

Diseases of Immunity

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The human immune system is a complex network of signals, which controls responses to antigenic stimulation and protects us from diseases.

The components of the immune system are:

- **Antigen-specific** (recognize and act against particular antigens)
- **Systemic** (elicit a response which affects the entire body and is not confined to the initial affected site)
- **Have memory** (recognize and mount an even stronger attack to the same antigen the next time)

The functions of the immune system are:

- **To provide resistance** against invading pathogens (viruses, bacteria, parasites, etc.) and foreign material (eg, transplanted organ)
- **To remove 'worn-out' cells** (eg, aged cells or tissue debris from site of injury or disease)
- **To provide primary defence** against cancer.

Inappropriate immune responses may manifest as

- **Allergies**
- **Autoimmune diseases**

An antigen is a substance (usually a **protein**) that evokes the production of antibodies. An epitope, also known as 'antigenic determinant', is the part of an antigen that is recognized by the immune system, specifically by antibodies, B cells or T cells.

An antibody is a Y-shaped protein (Fig. 5.1) on the surface of B cells that is secreted into the blood or lymph in response to an antigenic stimulus, such as a pathogen, or a transplanted organ. It binds to a specific antigen and neutralizes it. Antibodies are basically **glycoproteins** which belong to the immunoglobulin superfamily. Antibodies (immunoglobulins) have two basic structural units--each with two large heavy chains and two small light chains. The amino acid sequence in the tips of the 'Y' varies greatly among different antibodies and is labelled the '**variable region**'. It is composed of **110–130 amino acids** which give the antibody its specificity for binding antigen. The variable region includes the ends of the light and heavy chains. Digestion with the protease papain cleaves antibody molecules into three fragments. Two fragments are identical and contain the antigen-binding activity. These are termed the '**Fab fragments**' (for fragment antigen binding). The other fragment contains no antigen-binding activity but was originally observed to crystallize readily, and for this reason was named the '**Fc fragment**' (for Fragment crystallizable).

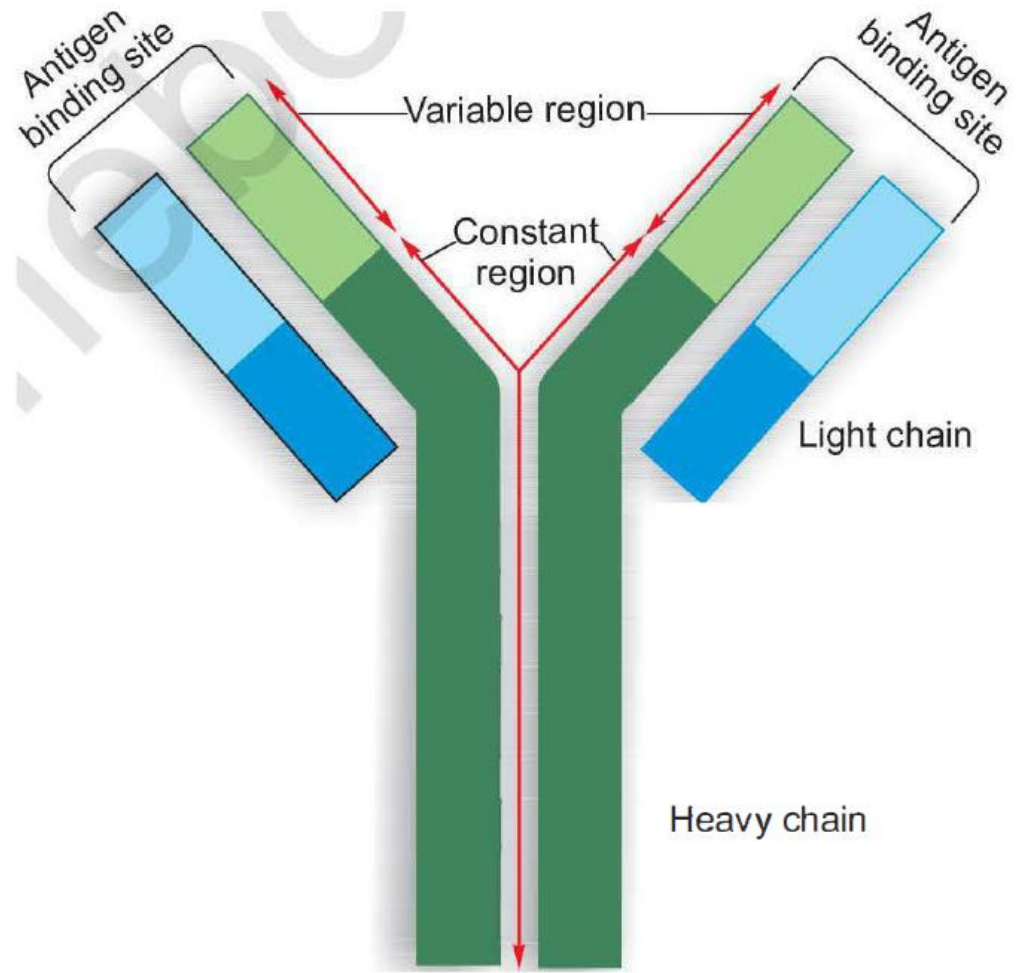
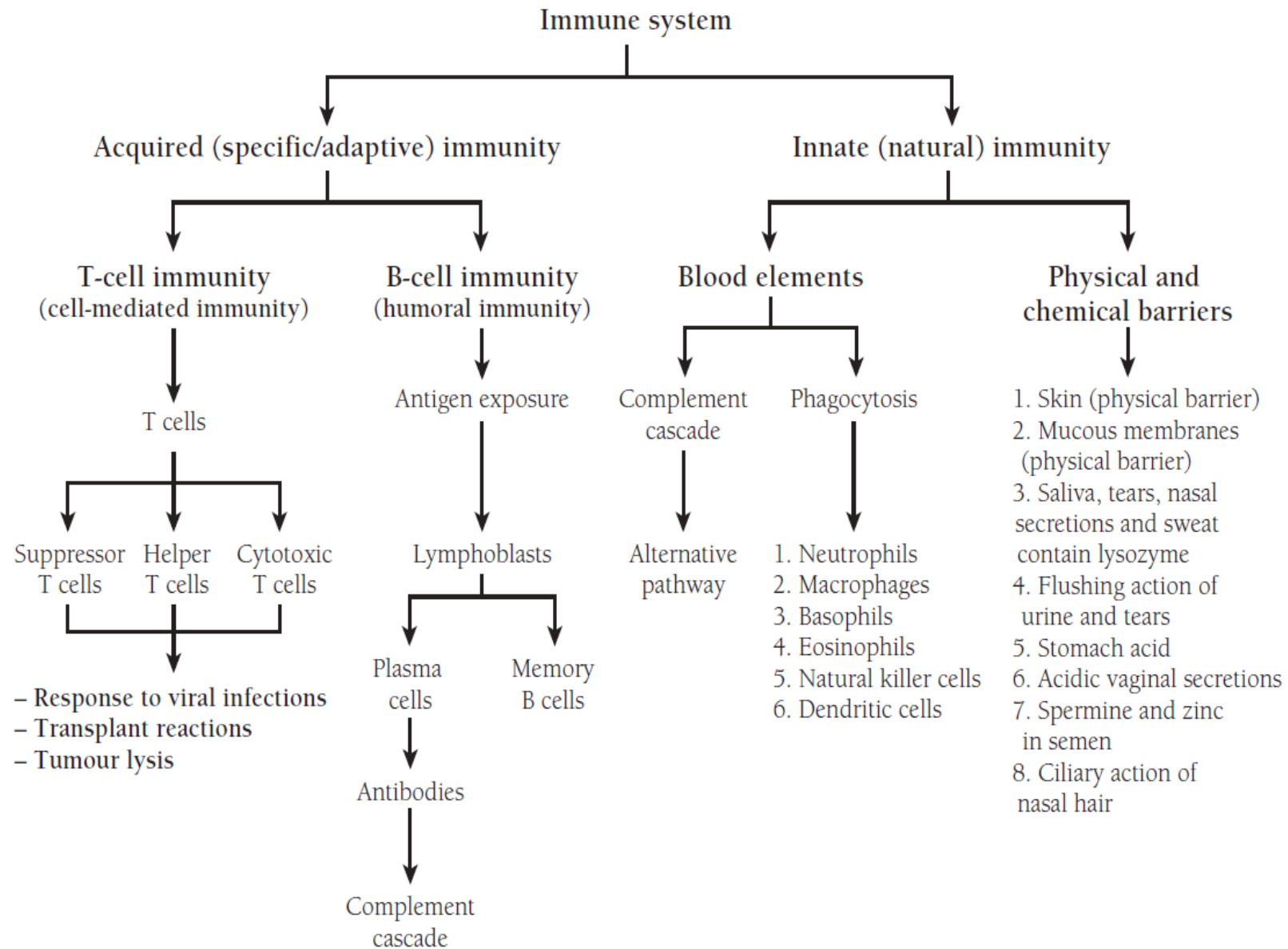


FIGURE 5.1. Structure of an immunoglobulin molecule.

