Nonspecific defence: also called Innate immunity.It is the defense system with which person is born.It protects against all antigens.This involves barriers which form the first line of defence in the immune response.

Phagocytosis: Phagocytic cells such as monocytes,tissue macrophages,dendritic cells and neutrophils are important in early defence against invading m.o. These phagocytic cells recognize,ingest and kill these invading m.o. by the process called phagocytosis.

Phagocytic cells use two basic molecular mechanism for recognition of m.o. (1) Opsonin independent and (2) Opsonin dependant. The phagocytosis can be largely increased by opsonization.

Pathogen recognition: The opsonin independent mech.is a receptor based system in which components common to many different pathogens are recognized to activate phagocytes.phagocytes can recognize pathogens by several means.(1) Lectin phagocytosis is based on binding of microbial lectin to a carbohydrate moiety of a cell receptor.(2) Protein-protein interactions between peptide sequence i.e. arginine-glycine-aspartic acid (RGD) on cell surface of m.o. and RGD receptors found on all phagocytes.(3) Hydrophobic interactions between bacteria and phagocytic cells.(4) This plays a crucial role in non specific host resistance. This recognition strategy is based on detection of molecular structures that occur in patterns and are called pathogen-associated molecular patterns (PAMPs) which are unique to m.o. The most known examples of PAMPs are lipopolysaccharides of Gram negative bacteria and peptidoglycan of Gram positive bacteria. They are recognized by receptors on phagocytic cells called pattern recognition receptors (PRPs) This is one way the innate immune system distinguishes self from microbial nonself.

- Toll like receptors: One class of PRPs known as TLRs recognize and bind unique PAMPs of different classes of pathogens (viruses,bacteria or fungi) For example TLR-4 signals the presence of bacterial LPS and heat shock protein. TLR-2 signals the presence of bacterial lipoprotein and peptidoglycan. This binding of specific microbial components to phagocyte receptors is an important first step in phagocytosis.
- Intracellular digestion: Once ingested by phagocytes,m.o. are delivered to lysosome by fusion of phagocytic vesicle called a phagosome.this will now form a new vacuole called phagolysosome.this is when the killing begins because lysosomes posess variety of hydrolases such as lysozyme,phospholipase,ribonuclease,deoxyribonuclease,and proteases.collectively these enzymes participate in destruction of entrapped m.o. In addition to these oxygen independent lysosomal hydrolases,macrophage and neutrophil lysosomes contain oxygen dependant enzymes which produce toxic reactive oxygen intermediates(ROIs) such as superoxide radicals and hydroxyl radicals.Neutrophils also contain myeloperoxidase.These reactions result from respiratory burst mech.that accompanies increased oxygen consumption and ATP generation required for phagocytosis.

Macrophages,neutrophils and mast cells also form reactive nitrogen intermediates(RNIs) which include nitric oxide,nitrite and nitrate. These RNIs are very potent cytotoxic agents. They are also used to kill tumor cells.

- Exocytosis: Once the m.o. are killed and digested into small antigenic fragments phagocytes may react differently. Neutrophils expel microbial fragments by exocytosis. This is a reverse of phagocytosis where phagolysosome unites with the cell membrane resulting in extracellular release of microbial fragments.

Other phagocytic cells like macrophage and dendritic cells continue to process microbial fragments by passing them from phagolysosome to endoplasmic reticulum. This so called antigen presentation is critical as it permits wandering lymphocytes to evaluate killed microbe as antigen and be activated. Thus,antigen presentation links a nonspecific immune response to a specific immune response.

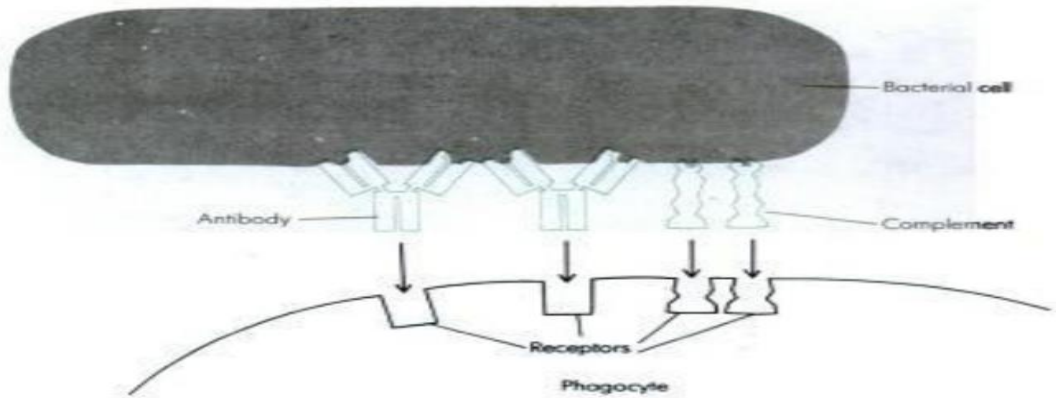


Figure 32-7. Attachment of bacterial cell antigen to surface of phagocyte. The phagocyte has receptors on its surface both for the antibody and for the complement. Phagocytosis occurs more readily with this kind of binding.

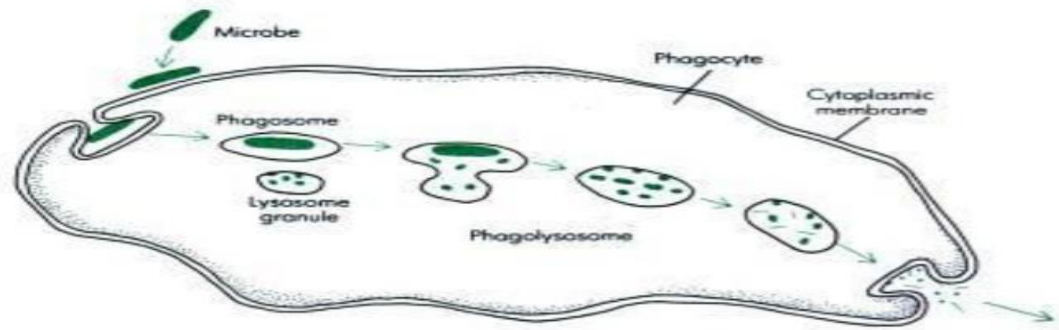


Figure 32-8. Phagocytosis of a microbial cell.

Phagocytic cells have a special receptor affinity for antibody attached to microorganisms. If complement is also bound to the microbial surface, there are complement receptors on the phagocytic cell which provide additional attachment forces. (See Fig. 32-7.)

