodes (leading to haemorrhagic lymphadenitis), in the liver (causing foci of parenchymal necrosis), in the gall bladder (producing typhoid cholecystitis), and in the spleen (resulting in splenic reactive hyperplasia).

MORPHOLOGIC FEATURES. The lesions are observed in the intestines as well as in other organs. 1. INTESTINAL LESIONS. Grossly, terminal ileum is affected most often, but lesions may be seen in the jejunumand colon. Peyer's patches show oval typhoid ulcers with their long axis along the length of the bowel, (c.f. tuberculous ulcers of small intestine, described above). The base of the ulcers is black due to sloughed mucosa. The margins of the ulcers are slightly raised due to inflammatory oedema and cellular proliferation. There is never significant fibrosis and hence fibrous stenosis seldom occurs in healed typhoid lesions. The regional lymph nodes are invariably enlarged (Fig. 20.31,A). Microscopically, there is hyperaemia, oedema and cellular proliferation consisting of phagocytic histiocytes (showing characteristic erythrophagocytosis), lymphocytes and plasma cells. Though enteric fever is an example of acute inflammation, neutrophils are invariably absent from the cellular infiltrate and this is reflected in the leucopenia with neutropenia and relative lymphocytosis in the peripheral blood (Fig. 20.31,B). The main complications of the intestinal lesions of typhoid are perforation of the ulcers and haemorrhage. 2. OTHER LESIONS. Besides the intestinal involvement, various other organs and tissues showing pathological changes in enteric fever are as under: i) Mesenteric lymph nodes—haemorrhagic lymphadenitis. ii) Liver—foci of parenchymal necrosis. iii) Gallbladder—typhoid cholecystitis. iv) Spleen—splenomegaly with reactive hyperplasia. v) Kidneys—nephritis. vi) Abdominal muscles—Zenker's degeneration. vii) Joints—arthritis. viii) Bones—osteitis. ix) Meninges—Meningitis. x) Testis—Orchitis.Persistence of organism in the gallbladder or urinary tract may result in passage of organisms in the faeces or urine creating a 'carrier state' which is a source of infection to others.

Meningitis

Meningitis is inflammatory involvement of the meninges. Meningitis may involve the dura called pachymeningitis, or the leptomeninges (pia-arachnoid) termed leptomeningitis. The latter is far more common, and unless otherwise specified, meningitis would mean leptomeningitis. Pachymeningitis is invariably an extension of the inflammation from chronic suppurative otitis media or from fracture of the skull. An extradural abscess may form by suppuration between the

bone and dura. Further spread of infection may penetrate the dura and form a subdural abscess. Other effects of pachymeningitis are localised or generalised leptomeningitis and cerebral abscess.Acute Pyogenic Meningitis Acute pyogenic or acute purulent meningitis is acute infection of the pia-arachnoid and of the CSF enclosed in the subarachnoid space. Since the subarachnoid space is continuous around the brain, spinal cord and the optic nerves, infection spreads immediately to whole of the cerebrospinal meninges as well as to the ventricles. ETIOPATHOGENESIS. The causative organisms vary with age of the patient: 1. Escherichia coli infection is common in neonates with neural tube defects. 2. Haemophilus influenzae is commonly responsible for infection in infants and children. 3. Neisseria meningitidis causes meningitis in adolescent and young adults and is causative for epidemic meningitis. 4. Streptococcus pneumoniae is causative for infection at extremes of age and following trauma. The routes of infection in acute pyogenic meningitis are as follows: 1. Most commonly by the blood stream. 2. From an adjacent focus of infection. 3. By iatrogenic infection such as introduction of microorganisms at operation or during lumbar puncture.

MORPHOLOGIC FEATURES. Grossly, pus accumulates in the subarachnoid space so that normally clear CSF becomes turbid or frankly purulent. The turbid fluid is particularly seen in the sulci and at the base of the brain where the space is wide. In fulminant cases, some degree of ventriculitis is also present having a fibrinous coating on their walls and containing turbid CSF. In addition, purulent material may interfere with CSF flow and result in obstructive hydrocephalus. Microscopically, there is presence of numerous polymorphonuclear neutrophils in the subarachnoid space as well as in the meninges, particularly around the blood vessels (Fig. 30.3). Gram-staining reveals varying number of causative bacteria.