Antibodies are divided into five major classes:

IgM, IgG, IgA, IgD and IgE, based on their constant region structure.

IgMs have mu-chains; IgAs have alpha-chains; IgEs have epsilon-chains and IgDs have delta-chains. Differences in heavy chain polypeptides determine the function of different immunoglobulins. The polypeptide protein sequences responsible for these differences are found primarily in the Fc fragment. While there are five different types of heavy chains, there are only two main types of light chains: kappa (k) and lambda (l). Each antibody binds to a specific antigen. The antigenic substance may be from the external environment or from within the body.



FLOWCHART 5.1. Types of immune responses.

1. Natural or innate

- This is the **initial, nonspecific** immune response of the body. Despite the generalized nature of the response, it is considered a critical component of the immune system, as defects in it often result in major consequences.
- **The main components of the innate immune system** are (1) physical epithelial barriers like skin and mucosal surfaces, (2) granulocytes and macrophages, (3) dendritic cells, (4) a special class of lymphocytes called a natural killer (NK) cells, (5) circulating plasma proteins and (6) chemical barriers present in different bodily secretions (saliva, tears, nasal secretions and sweat contain lysozyme, an enzyme that destroys Gram-positive bacterial cell walls causing cell lysis; vaginal secretions are acidic; spermine and zinc in semen destroy some pathogens and lactoperoxidase is a powerful enzyme found in mother's milk).
- Pathogens are also prevented from entering the respiratory tract by ciliary action of the tiny nostril hair and the coughing and sneezing reflexes. The flushing actions of tears, saliva and urine also force out pathogens, as does the sloughing off of skin.

The complement system has several important functions in innate immunity and consists of at least 20 serum glycoproteins, which are activated in a cascade sequence, meaning that activation of a single molecule will lead to thousands of molecules being generated and therefore amplification of the response.

2. Acquired or adaptive

- The adaptive immune system is the second line of defence against pathogens that are able to evade or overcome innate immune defences. This is an antigen-specific immune response.
- There are two types of adaptive immune responses: humoral immunity, mediated by antibodies produced by B lymphocytes and cell-mediated immunity (CMI), mediated by T lymphocytes.
- The T and B cells of the adaptive immune response are responsible for long-term memory. Upon secondary exposure to a specific antigen, the cells of the adaptive immune response exert their effects in a stronger and quicker way than the natural or innate response.

The immune system has several functions, most important of which is self-recognition and non-self-recognition. When the process of self-recognition breaks down and the immune system begins to attack self-antigens, the condition is labelled as autoimmunity. Examples of autoimmune diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and diabetes mellitus (DM).

Q. Write briefly on HLA complex.

HLA complex (Fig. 5.3) is a set of multiple genes located on chromosome 6. It binds peptide fragments of foreign proteins for presentation to appropriate antigen-presenting cell, and has the following components:

- HLA's corresponding to MHC class I (A, B and C) present peptides coming from intracellular proteins, which are produced when the latter are broken down in the proteasomes.

These MHC–peptide complexes are recognized by cytotoxic T cells (killer T cells) with the help of the coreceptor CD8. Class I proteins are expressed on the surfaces of nearly all cells.

- HLA's corresponding to MHC class II (DP, DQ and DR) present antigens from outside of the cell to T-lymphocytes. These extracellular peptides are taken into the cell with the help of endosomes. The MHC–peptide complexes are recognized by helper T cells with the help of the CD4 coreceptor. These antigens stimulate the multiplication of T-helper cells, which in turn stimulate antibody-producing B cells to produce antibodies to that specific antigen. Self-antigens are suppressed by suppressor T cells. Class II proteins are expressed only on B cells, macrophages and dendritic cells.

- HLA's corresponding to MHC class III encode components of the complement system.

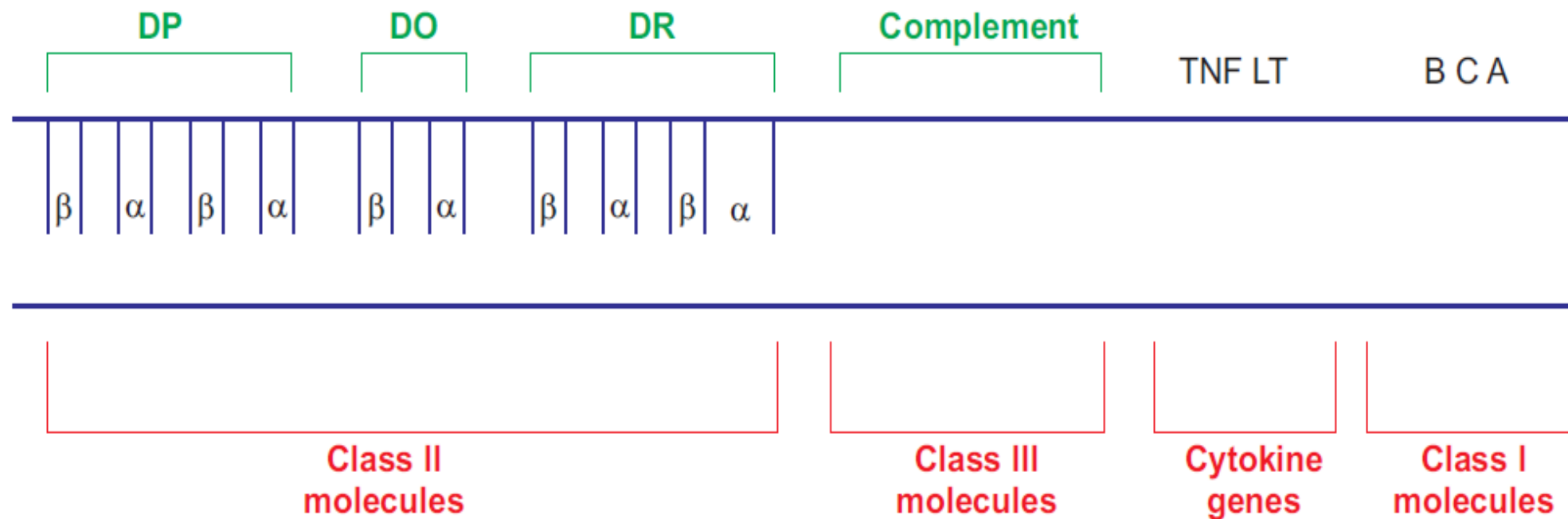


FIGURE 5.3. Components of HLA complex.

HLA complex has diverse roles in the human body:

1. Role in disease

HLA has been found to be associated with a growing number of diseases

These include

- **Inflammatory** diseases like postinfectious arthropathy and ulcerative colitis.
- **Inherited errors of metabolism**, like 21-hydroxylase deficiency
- **Autoimmune diseases**, like endocrinopathies, ankylosing spondylitis, SLE, myasthenia gravis and Sjögren syndrome. People with certain HLA antigens are more likely to develop certain autoimmune diseases, and HLA typing in autoimmunity is being increasingly used as a tool in diagnosis.

2. Role in graft rejection

If the immune system recognizes a 'non-self' antigen, it rejects the tissue bearing those antigens. This forms the basis of transplant rejection. Because of the importance of HLA in transplantation, the HLA loci are some of the most frequently typed by serology and PCR.

3. Role in cancer

Some HLA-mediated diseases are directly involved in the **promotion of cancer**; for example, gluten-sensitive enteropathy is associated with increased prevalence of enteropathy-associated T cell lymphoma, and DR3-DQ2 homozygotes comprise the highest risk group.

Q. Differentiate between MHC class I and class II.

Ans. Differences between MHC class I and class II are shown in [Table 5.3](#).

TABLE 5.3. Differences between MHC class I and class II		
Features	MHC I	MHC II
Location	Present on all nucleated cells and platelets	Found on antigen-presenting cells—macrophages, dendritic cells and activated T and B cells
Constituted by	Alpha chains ($\alpha 1$, $\alpha 2$, $\alpha 3$) and $\beta 2$ microglobulin	Alpha chains ($\alpha 1$, $\alpha 2$) and beta chains ($\beta 1$, $\beta 2$)
Genes coding region	HLA-A, HLA-B, HLA-C	HLA-D (DP, DQ, DR)
Antigen presentation in association with	CD8+ T cells	CD4+ T cells
Functions	Graft rejection, lysis of virus-infected cells and tumour cells	Graft-versus-host response and immunologic reactions involving CD4+ T cells

Q. Enumerate the characteristics of CD4+ and CD8+ T lymphocytes.

CD4+ T lymphocyte

- Expressed on 60% of mature T cells (normal CD4 to CD8 ratio is 2:1)
- Called 'helper T cells' because they secrete cytokines, which help B cells in producing antibodies and macrophages in the destruction of phagocytosed microbes
- Also called 'master regulator' of immune system
- Binds to MHC class II
- Helper T cells have three subsets; their features are summarized in Table 5.4

CD8+ T lymphocyte

- Expressed on 30% of mature T cells
- Binds to MHC class I
- Mediates its function primarily as cytotoxic T cell or CTL (directly kill virus-infected cells or tumour cells)

TABLE 5.4.