In phagocytosis, the phagocyte extends small pseudopods around the microbe after adherence. These pseudopods fuse and form a vacuole by means of invagination of the phagocyte plasma membrane engulfing or surrounding the bacterium. The vacuole is now called a phagosome. Subsequent events depend on the activity of the lysosomal granules. These move toward the phagosome, fuse with its membrane to form a phagolysosome. and discharge their contents

- Inflammation: It is an important nonspecific defense reaction to tissue injury such as that caused by pathogen or wound. It is of two types
- 1) Acute inflammation: It is an immediate response of body to injury or cell death.The gross features are known as cardinal signs of inflammation which include redness(rubor),warmth(calor),pain(dolor),swelling(tumor) and altered function(function laesa).

The acute inflammatory response begins when injured tissue cells release chemical signals(chemokines) that activate the inner lining(endothelium) of nearby capillaries.Within capillaries,selectins i.e.cell adhesion molecules are displayed on the activated endothelial cells. These adhesion molecules attract and attach wandering neutrophils to the endothelial cells. This slows the neutrophils and causes them to roll along the endothelium where they encounter activating signals. These signals activate integrins i.e. adhesion receptors on the neutrophil. The neutrophil integrins then attach tightly to selectins. This causes neutrophil to stick to endothelium and stop rolling. The neutrophils then squeeze through endothelial wall into interstitial tissue fluid,migrate to the site of injury and attack the pathogen or other cause of tissue damage.Neutrophils and other leukocytes are attracted to infection site by chemotactic factors also called chemotaxins which include substances released by bacteria,endothelial cells and tissue breakdown products. Depending on the severity and nature of tissue damage other leukocytes like lynphocytes and macrophages may follow neutrophils.

The release of inflammatory mediators from injured tissue cells sets a series of events which results into signs of inflammation. The mediators increase the acidity in the surrounding extracellular fluid which activates extracellular enzyme kallikrein which releases bradykinin from its long precursor chain. Bradykinin then binds to receptors on capillary wall,opening the junction between cells and allowing fluid and leukocytes to leave the capillary and enter the infected tissue. Simultaneously bradykinin binds to mast cells in connective tissue. This activates the mast cells and release of histamine which inturn makes the intercellular junction in the capillary wall wider which causes swelling or edema.

During acute inflammation,pathogen is neutralized and eliminated by:

1) The increase in blood flow and capillary dilation bring into the area more antimicrobial factors and leukocytes that destroy the pathogen. Dead cells also release antimicrobial factors.

2) Blood leakage into tissue spaces increases the temperature which inhibit microbial growth.

3) A fibrin clot often forms that may limit the spread of the pathogen so that they remain localized.

4) Phagocytes gather in the inflamed area and phagocytose the pathogen. In addition chemicals stimulate bone marrow to increase the rate of neutrophil production.

- Chronic inflammation: It is a slow process,characterized by formation of a new connective tissue and it usually causes permanent tissue damage. Regardless of the cause, chronic inflammation lasts two weeks or longer. The persistence of bacteria by variety of mech. Can cause chronic inflammation for e.g. Mycobacteria that cause T.B. and leprosy have cell wall with very high lipid and wax content making them resistant to phagocytosis. Some bacteria also produce toxins which stimulate tissue damaging reactions even after bacterial death.

Chronic inflammation is characterized by dense infiltration of lymphocytes and macrophages. If macrophages are unable to protect the host from tissue damage, the body attempts to wall off and isolate the site by forming a granuloma means chronic inflammation. Examples include listeriosis and brucellosis (by bacteria) histoplasmosis (fungi) leishmaniasis (protozoa) etc.

The Complement system

- The term complement refers to a system of factors which occur in normal serum and are activated by antigen-antibody interactions.
- It is a nonspecific serological reagent means complement from one species can react with antibodies from other species. Though some of its components are heat stable, complement as a whole is heat labile. Its cytolytic action undergoes spontaneous denaturation at room temp. and is destroyed in 30 minutes at 56C A serum deprived of its complement activity is said to be inactivated.
- Complement (C) does not normally bind to free antigen or antibody but only to antibody which has combined with its antigen.
- Complement is a complex of nine different fractions called C1 to C9. The fraction C1 occurs in serum as a calcium ion dependant complex which on chelation with EDTA gives three protein subunits called C1q ,r and s Thus C is made up of total of 11 different proteins.
- The model used to explain C activity in immune cytolysis is the lysis of erythrocytes sensitized by its antibody.This is called EA or erythrocyte antibody complex. When a component of complement acquires enzymatic or other biological activity , it is indicated by a bar over component number. Fragments cleaved from C components are indicated by small letters. Inactivated forms of C components are indicated by suffix i.

- Complement activation: Complement is normally present in the body in an inactive form but when its activity is induced by Ag-Ab combination, C components react in a specific sequence as a cascade. Basically C cascade is a series of reaction in which preceding components act as enzyme on the succeeding components cleaving them into dissimilar fragments. The larger fragments usually join the cascade. The smaller fragments which are released often possess biological effects which contribute to defence mechanisms by inflammatory process, increasing vascular permeability, promoting virus neutralization, detoxifying endotoxins and effecting the release of histamine from mast cells.
- Classical pathway: It consists of following steps
- 1) There is a binding of C1 to Ag-Ab complex which is represented as EA complex.The recognition unit of C1 is C1q and C1q binding in presence of calcium ions leads to sequential activation of C1r and s.
- 2) Activated C1 is an esterase which can cleave C4 into C4a and C4b which binds with C1.
- 3) C14b in the presence of magnesium ion cleaves C2 into C2a and C2b C2a remains linked to cell bound C14b and C2b is released into fluid phase.C14b2a has enzymatic activity and known as classical pathway C3 convertase.

- 4) C3 convertase splits C3 into two fragments-C3a is anaphylatoxin and C3b which remains bound with C14b2a to form trimolecular complex called C14b2a3b which has enzymatic activity and called C5 convertase.
- 5) The membrane attack phase of complement activity begins at this stage with C5 convertase cleaving C5 into C5a which is anaphylatoxin and C5b which continues with the cascade. C6 and C7 then join together and prepares cell membrane for lysis. C8 and C9 join the cascade subsequently. This finally disrupts the osmotic integrity of membrane and leading to release of cell contents.

Although classical pathway is generally activated by antigen-antibody complexes, activation can also occur due to c-reactive protein, trypsin-like enzymes or some retroviruses.

Anaphylatoxin are C3a, C4a C5a produced as a part of activation of complement system and have important function in immune response and host defence.