CLINICAL FEATURES AND DIAGNOSIS. Acute bacterial meningitis is a medical emergency. The immediate clinical manifestations are fever, severe headache, vomiting, drowsiness, stupor, coma, and occasionally, convulsions. The most important clinical sign is stiffness of the neck on forward bending. The diagnosis is confirmed by examining CSF as soon as possible. The diagnostic alterations in the CSF in acute pyogenic meningitis are as under: 1. Naked eye appearance of cloudy or frankly purulent CSF.

2. Elevated CSF pressure (above 180 mm water). 3. Polymorphonuclear neutrophilic leucocytosis in CSF (between 10-10,000/µl). 4. Raised CSF protein level (higher than 50 mg/dl). 5. Decreased CSF sugar concentration (lower than 40 mg/ dl). 6. Bacteriologic examination by Gram's stain or by CSF culture reveals causative organism.

Acute Lymphocytic (Viral, Aseptic) Meningitis Acute lymphocytic meningitis is a viral or aseptic meningitis, especially common in children and young adults. Among the etiologic agents are numerous viruses such as enteroviruses, mumps, ECHO viruses, coxsackie virus, Epstein-Barr virus, herpes simplex virus-2, arthropode-borne viruses and HIV. However, evidence of viral infection may not be demonstrable in about a third of cases.

MORPHOLOGIC FEATURES. Grossly, some cases show swelling of the brain while others show no distinctive change. Microscopically, there is mild lymphocytic infiltrate in the leptomeninges.

CLINICAL FEATURES AND DIAGNOSIS. The clinical manifestations of viral meningitis are much the same as in bacterial meningitis with features of acute onset meningeal symptoms and fever. However, viral meningitis has a benign and self-limiting clinical course of short duration and is invariably followed by complete recovery without the lifethreatening complications of bacterial meningitis. The CSF findings in viral meningitis are as under: 1. Naked eye appearance of clear or slightly turbid CSF. 2. CSF pressure increased (above 250 mm water). 3. Lymphocytosis in CSF (10-100 cells/µl).4. CSF protein usually normal or mildly raised. 5. CSF sugar concentration usually normal. 6. CSF bacteriologically sterile.

Chronic (Tuberculous and Cryptococcal) Meningitis There are two principal types of chronic meningitis—one bacterial (tuberculous meningitis) and the other fungal (cryptococcal meningitis). Both types cause chronic granulomatous reaction and may produce parenchymal lesions. Tuberculous meningitis occurs in children and adults through haematogenous spread of infection from tuberculosis elsewhere in the body, or it may simply be a manifestation of miliary tuberculosis. Less commonly, the spread may occur directly from tuberculosis of a vertebral body. Cryptococcal meningitis develops particularly in debilitated or

immunocompromised persons, usually as a result of haematogenous dissemination from a pulmonary lesion. Cryptococcal meningitis is especially an important cause of meningitis in patients with AIDS.

MORPHOLOGIC FEATURES. Grossly, in tuberculous meningitis, the subarachnoid space contains thick exudate, particularly abundant in the sulci and the base of the brain. Tubercles, 1-2 mm in diameter, may be visible, especially adjacent to the blood vessels. The exudate in cryptococcal meningitis is scanty, translucent and gelatinous. Microscopically, tuberculous meningitis shows exudate of acute and chronic inflammatory cells, and granulomas with or without caseation necrosis and giant cells. Acidfast bacilli may be demonstrated. Late cases show dense fibrous adhesions in the subarachnoid space and consequent hydrocephalus. Cryptococcal meningitis is characterised by infiltration by lymphocytes, plasma cells, an occasional granuloma and abundant characteristic capsulated cryptococci.

CLINICAL FEATURES AND DIAGNOSIS. Tuberculous meningitis manifests clinically as headache, confusion,

malaise and vomiting. The clinical course in cryptococcal meningitis may, however, be fulminant and fatal in a few weeks, or be indolent for months to years. The CSF findings in chronic meningitis are as under: 1. Naked eye appearance of a clear or slightly turbid CSF which may form fibrin web on standing. 2. Raised CSF pressure (above 300 mm water). 3. Mononuclear leucocytosis consisting mostly of lymphocytes and some macrophages (100-1000 cells/µl). 4. Raised protein content. 5. Lowered glucose concentration. 6. Tubercle bacilli may be found on microscopy of centrifuged deposits by ZN staining in tuberculous meningitis. Pathognomonic capsulated cryptococci with a halo are appreciated in India ink preparation of CSF in cases of cryptococcal meningitis, while the capsule is better demonstrated by mucicarmine stain.