Subsets of helper T cells

Features	T _H 1 cells	T _H 2 cells	T _H 17 cells
Cytokines that induce this subset	IFN- γ and IL-12	IL-4	TGF- β , IL-6, IL-1 and IL-23
Cytokines produced by this subset	IFN- γ	IL-4, 5 and 13	IL-17 and IL-22
Function	Responsible for delayed hypersensitivity, macrophage activation and synthesis of IgG; they provide defence against intracellular microbes.	Responsible for synthesis of other classes of antibodies including IgE; they provide defence against helminthic parasites.	Release IL17, which is a powerful recruiter of neutrophils and monocytes and is important in defence against extracellular bacteria and fungi.
Role in disease	Autoimmune and chronic inflammatory diseases	Allergies	Autoimmune and chronic inflammatory diseases

Q. Differentiate between helper and suppressor T cells.

Ans. Differences between helper and suppressor T cells are shown in [Table 5.5](#).

TABLE 5.5. Differences between helper and suppressor T cells		
Features	Helper/inducer T cells	Suppressor/cytotoxic T lymphocytes
Type	• CD4-positive • CD8-negative	• CD8-positive • CD4-negative
Percentage of peripheral T cells	60%	30%
Antigen recognition in association with	HLA class II	HLA class I
Functions	Release lymphokines and activate macrophages and B cells, responsible for delayed hypersensitivity	Cytotoxicity mediated by pore formation and release of granzymes. Also Fas/FasL-dependent killing
Subsets	Two subsets, TH1 and TH2	No subsets

Q. Define hypersensitivity.

Hypersensitivity is defined as an excessive and potentially harmful reaction to an endogenous or exogenous antigen.

It generally occurs in a previously sensitized individual when the balance between the effector and control immune mechanisms gets disturbed.

It is usually associated with inheritance of susceptibility genes (both HLA and non-HLA).

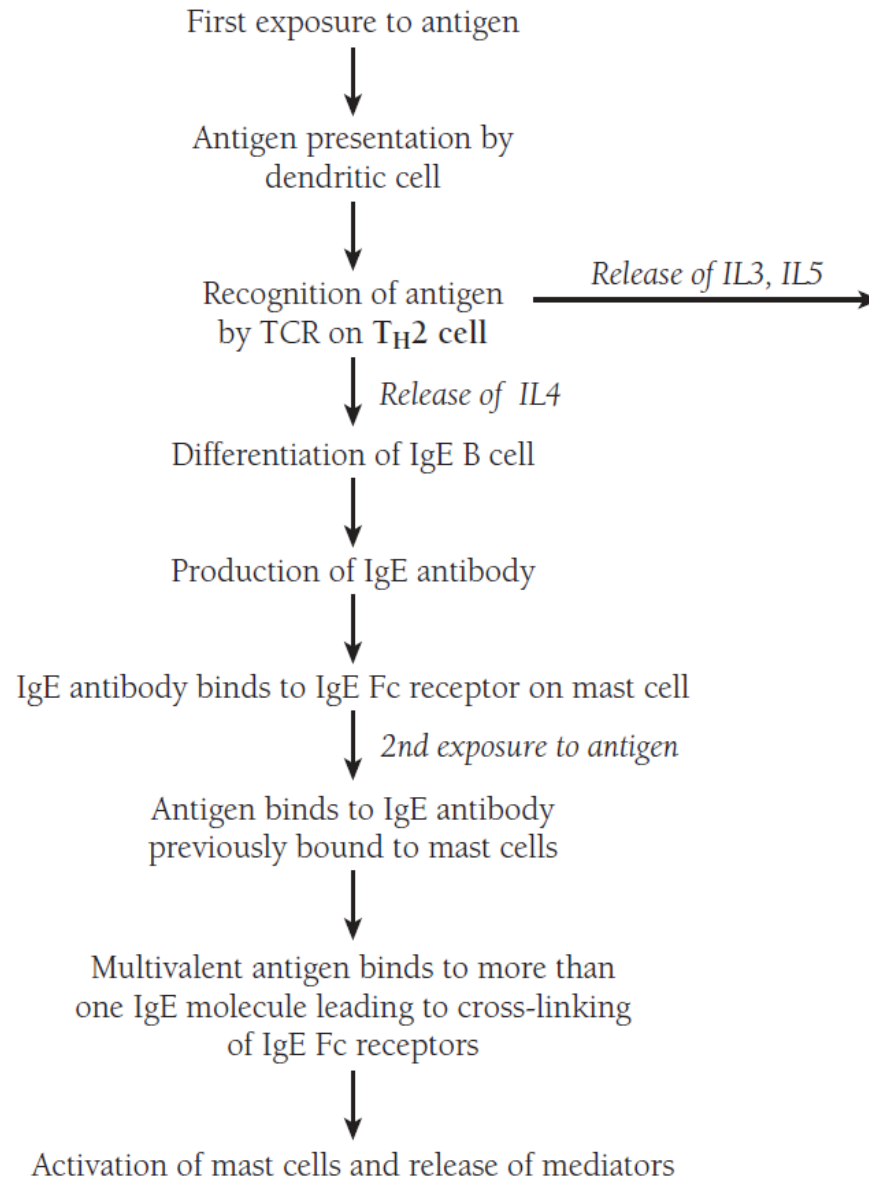
Hyper sensitivity is classified into four types based on the underlying immune mechanism.

Type I Hypersensitivity

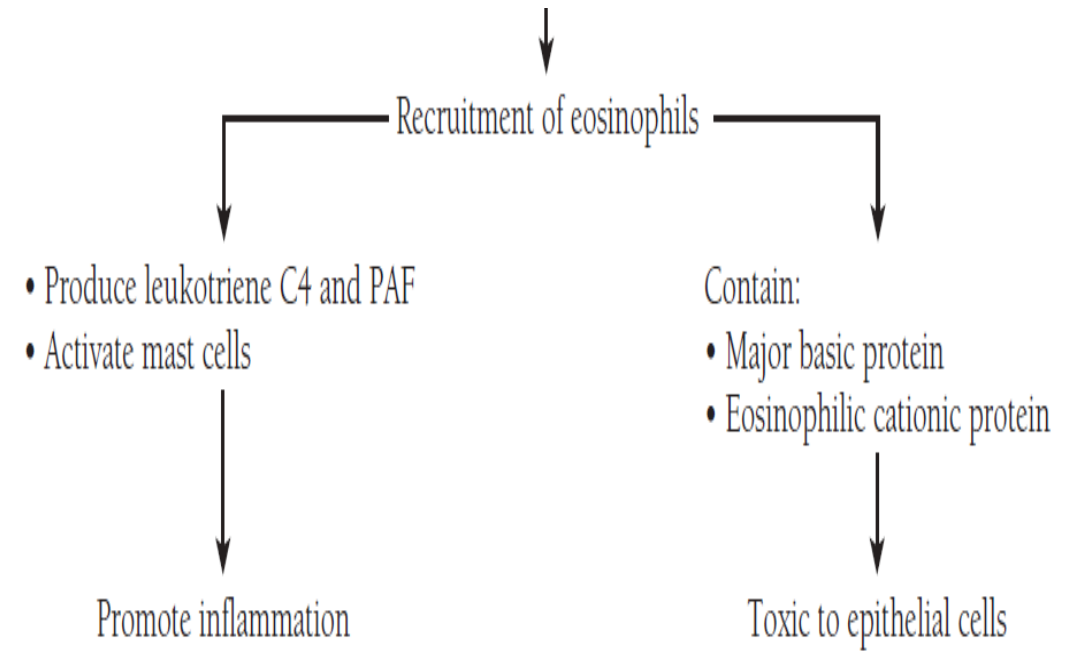
An immunologic reaction, developing within minutes after combination of an antigen with antibody bound on mast cells or basophils, in already sensitized individuals. Based on the portal of entry type I hypersensitivity is classified into two types:

1. Local (atopy): Occurs when the antigen is confined to a particular site. Manifests with skin allergy, hives, nasal and conjunctival discharge, bronchial asthma and allergic gastroenteritis. May have two distinct phases, **immediate** (occurs within minutes of exposure to the antigen and subsides in a few hours) and a **late phase** (starts 2–24 h later and lasts for days).

2. Systemic: Mostly follows **parenteral administration** (bee venom or an intravenous injection of antisera, hormones, enzymes, drugs, etc.) but can **also result from ingestion** of the allergen (peanuts). Results in **systemic anaphylaxis** within minutes of exposure (urticaria, laryngeal oedema, pulmonary bronchoconstriction, vomiting, abdominal cramps and diarrhoea).