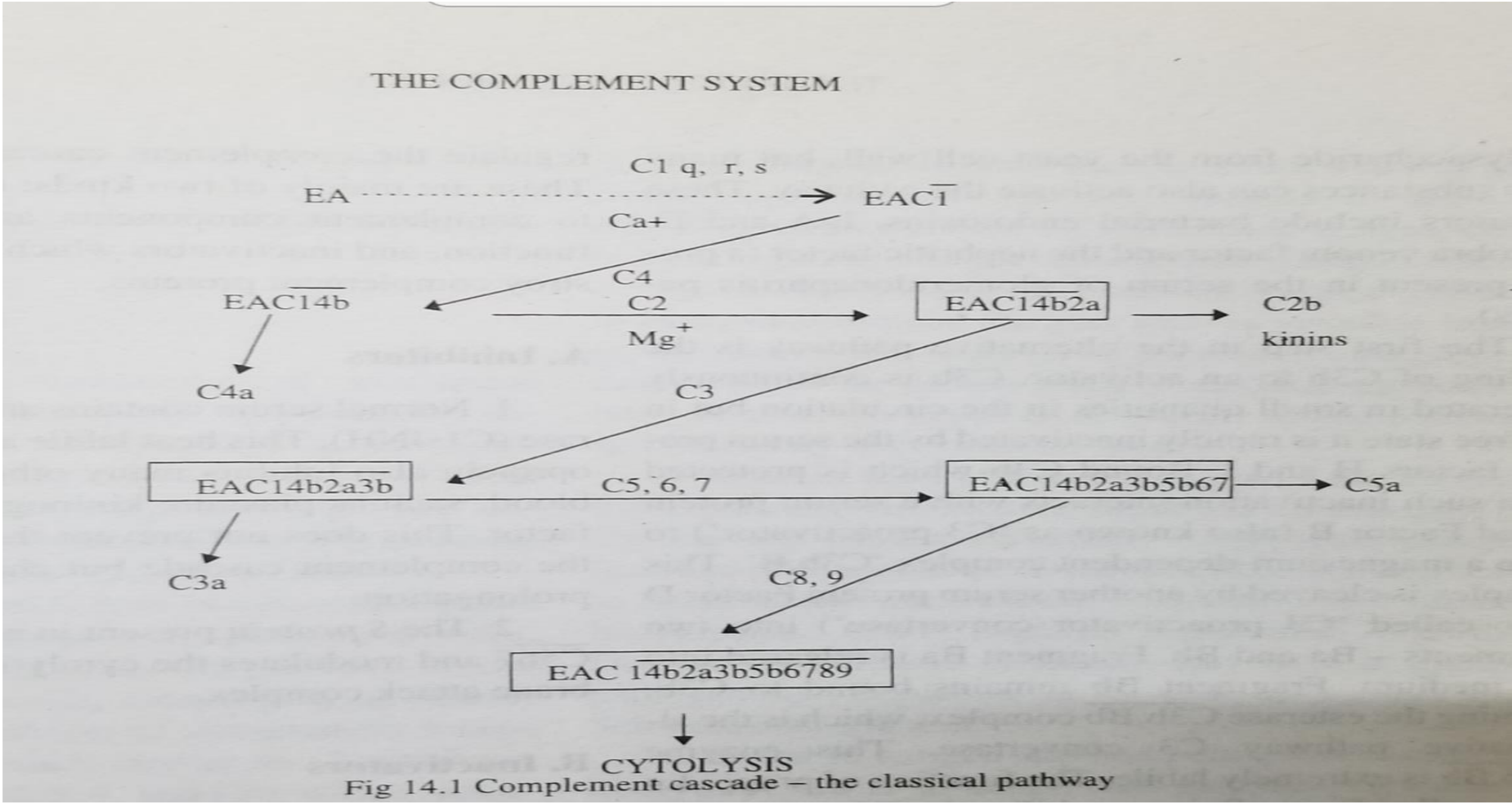


Fig 14.1 Complement cascade – the classical pathway

- Alternative pathway: The central process in the complement cascade is the activation of C3 which is the major component of complement. In the classical pathway activation of C3 is achieved by classical C3 convertase. The activation of C3 without prior participation of C142 is known as alternative pathway. The activator in this system was zymosan which is a polysaccharide from the yeast cell wall but many other substances can also activate this pathway such as bacterial endotoxins, IgA and D, cobra venom factor and nephritic factors.
- The first step in this pathway is the binding of C3b to an activator. C3b is continuously generated in small quantities in the circulation but in a free state it is rapidly inactivated by the serum protein factors H and I. Bound C3b which is protected from such inactivation interacts with a serum protein called factor B (Also called C3 proactivator) to form a magnesium –dependent complex C3b B. This complex is cleaved by another serum protein factor D (also called C3 proactivator convertase) into two fragments – Ba and Bb. Fragment Ba is released into the medium. Fragment Bb remains bound to C3b forming the complex C3b Bb which is the alternative pathway C3 convertase. This enzyme i.e. esterase C3b Bb is exteremely labile. The function of properdin also called factor P is to stabilize the C3 convertase which hydrolyses C3 leading to further steps in the cascade as in the classical pathway.
- This pathway plays important role against intravascular invasion by bacteria and some fungi.Here cleavage of C3 into C3a and C3b is done by blood enzyme.