FLOWCHART 5.2. Mechanism underlying type I hypersensitivity.



FLOWCHART 5.3. Role of eosinophils in type I hypersensitivity.

1. Primary mediators: These are immediately released already formed stored mediators which induce smooth muscle contraction, increased vascular permeability, increased mucous production (by nasal, bronchial, gastric glands) as well as platelet granule release.

They include

(a) Biogenic amines

(i) Histamine

(ii) Adenosine

(iii) 5-Hydroxytryptamine (5HT)

(b) Chemotactic mediators

(i) Eosinophil chemotactic factor (ECF)

(ii) Neutrophil chemotactic factor (NCF)

(c) Enzymes

Contained in granule matrix, eg, proteases (tryptase, chymase) and acid hydrolases

(d) Proteoglycans

Heparin and chondroitin sulphate (serve to package and store other mediators in the granules)

2. Secondary mediators: These are synthesized de novo and released late.

(a) Lipid mediators

(i) Leukotrienes

- C4, D4 (vasoactive and spasmogenic)
- B4 (chemotactic for neutrophils, eosinophils and monocytes)

(ii) Prostaglandin D2

- Generated by cyclooxygenase pathway
- Induce bronchospasm and increased mucous secretion

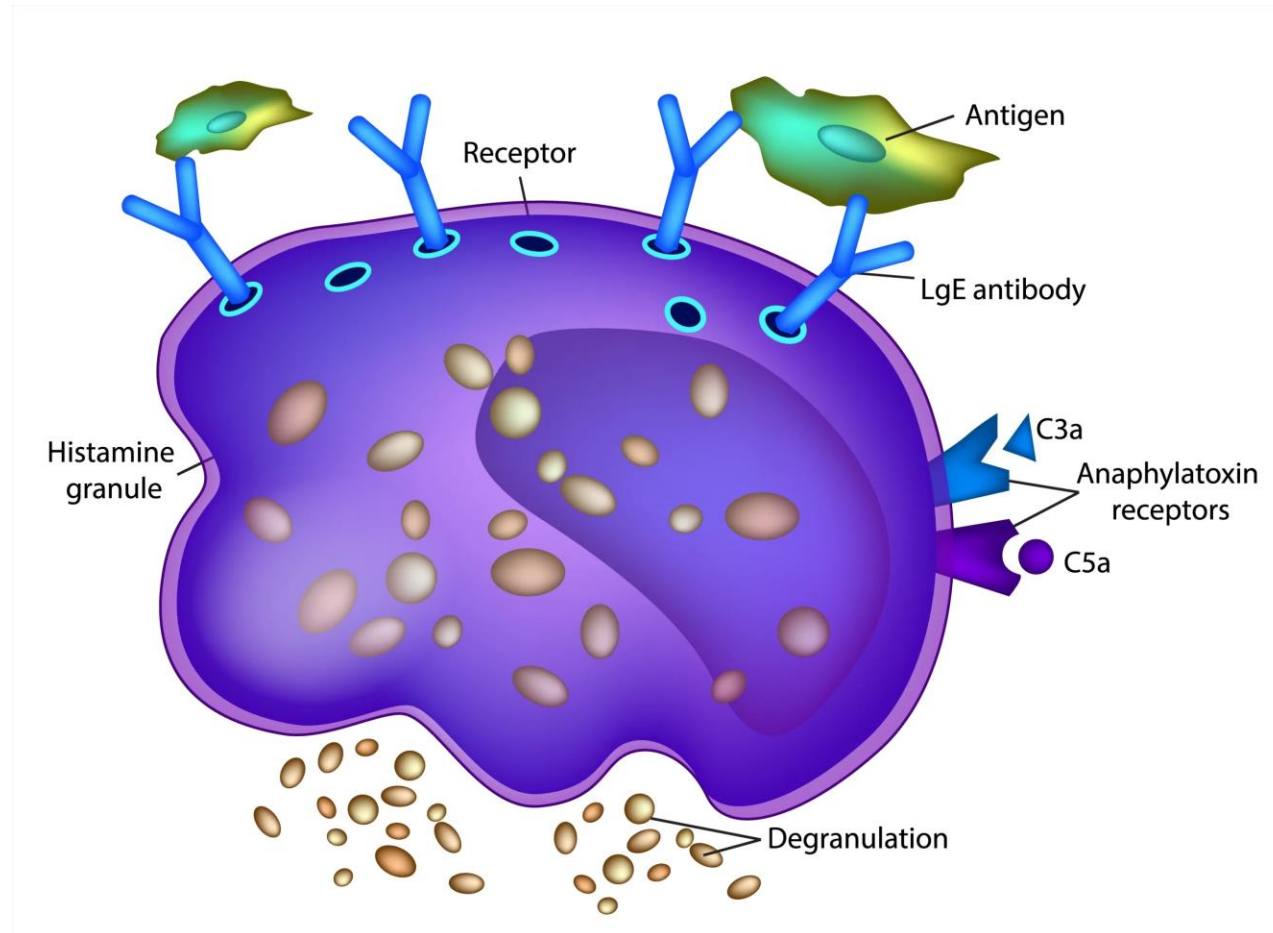
(iii) Platelet-activating factor (PAF)

- Induces platelet activation and bronchospasm
- Releases histamine
- Increased vascular permeability
- Is chemotactic for neutrophils and eosinophils
- Activates inflammatory cells and causes their aggregation and degranulation

(b) Cytokines include TNF- α , ILs-1, -3, -4, -5, -6 {TH2 response}, GM-CSF, chemokines, and macrophage inhibitory protein (MIP-1a and b). Cytokines recruit and activate inflammatory cells and mast cells

Q. What are mast cells? How do they contribute to type I hypersensitivity?

Mast cells are bone marrow-derived cells, widely distributed in tissues near blood vessels and nerves and in subepithelial sites. They contain membrane-bound granules that possess a variety of biological mediators including PAF, **histamine**, leukotrienes C4, D4, E4, prostaglandins, cytokines, ECF and NCF.



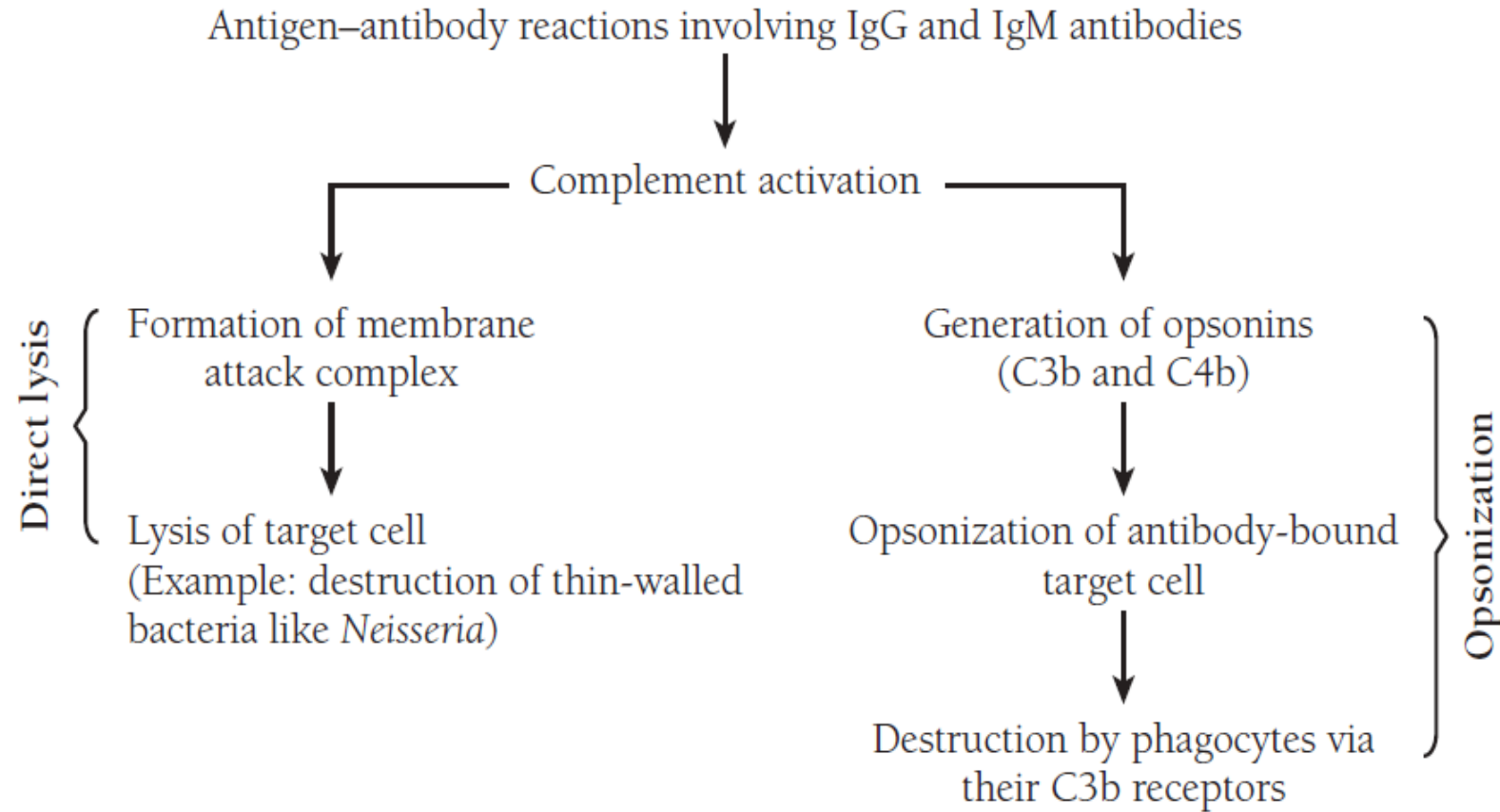
Q. Write in detail on type II hypersensitivity.

Type II hypersensitivity is mediated by antibodies directed towards antigens present on the surface of the cells or other tissue components. These antigens may be intrinsic to cell membrane or exogenous antigens absorbed on the cell surface (eg, a drug metabolite).

Reaction occurs when antibodies bind to normal or altered cell surface antigens.

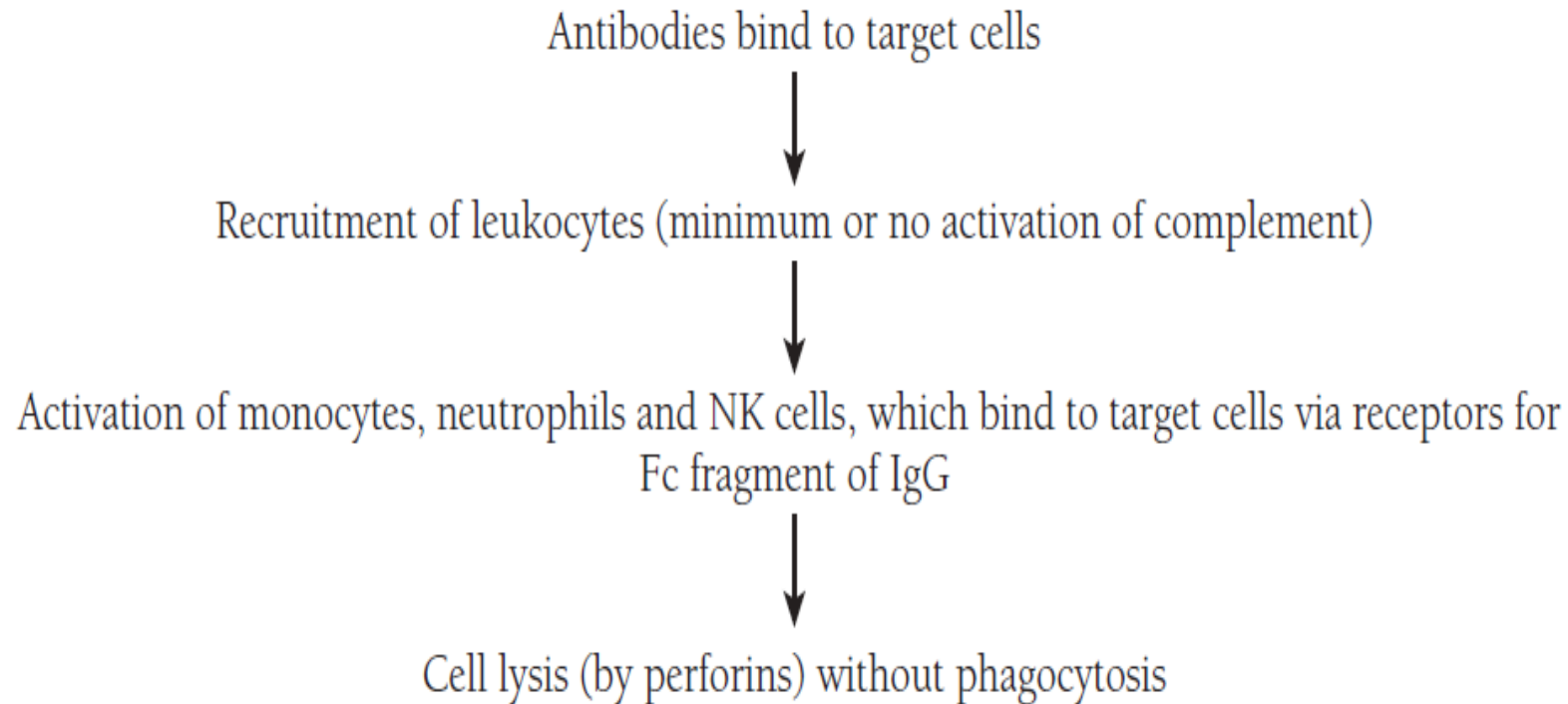
Mechanisms Underlying Type II Hypersensitivity

1. Opsonization and phagocytosis (Flowchart 5.4)



FLOWCHART 5.4. Steps in opsonization and phagocytosis.

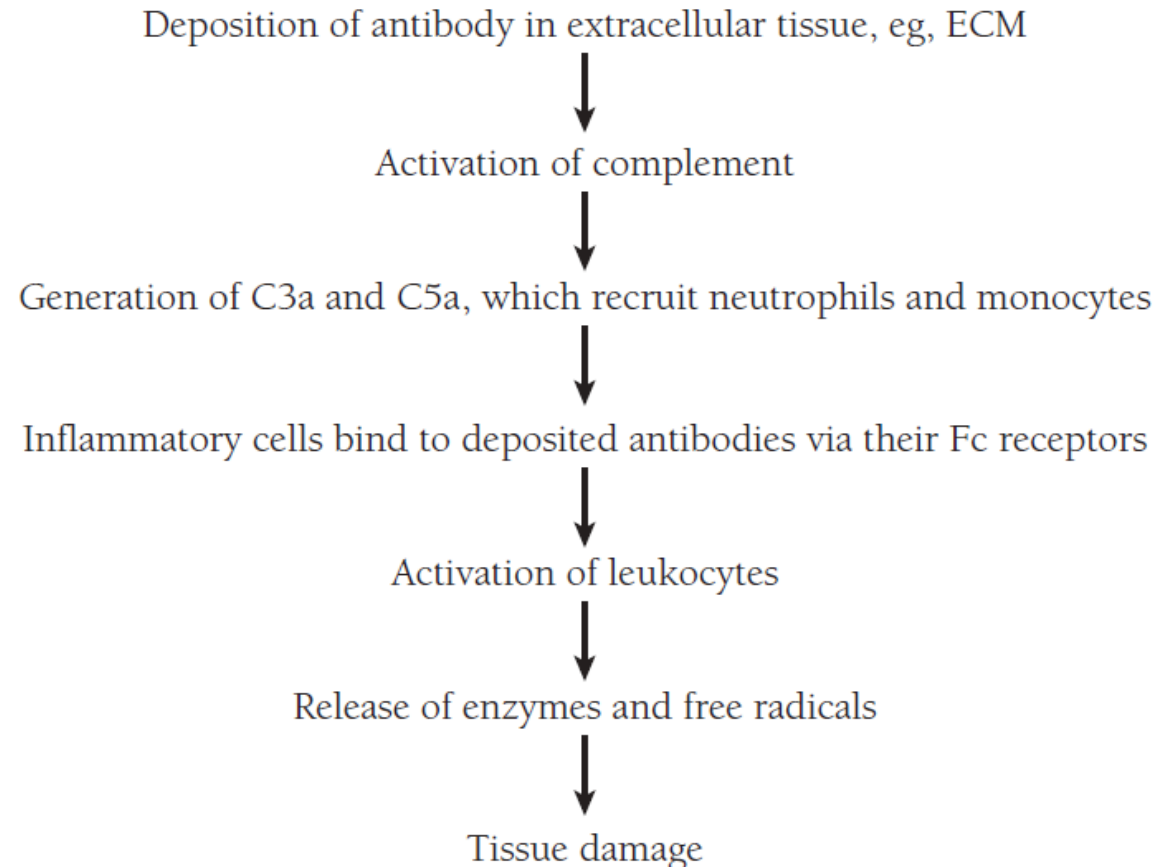
2. **ADCC (antibody-dependent cellular cytotoxicity; Flowchart 5.5):** ADCC involves cell lysis without phagocytosis mediated by monocytes, neutrophils and NK cells.
Examples: Transfusion reactions, autoimmune haemolytic anaemia, erythroblastosis fetalis, agranulocytosis, thrombocytopenia and drug reactions



FLOWCHART 5.5. ADCC.

3. **Complement and Fc receptor-mediated inflammation** (Flowchart 5.6): Deposition of antibody in extracellular tissue initiates an antigen-antibody reaction leading to complement activation. Complement activates inflammatory cells to cause the cell injury.