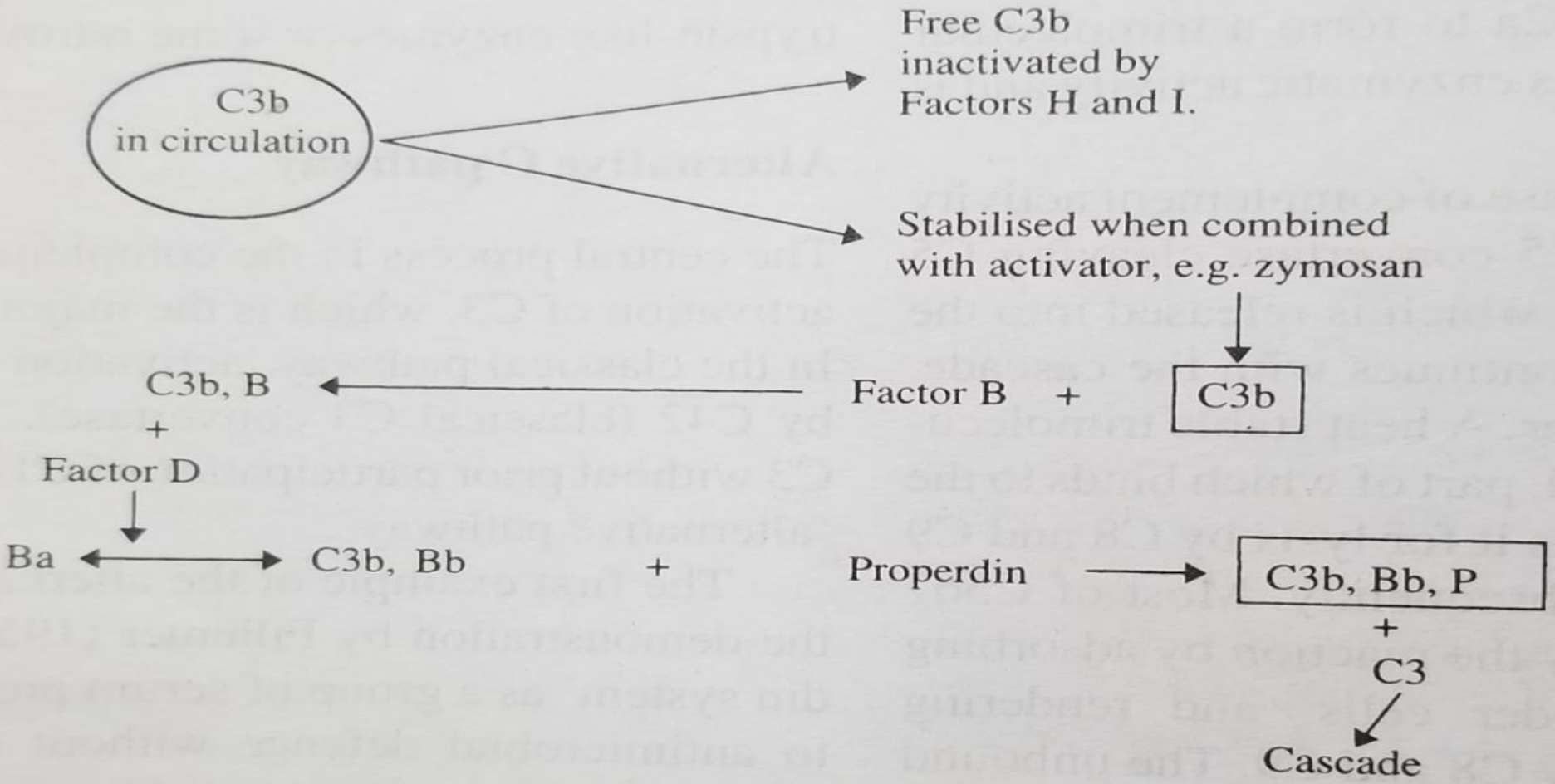


Fig 14.2 Complement cascade – the alternative pathway

- The Lectin pathway: This pathway also called the mannan-binding lectin pathway also begins with the activation of C3 convertase. However, in this case a lectin,a special protein that binds to specific carbohydrates, initiates the proteolytic cascade. When macrophages ingest viruses, bacteria or other foreign material, they release chemicals that stimulate liver cells to secrete acute phase proteins such as mannose-binding protein (MBP). Because mannose is a major component of bacterial cell walls and of antigen-antibody complexes, MBP binds to these components.

MBP enhances phagocytosis and is therefore an opsonin. When MBP is bound to the MBP-associated serine esterase (MASP), it activates the same C3 convertase found in the alternative pathway. Thus the lectin pathway activates the same complement cascade that the classical and alternative pathway do. However it uses the mechanism that is independent of antigen- antibody interaction(classical pathway) and it does not require the interaction of complement with pathogen surfaces (alternative pathway).

- Cytokines: They are required for immunoregulation of both specific and nonspecific immune responses.Cytokine is a generic term for any soluble protein or glycoprotein released by one cell population that acts as intercellular mediator.
- When released from mononuclear phagocytes they are called monokines. When release from T lymphocytes they are called lymphokines. When produced by a leukocyte and action is on another leukocyte they are interleukins and if their effect is to stimulate growth of immature leukocytes in bone marrow they are called colony stimulating factors (CSFs) cytokines have been grouped into following catagories or families: chemokines,hematopoietins,interleukins and members of tumor necrosis factors (TNF)
- Cytokines can affect the same cell responsible for their production (autocrine function) or nearby cells (paracrine function) or they can be distributed by circulatory system to distant target cells (endocrine function) their production is induced by nonspecific stimuli such as viral,bacterial or parasitic infection,cancer or inflammation.
- Cytokines produce biological actions only when they bind to specific,high affinity receptors on the surface of target cells.cytokines can also inhibit cell division and cause apoptosis i.e. programmed cell death.

- Interferons are a group of low molecular weight cytokines produced by certain eukaryotic cells in response to viral infection.they also regulate immune response.they prevent viral replication and assembly.
- Another group of cytokines are endogenous pyrogens which induce fever in the host examples of such pyrogens include IL 1,IL 6 and TNF
- Acute phase proteins: Macrophages release cytokines upon activation by bacteria which stimulate the liver to rapdly produce acute phase proteins.These include C- reactive protein (CRP),Mannose binding lectin(MBL) and surfactant proteins A and D. All of these can bind bacterial surfaces and act as opsonins.CRP can interact with C1q to activate classical pathway while MBL activates alternative pathway. Thus these proteins protect host tissues by binding to and help in the removal of bacteria.

- The Lymphoid system: It consists of lymphoid organs and cells. The thymus and bone marrow are primary lymphoid organs and spleen and lymph nodes are secondary lymphoid organs. The lymphoid cells consist of lymphocytes and plasmacells.
- Central (Primary) lymphoid organs: Thymus: It performs the important function of generating T cells that will protect the body from infection.In humans thymus continues to grow till about twelve years.It is located behind the upper part of sternum. It produces thymic lymphocytes however only about one percent leave thymus. Some T cells with receptors are capable of recognizing Ag-MHC complexes. The thymus induces death of those T cells which can not recognize Ag-MHC complex.
- Clinical significance: DiGeorge syndrome where deficient CMI is seen in congenital aplasia of thymus in humans.Deficiency of CMI is evident from lymphopenia, graft rejection and so called runt disease in mice.
- Bone marrow: It is the site of B cell origin and development. All lymphocytes except T lymphocytes originate in bone marrow.

- Peripheral (secondary) lymphoid organs: Lymph nodes: They are placed along the course of lymphatic vessels and differentiated into outer cortex and inner medulla.In the cortex primary lymphoid follicles accumulate within which secondary follicles develop during antigenic stimulation.The follicles contain dendritic macrophages which capture and process antigen. In the medulla lymphocytes,plasma cells and macrophages are arranged in bands.

Lymph nodes act as a filter for lymph. They phagocytose foreign materials. Also help in proliferation and circulation of T and B cells. They enlarge following antigenic stimulation.

Spleen: It is the largest of lymphoid organs. It serves as graveyard for affected blood cells and filter for trapping foreign particles.

MALT-Mucosa associated lymphoid tissue

GALT- Gut associated lymphoid tissue

SALT- Skin associated lymphoid tissue

BALT- Bronchus associated lymphoid tissue

- Cells of lymphoreticular system: Lymphocytes: Lymphocytes constitute 30-40 per cent of the body's blood cells. On the basis of function lymphocytes can be broadly subdivided into three types: B cells, T cells and natural killer cells.