Examples: Parasitic infections and tumours



FLOWCHART 5.6. Complement and Fc receptor-mediated inflammation.

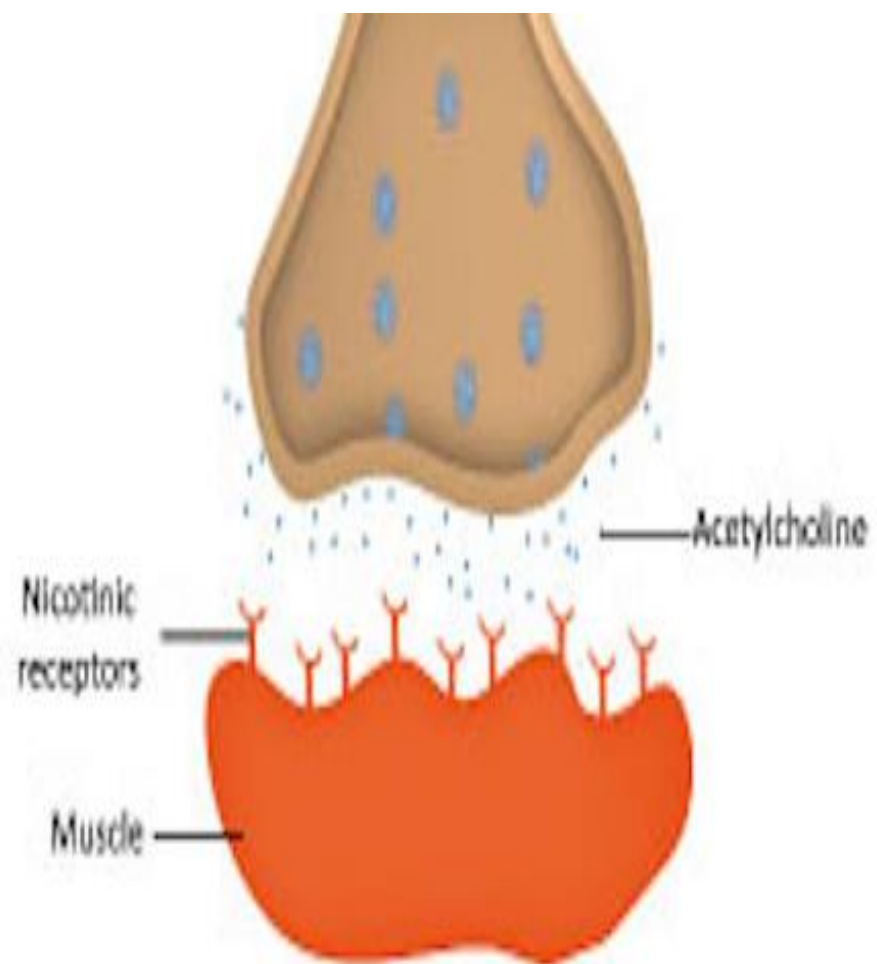
4. Antibody-mediated cellular dysfunction

Antibodies against cell surface receptors deregulate function without causing cell injury or inflammation.

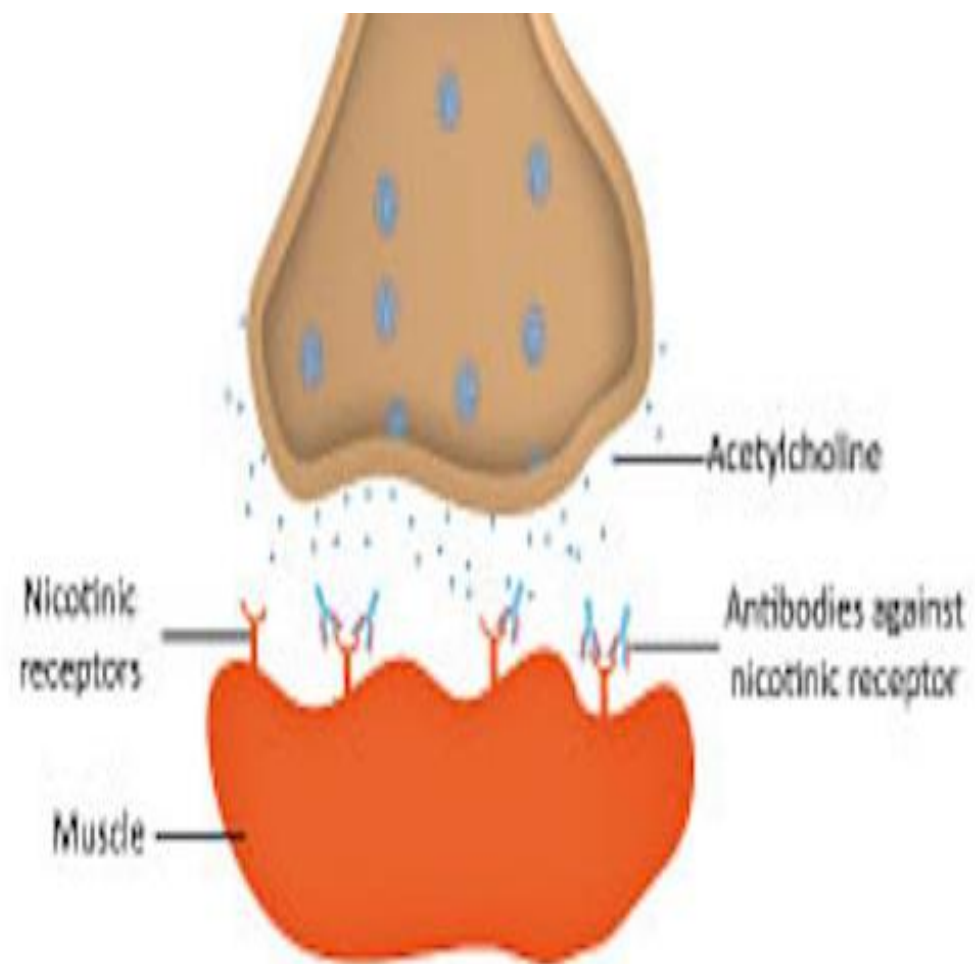
Examples

- **Myasthenia gravis**, which is due to antibodies against acetylcholine receptors in the motor end plates of skeletal muscle. These antibodies impair neuromuscular transmission and cause muscle weakness.
- **Pemphigus vulgaris**, which is due to antibodies against desmosomes. These antibodies disrupt the intercellular junction and result in the formation of vesicles.

Normal Neuromuscular Junction



Myasthenia Gravis



Q. Write in detail on type III hypersensitivity.

Type III hypersensitivity is induced by antigen–antibody complexes that produce tissue damage as a result of their capacity to activate the complement system.

Antigen–antibody complexes may be:

1. Circulating or in situ

2. Exogenous (eg, infectious agents and drugs) or endogenous (eg, ‘nuclear antigens’ in SLE, ‘immunoglobulins’ in reactive arthritis, ‘streptococcal cell wall antigens’ in acute post-streptococcal glomerulonephritis and ‘HBS antigen’ in polyarteritis nodosa)

3. Systemic (acute serum sickness—prototype of a systemic immune complex disease) or local (Arthus reaction—local immune complex disease)

Pathogenesis

- Formation of antigen–antibody complexes (first phase)
- Deposition of immune complexes in various tissues (second phase)
- Initiation of an inflammatory reaction in dispersed sites throughout the body (third phase)

Q. Write in detail on type IV hypersensitivity.

Type IV (delayed) hypersensitivity is initiated by specifically sensitized T cells and

may be of two types:

1. Classic delayed hypersensitivity (DTH) mediated by CD4+ T cells
2. Direct cell toxicity (cytolysis) mediated by CD8+ T cells

Classic Delayed Hypersensitivity (DTH)

It is the immunologic response to a variety of intracellular microbiologic agents, eg, M. tuberculosis, viruses, fungi, protozoa, parasites, as well as conditions like contact dermatitis, type 1 diabetes mellitus, multiple sclerosis and graft rejection. The classic prototype of DTH is tuberculin reaction (intracutaneous injection of tuberculin (protein–liposaccharide component of tuberculous bacillus) in a previously sensitized individual resulting in reddening and induration, which starts after 8–12 h and peaks in 24–72 h.

Morphology of DTH

- Accumulation of mononuclear cells around small veins and venules producing perivascular cuffing
- Increased microvascular permeability
- Escape of plasma proteins leading to dermal oedema or deposition of fibrin in interstitium (induration)
- Fully developed lesions show endothelial hypertrophy and hyperplasia
- Persistent/nondegradable antigens induce perivascular lymphocytic infiltrate replaced by macrophages in 2–3 weeks. Macrophages are converted into epithelium-like (epithelioid) cells, which aggregate to form granulomas.