Depending on their life span, they can be classified as short-lived and long-lived lymphocytes. In humans, the short-lived lymphocytes have a life span of about two weeks, while the long lived cells may last for three years or more. Short-lived lymphocytes are the effector cells in immune response, while the long-lived cells act as immunological memory. Long-lived cells are mainly thymus derived.

Lymphocytic recirculation: Lymphopoiesis takes place mainly in the central lymphoid organs where they mature. These populations of lymphocytes do not remain distinct but mix together in a process known as lymphocyte recirculation.

Following introduction of antigen into any part of the body, lymphocytes reach the site and mount an immune response. Recirculating lymphocytes are mainly T cells.

- Functions: A lymphocyte which has been educated by primary lymphoid organs becomes ICC i.e.immunologically competent cells.Mature T cells and B cells, before they encounter antigens, are called naïve cells. They carry out the functions such as recognition of antigens, storage of immunological memory and immune response to specific antigens.

Lymphocytes have antigen recognition mechanisms on their surface helping each cell to recognize only one antigen. The nature of immune response depends on whether the lymphocyte is a B or T cell.

Stimulated T cells produce lymphokines and induce CMI while B cells divide and transform into plasma cells which synthesize immunoglobulins.

Pathogenicity is the capability of a microbial species to cause disease. However, various strains of a pathogenic species may differ with regard to their *degree* of pathogenicity, i.e., with regard to their **virulence**. For instance, some strains are highly virulent: only a few bacterial cells from a highly virulent strain are needed to cause disease in a host. Other strains may be less virulent, and larger numbers of cells of such strains are needed to cause the disease. Some strains may be avirulent, incapable of causing the disease even when large numbers of cells are inoculated into the host. Virulent strains of many pathogens, when repeatedly cultured on laboratory media or grown in vivo in hosts other than their normal hosts, may lose their virulence: such avirulent strains are called **attenuated** strains and are widely used as vaccines to elicit immunity to various diseases.

The virulence of a pathogen is usually measured by determining its LD_{50} dose for a particular type of laboratory animal. The LD_{50} dose is defined as that number of organisms which, when administered to a number of laboratory animals, will kill 50 percent of them. For example, an LD_{50} dose of 10 cells of strain X compared with 100,000 cells of strain Y would indicate that X is 10,000 times more virulent than Y. The LD_{50} dose can be determined more precisely than other endpoints such as the dose that kills 100 percent of the animals (LD_{100} dose, sometimes also termed **minimum lethal dose** or **MLD**) because the rate of change in mortality versus change in dose is greatest around the point of 50 percent mortality.

Infection represents the most intimate way in which a microorganism may cause disease: the host is invaded by the microorganisms which subsequently multiply in close association with the host's tissues. Most, but not all, microbially caused diseases are infections. An example of one that is not is a type of food poisoning called botulism, in which there is no invasion of the body by the causative microorganism; rather, the disease is contracted by ingesting the poison (toxin) in a food in which the bacterium *Clostridium botulinum* has previously grown.

In order to cause infectious disease a pathogen must accomplish the following:

1. It must enter the host.
2. It must metabolize and multiply on or in the host tissue.
3. It must resist host defenses (see Chaps. 32 and 33).
4. It must damage the host.

Each process is complex, and all four processes must be fulfilled to produce infectious disease. Some infections may result in only a very minor amount of damage to the host, so minor that there are no detectable clinical symptoms of

Table 31-1. Some Types of Infections

Term	Definition	Example
Acute	Has a short and relatively severe course	Streptococcal pharyngitis (sore throat caused by *Streptococcus pyogenes*)
Chronic	Has a long duration	Tuberculosis
Fulminating	Occurs suddenly and with severe intensity	Cerebrospinal meningitis caused by *Neisseria meningitidis*
Localized	Restricted to a limited area of the body	Urinary tract infection caused by *Escherichia coli*
Generalized	Affects many or all parts of the body	Blood infections, such as typhoid fever
Mixed, or polymicrobial	More than one kind of microorganism contributes to the infection	Gaseous gangrene, in which a combination of *Clostridium* species may occur
Primary	An initial localized infection that decreases resistance and thus paves the way for further invasion by the same microorganism or other microorganisms	Viral influenza
Secondary	Infection that is established after a primary infection has caused a decreased resistance	Pneumococcal pneumonia following viral influenza

the infection; such infections are called **subclinical infections**. Other infections vary in regard to severity, location, and the number of microbial species involved (see Table 31-1).

MICROBIAL ADHERENCE

Unless a pathogen is introduced directly into the tissues (as by a wound, injection by an arthropod, or other similar means), the first step in initiation of infection is usually **adherence** or **attachment** of the pathogen to some surface of the host. As indicated in Chap. 30, such surfaces represent hostile environments and the microorganism must compete with normal flora organisms for surface attachment. Moreover, the attachment is selective: various pathogens attach only to certain tissues. For most pathogens, the precise means of attachment are not yet understood, particularly for pathogenic fungi and protozoa.

Examples of Adherence of Pathogenic Bacteria

Neisseria gonorrhoeae, the causative agent of gonorrhea, adheres specifically to the epithelial cell layer of the human cervix, urethra, and conjunctiva by means of pili and thus avoids being washed away by the flow of mucus or tears. *Escherichia coli* strains that cause "scours," a diarrheal disease of newborn pigs, also possess pili that allow the bacteria to attach firmly to the mucosal lining of the small intestine. *Vibrio cholerae* adheres to the epithelial layer of the small intestine of humans (see Fig. 31-1); although the bacterial surface component responsible for the attachment is not yet certain, it may be a **hemagglutinin** (so named because it also permits attachment to erythrocytes in laboratory experiments). In another example, certain proteins located on the outer surface of the bacterial cell wall have been shown to be essential for the initiation of infection. For instance, *Streptococcus pyogenes*, the causative agent of streptococcal sore

Skin

The skin is composed of the **epidermis** at the outer surface and of the connective tissue layer, **dermis**, underneath it (Fig. 30-3). The outermost layer of the epidermis consists of a layer of dead, anucleated, horny cells and is constantly in contact with bacteria from the surrounding environment. It is normally impermeable to bacteria; however, cuts, abrasions, or burns can allow bacteria to penetrate. The skin has a wide variation in structure and function in various sites of the body. These differences serve as selective ecological features, determining the types and numbers of microorganisms that occur on each skin site.

The skin surface is hostile to survival and growth of many kinds of bacteria.

For instance, the pathogen *Streptococcus pyogenes* does not survive for more than a few hours when applied to the skin, whereas it may survive for weeks in room dust. Several factors are responsible for discouraging skin colonization:

1 ***Dryness.*** The relatively dry surface of the skin is inhibitory to microbial growth. When allowed to dry, many bacteria remain in a dormant condition; some species die in a matter of hours. Some regions of the skin are more moist than others, e.g., the axillary region, toe webs(skin between the toes), and the perineum(skin at the lower end of the trunk between the thighs). These regions have higher numbers of normal flora organisms [about 10^6 colony-forming units (cfu)/cm^2] than do the drier areas of skin (about 10^2 to 10^4 cfu/cm^2).
2 ***Low pH.*** Skin has a normal pH between 3 and 5 (higher in moist regions), which is due in part to lactic or other organic acids produced by normal skin microorganisms such as staphylococci. This low pH can discourage the growth of many kinds of microorganisms.
3 ***Inhibitory substances.*** Several bactericidal or bacteriostatic compounds occur on the skin. For example, **sweat glands**(Fig. 30-3) secrete lysozyme, an enzyme that destroys bacterial cell walls. **Sebaceous glands**(Fig. 30-3) secrete complex lipids, which may be partially degraded by some bacteria such as *Propionibacterium acnes*; the resulting long-chain unsaturated fatty acids, e.g., oleic acid, are highly toxic to other bacteria.

Despite these formidable antimicrobial factors, some bacteria not only survive on the skin but even grow, forming the normal flora. The secretions of the sweat glands and sebaceous glands provide water, amino acids, urea, salts, and fatty acids, which can serve as nutrients for these microorganisms. Most of these bacteria are species of *Staphylococcus* (mainly *Staphylococcus epidermidis*) and aerobic corynebacteria, or diphtheroids. In the deep sebaceous glands are found lipophilic anaerobic bacteria such as *P. acnes*. The latter organism is a normal skin inhabitant and is usually harmless; however, it has been associated with the skin disease known as acne vulgaris. The numbers of these propionibacteria are little affected by washing because of their deep location. The location of various skin bacteria in or on the skin is shown in Fig. 30-3.

Propionibacterium acnes and Acne Vulgaris

Acne vulgaris is a disease of the sebaceous glands of the skin. In the first stage of the disease **comedones**(singular, *comedo*) are formed, i.e., distensions of the glands caused by an accumulation of sebum (fluid secreted by the gland), hair, and bacteria. Comedones may progress no further, or they may become closed (no longer able to eliminate their contents to the skin surface); such comedones can develop into disfiguring inflammatory lesions (papules, pustules, and nodules). *P. acnes* is the predominant organism in comedones; however, since it is also abundant in normal sebaceous glands, it is not yet clear that the organism is actually the causative agent of acne vulgaris. The ability of antibiotics to achieve clinical improvement in acne and at the same time reduce the number of *P. acnes* suggests that the organism may play an important role.

Eye

Lining the eyelids and covering the eyeball is a delicate membrane called the **conjunctiva**.This membrane is continually being washed by a flow of **fluid** (tears), which tends to remove microorganisms. Moreover, lysozyme is secreted in tears. Consequently, the conjunctival flora is sparse. The main or-

T CELL MATURATION

T cell precursors from the yolk sac, fetal liver and bone marrow migrate to the thymus during the embryonic and postnatal stages. The earliest identifiable cells of T lineage are the $CD7^+$ pro-T cells, which acquire CD2 on entering the thymus. They synthesise CD3 in the cytoplasm and become pre-T cells. T cell receptor (TCR) synthesis also takes place.

T cell receptors

TCR is a heterodimer of glycoprotein chains expressed on the T cell surface, which in association with CD3

The function of TCR γδ cells is not well understood, but they are believed to be immune surveillance cells on epithelial surfaces and a form of defense against intracellular bacteria and participate in innate immunity and immune response homeostasis.

Sequential antigenic changes characterising T cell maturation enable their easy identification. This has application in defining T cell malignancies. Acute T cell malignancies such as lymphoblastic leukemia and lymphomas involve early T cells, pro-T cells and other immature forms. Chronic T cell malignancies like mycosis fungoides, peripheral T cell lymphomas and HTLV-1-associated adult T cell leukemias involve mature T cells, mainly $CD4^+$ cells.

Types of T cells

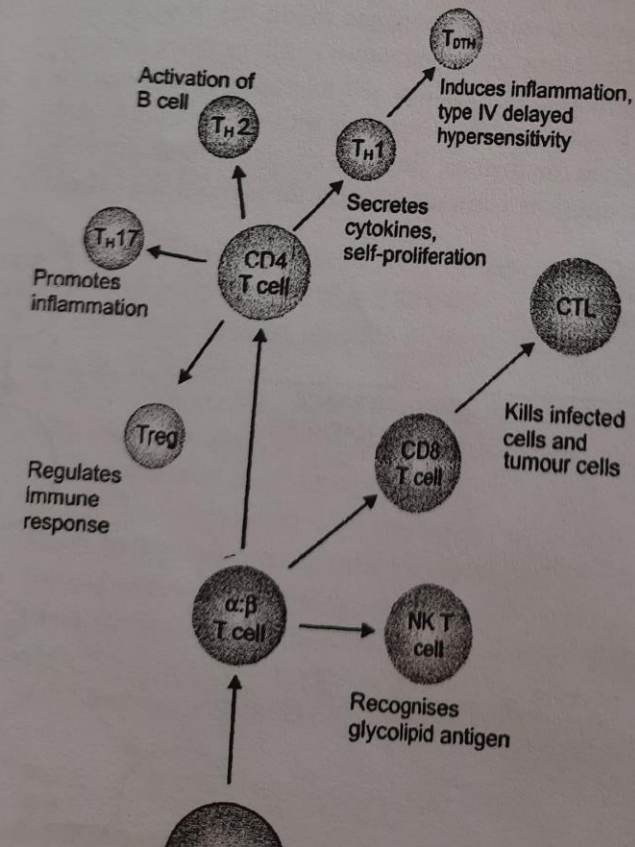
Based on their surface markers, target cells and functions, the following T cell categories have been identified. Minor subsets of CD4+ cells and CD8+ cells also exist. Figure 14.8 shows the major and minor subsets of T cells along with their functions.

T cells are classified as regulatory or effector cells. They may be CD4+ or CD8+ on their surface:

- **Helper/Inducer (T_H) cells,** with a CD4 surface marker and major histocompatibility complex (MHC) class II restriction, generally stimulate and

promote the growth of T cells and macrophages. CD4+ cells can differentiate into T_H cells or T regulatory cells. T_H cells are further differentiated into:

- T_H 1 cells, which produce cytokines, interferon gamma and interleukin-2, which activate macrophage and T cells, promoting cell-mediated immunity, destruction of target cells and killing of intracellular pathogens (tubercle and lepra bacilli)
- T_H 2 cells produce cytokines IL4, 5 and 6 which stimulate B cells to form antibodies
- T_H 17 cells produce cytokine IL17 and promote inflammation, for example, autoimmune diseases (systemic lupus erythematous [SLE] and rheumatic arthritis) and cancer.