T Cell-Mediated Cytotoxicity/Cytolysis :

- Sensitized CD8+ T cells (cytotoxic T lymphocytes or CTLs) kill antigen-bearing target cells and seem to have an important role in:

- Graft rejection
- Resistance to viral infections

Two principal mechanisms of T cell-mediated damage:

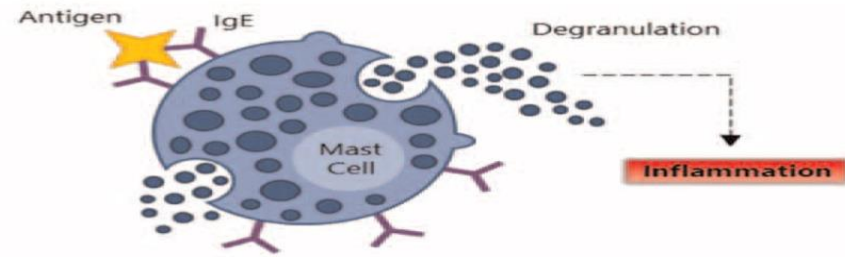
- Perforins- and granzyme-dependent killing: Perforins and granzymes are soluble mediators contained in the lysosome-like granules of CTLs
- Fas–Fas ligand-dependent killing: Apoptosis of the target cells is caused by Fas–Fas ligand-dependent mechanism.

Table 6.5 T Cell–Mediated Diseases

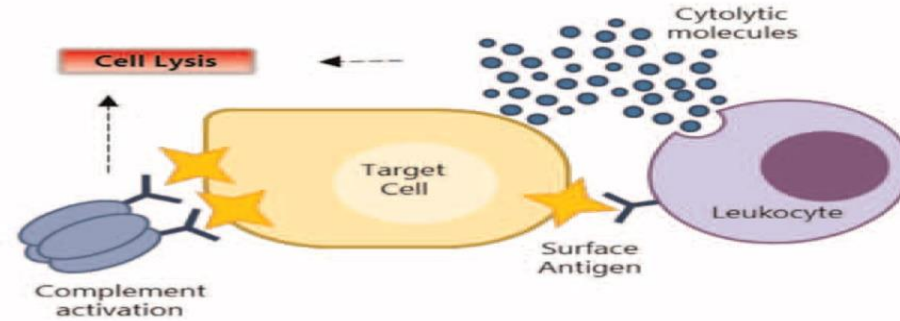
Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury	Clinicopathologic Manifestations
Rheumatoid arthritis	Collagen? Citrullinated self proteins?	Inflammation mediated by Th17 (and Th1?) cytokines; role of antibodies and immune complexes?	Chronic arthritis with inflammation, destruction of articular cartilage
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by Th1 and Th17 cytokines, myelin destruction by activated macrophages	Demyelination in CNS with inflammation; paralysis, optic neuritis
Type 1 diabetes	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T-cell–mediated inflammation, destruction of islet cells by CTLs	Insulinitis (chronic inflammation in islets), destruction of β cells; diabetes
Inflammatory bowel disease	Enteric bacteria; self antigens?	Inflammation mediated by Th1 and Th17 cytokines	Chronic intestinal inflammation, obstruction
Psoriasis	Unknown	Inflammation mediated mainly by Th17 cytokines	Destructive plaques in the skin
Contact sensitivity	Various environmental chemicals (e.g., urushiol from poison ivy or poison oak)	Inflammation mediated by Th1 (and Th17?) cytokines	Epidermal necrosis, dermal inflammation, causing skin rash and blisters

Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred based on the similarity with experimental animal models of the diseases. *CTLs*, Cytotoxic T lymphocytes.

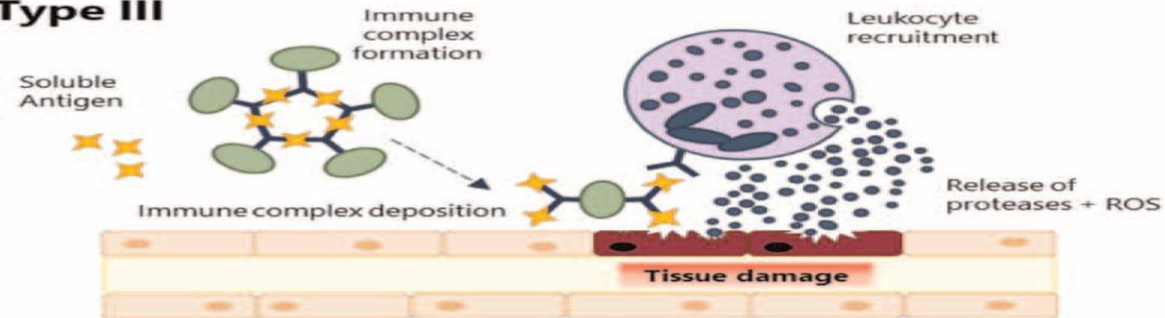
Type I



Type II



Type III



Type IV

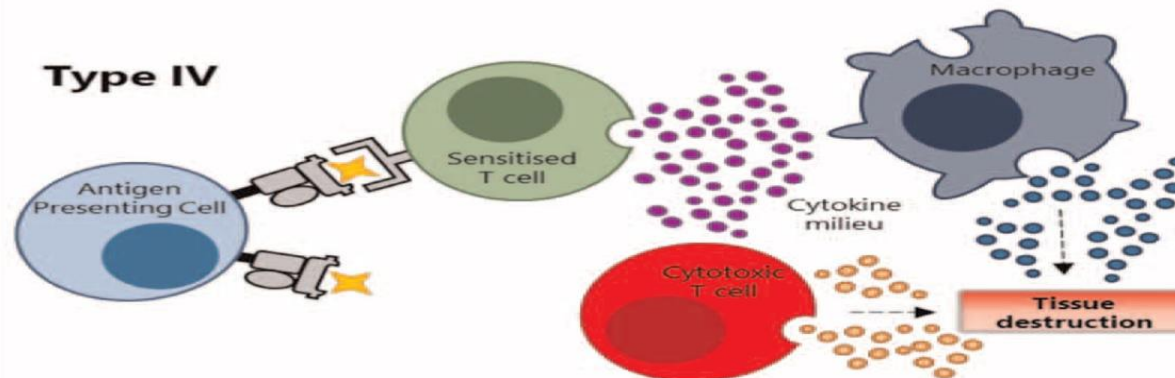
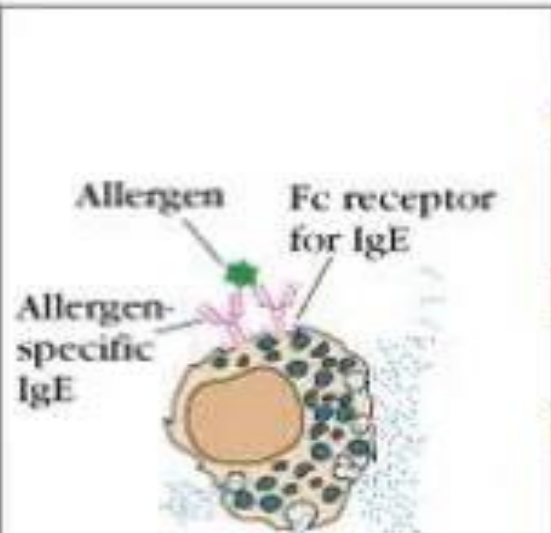
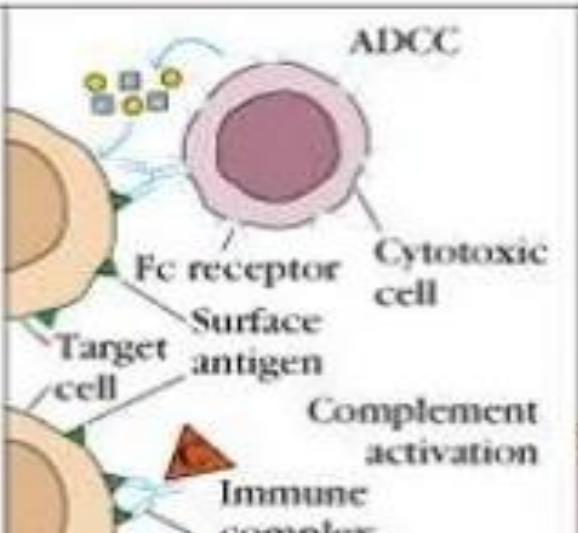
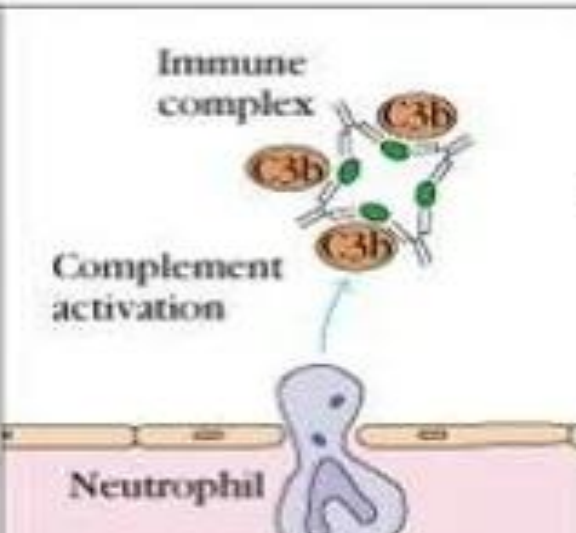
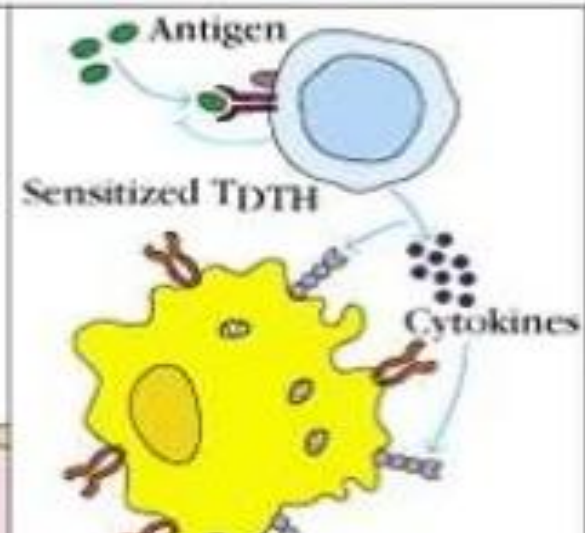


TABLE 5.6.