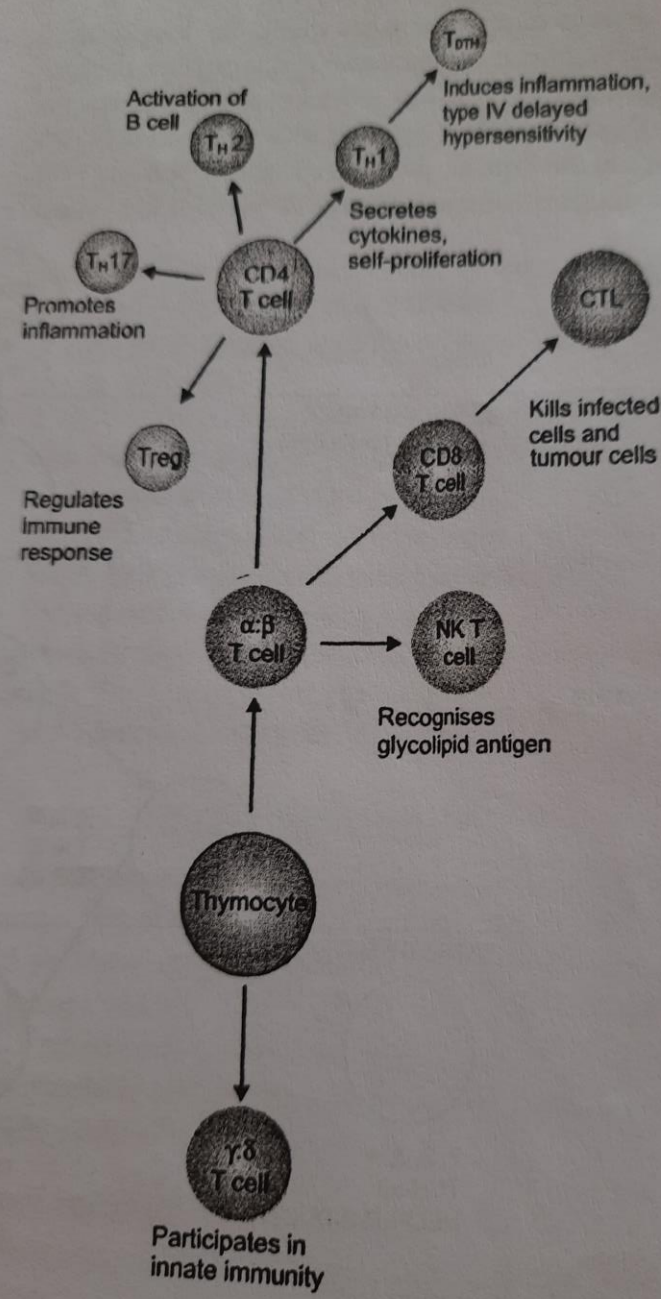


Fig. 14.8 Types of T cells and their functions

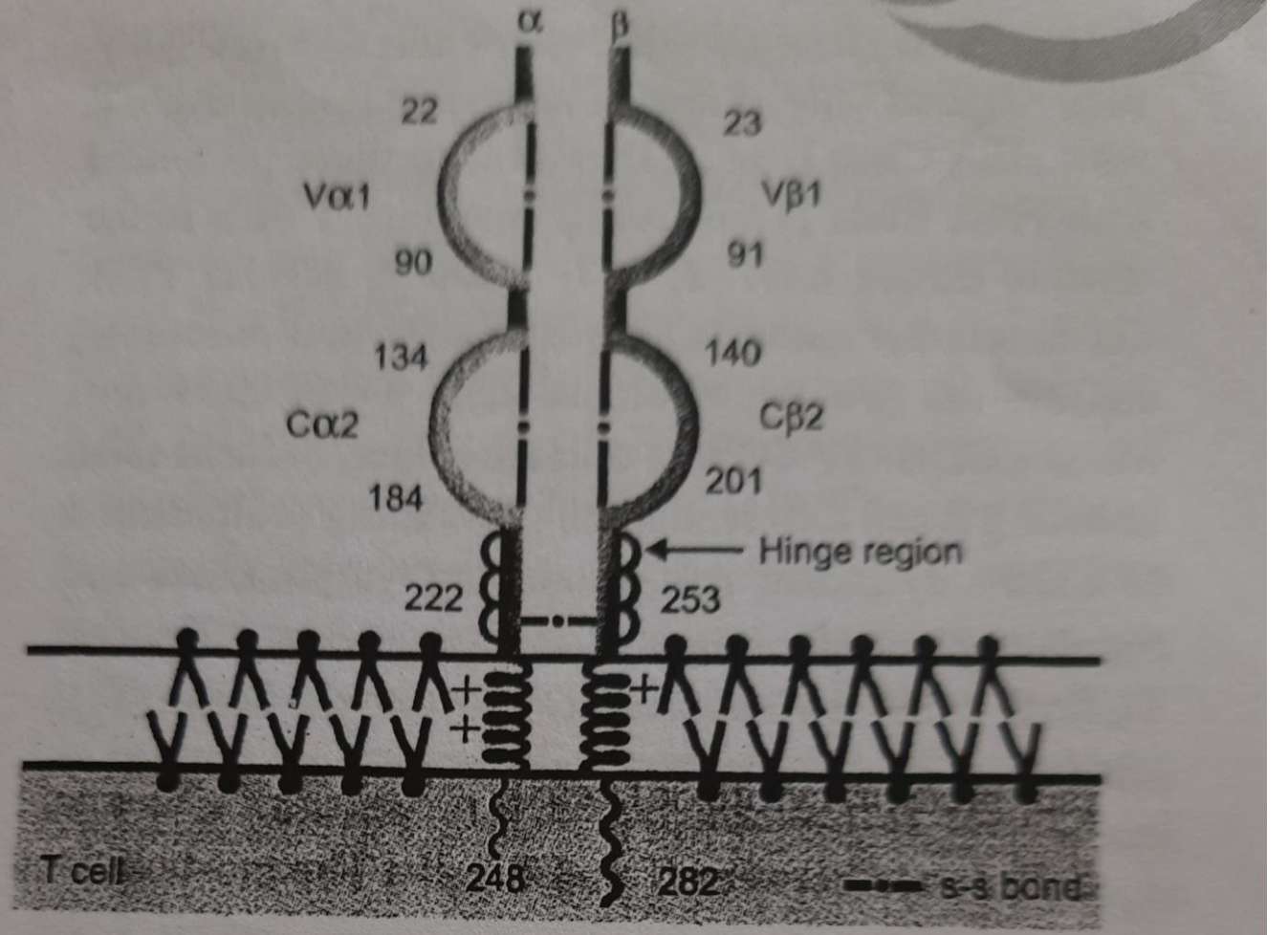
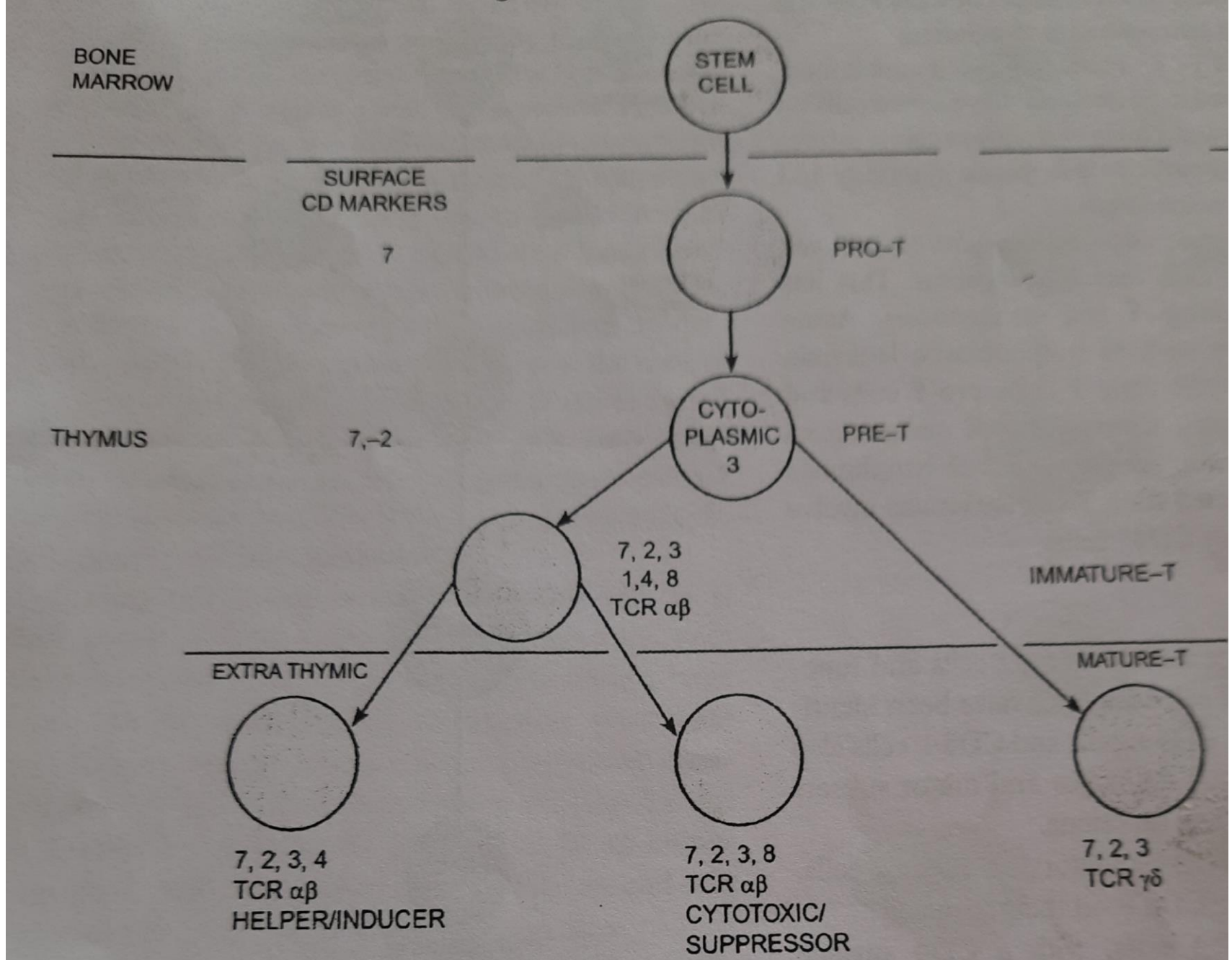


Fig. 14.6 Structure of T cell receptor (TCR)

potentially harmful 'forbidden clones' are deleted by antigen-specific suppressor cells. Immunocompetence against foreign antigens is also developed in the thymus.



ig. 14.7 T cell maturation

T cells also develop MHC restriction so that CD8+ cells respond only to foreign antigens presented along with HLA Class I, and CD4+ cells to those presented with HLA Class II molecules. Immature T cells in the thymus exhibit CD7, 2, 3, 1, 4 and 8, besides TCR. On functional maturity, they lose CD1 and differentiate into the two major subsets CD8–4+ or CD4–8+. Mature CD8–4+ TCRαβ cells are helper/inducer cells, inducing B cell differentiation, stimulating proliferation of CD8+ cytotoxic cells, producing lymphokines and regulating certain stages of erythropoiesis. CD4–8+ TCRαβ cells are suppressor/T cytotoxic cells (T_C), inhibiting B cell antibody synthesis and acting as cytotoxic effector cells. T_C cells are activated when they interact with an antigen–class I MHC complex on the surface of an altered self-cell (for example, a virus-infected cell or a tumour cell) in the presence of appropriate cytokines. This activation, which results in proliferation, causes the T_C cell to differentiate into an effector cell called a **cytotoxic T lymphocyte (CTL)**, and hence acquire the ability to recognise and eliminate altered self-cells. Small numbers of CD4+8+ and CD4–8– cells are also present in circulation.

T CELL MATURATION

T cell precursors from the yolk sac, fetal liver and bone marrow migrate to the thymus during the embryonic and postnatal stages. The earliest identifiable cells of T lineage are the $CD7^+$ pro-T cells, which acquire CD2 on entering the thymus. They synthesise CD3 in the cytoplasm and become pre-T cells. T cell receptor (TCR) synthesis also takes place.

T cell receptors

TCR is a heterodimer of glycoprotein chains expressed on the T cell surface, which in association with CD3

acts as the antigen recognition unit, analogous to Ig on the surface of B cells. TCR occurs as two pairs of glycoprotein chains, either αβ or γδ. Pre-T cells differentiate into two lineages, expressing either αβ or γδ TCR chains. The large majority of T cells carry αβ TCR (Fig. 14.6). The two chains are held together by a disulphide bond near the T cell membrane at the hinge region. TCRs have positive charges in the transmembrane portion and a short cytoplasmic tail. TCR chains contain four separately encoded regions: V or variable, D or diversity, J or joining and C or constant, as in the case of immunoglobulins and hence belong to the immunoglobulin gene superfamily. By re-assortment of these regions, a very wide repertoire of antigen specificities can be formed on the T cell surface (Fig. 14.7).

Contact with self-antigens within the thymus leads to the destruction of immature T cells carrying the corresponding TCR. Thus, self-tolerance or elimination of T cells capable of reacting with self-antigens takes place in the thymus. But cells capable of reacting with autoantigens continue to arise throughout life. These