Differences between types I, II, III and IV hypersensitivity

Features	Type I	Type II	Type III	Type IV
Reaction type	Anaphylactic	Cytotoxic	- Serum sickness - Arthus reaction	Delayed hypersensitivity
Cells involved	Mast cells, basophils, eosinophils, neutrophils, monocytes, CD4+ T cells, B cells	Nonsensitized macrophages, NK cells, neutrophils, eosinophils, B cells	Neutrophils, B cells	CD4+ T cells, macrophages, CD8+ T cells
Antibody type	IgE	IgG, IgM	IgG, IgM	None
Chemical mediators	IL-3, 4, 5; vasoactive amines	Complement system	Complement system	Lymphokines, IL-12, IL-2, INF- γ , TGF- β , TNF- α
Antigen presentation by APC	Required	Not required	Required	Required
Pre-sensitization	Required	Not required	Required	Required
Pathogenesis	Formation of IgE and immediate release of mediators to recruit inflammatory cells inducing inflammatory changes	Opsonization and phagocytosis, ADCC, antireceptor antibody type	Formation and deposition of Ag-Ab complexes $\rightarrow$ activates complement system $\rightarrow$ neutrophils recruited $\rightarrow$ release of lysosomal enzymes and other toxic agents	- Sensitized T-lymphocytes mediate release of lymphokines - T cell-mediated cytotoxicity
Time for onset	Minutes	Hours to days	Hours to days	Hours to days
Examples	Allergic bronchial asthma	Transfusion haemolytic reactions	Glomerulonephritis, rheumatoid arthritis	Transplant rejection

 Type I	 Type II	 Type III	 Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T1TH cells release cytokines that activate macrophages or TC cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Q. Write briefly on lepromin reaction. ??????

Q. Define immunologic tolerance. What are its different types?

An individual is incapable of developing an immune response to a specific self-antigen and, hence, is capable of living in harmony with one's own cells and tissues. This is called immunologic tolerance.

Tolerance is of two types—central tolerance and peripheral tolerance.

Central tolerance develops very early in the life of an immune cell. It encounters the self-molecules in the body during development and this initiates a self-destruction pathway, which leads to the death of the cell before it attains maturity. This process, called clonal deletion, helps ensure that 'self-reactive' T cells and B cells, that could develop the ability to destroy the body's own cells, do not mature and attack healthy tissues.

In peripheral tolerance, the body's immune cells might recognize a self-molecule but do not build up an immune response to it (switch off) because some of the chemical signals required to activate the T or B cell are absent. This is labelled clonal anergy. A special class of regulatory T cells that inhibits helper or cytotoxic T cell is involved in the development of peripheral tolerance.

Homework

Mechanisms of development of central tolerance (clonal elimination or deletion):

Mechanisms of development of peripheral tolerance

TABLE 5.7.**Differences between central and peripheral tolerance**

Features	Central tolerance	Peripheral tolerance
Origin	Thymus/bone marrow	Peripheral tissue
Mechanism	Clonal deletion of self-T/B cells	Clonal deletion, clonal anergy, peripheral suppression by T cells
Role in autoimmune diseases	Failure may not result in autoimmune diseases	Failure usually results in autoimmune diseases

Q. Write in detail on mechanism of development of autoimmunity.

Development of autoimmunity is related to:

- **Susceptibility genes** which influence the maintenance of self-tolerance
- **Environmental triggers**, particularly infections, which promote the activation of self-reactive lymphocytes

Mechanisms of Development of Autoimmunity

1. Breakdown of T cell anergy

(a) Autoreactive T cells that escape clonal deletion are rendered anergic when they encounter self-antigens expressed on costimulator deficient antigen-presenting cells (APCs).

(b) Anergy is broken if APCs are induced to express costimulatory molecules (induction may occur consequent to infections, tissue necrosis, inflammation, etc.).

2. Failure of activation-induced cell death: Defects (congenital or acquired) in the Fas–Fas ligand system (responsible for apoptosis) may lead to persistence and proliferation of autoreactive T cells in the peripheral tissues.

3. Failure of T cell-mediated suppression:

Loss of regulatory/suppressor T cells that can limit the function of autoreactive T and B cells.

4. Molecular mimicry

(a) Some infective agents share epitopes with self-antigens.

(b) Immune response against such microbes produces a tissue damaging reaction, eg, rheumatic heart disease: cross-reaction between antibodies to streptococcal M protein and cardiac glycoproteins

5. Polyclonal lymphocyte activation

(a) Several microorganisms and their products (eg, bacterial lipopolysaccharides or endotoxins) are capable of inducing polyclonal B cell activation or CD4+ T cells activation in an antigen-independent manner. Because they stimulate all T cells that are associated with a set of V TCRS, they are called **super antigens (SAGs)**.

(b) They do so by binding to MHC class II on APC and b chains on TCR outside the antigen-binding groove.

(c) This causes a massive immune response that is not specific to any particular epitope on the SAg.

(d) Among T cells activated by super antigens, some may be reactive to self-antigens leading to autoimmunity.

(e) SAGs produce an immune response that is effectively useless. Microbes produce SAGs as a defence mechanism to aid them in evading the immune system.

6. Release of sequestered antigens (anatomic sequestration):

Any self-antigen that is completely sequestered during development is likely to be viewed as foreign when introduced in the circulation, eg, spermatozoa {post-traumatic orchitis} and ocular antigens (uveitis).

Evidence Implicating Genetic Factors in Development of Autoimmunity

- Familial clustering
- Linkage of autoimmune diseases with HLA
- Induction of autoimmune diseases in HLA-B27 transgenic rats
- Linkage of autoimmune diseases with non-MHC genes, which may be either disease specific or associated with the multiple disorders, eg, polymorphisms in PTPN22, polymorphisms in NOD2 and the genes coding for IL-2 receptor and IL-23 receptor

TABLE 5.8. Linkage of autoimmune diseases with HLA

S. No.	Disease	HLA allele
1.	Rheumatoid arthritis anti-cyclic citrullinated peptides (CCP) antibody positive.	DR4
2.	Type 1 diabetes	DR3, DR4, DQB1 position- β 57
3.	Multiple sclerosis	DR15
4.	Systemic lupus erythematosus	DR3, DR8, DR15
5.	Ankylosing spondylitis	B27
6.	Celiac disease	DQ2, DQ8

TABLE 5.9.**Linkage of autoimmune diseases with non-MHC genes**

Gene involved	Disease	Function
PTPN22	RA, IBD	Protein tyrosine phosphatase; affects signalling in lymphocytes
IL2RA	MS	α -chain of the receptor for IL-2; important in growth and survival of activated and regulatory T cells
IL23R	IBD, PS, AS	Receptor for TH17 inducing cytokine IL-23; may affect differentiation of CD4+ cells into pathogenic TH17 effector cells
CTLA4	RA	Terminates activation and promotion of regulatory T cells; inhibit T cell responses and interfere with self-tolerance
NOD2	IBD	May control resistance to gut commensals
ATG16	IBD	May be involved in autophagy of microbes

Q. Describe the aetiopathogenesis and clinicopathological features of systemic lupus erythematosus (SLE).

SLE is a classical prototype of a multisystem disease of autoimmune origin.

Clinical Features

- Chronic, remitting, relapsing commonly febrile illness characterized by injury to skin, joints, kidneys and serosal membranes
- Females are more commonly affected than males
- May be acute or insidious in onset; usually arises in the second or third decade.

Aetiology

- Fundamental defect in regulatory mechanisms that sustain self-tolerance
- Characterized by presence of antibodies to:
 1. Nuclear antigens
 2. Cytoplasmic antigens
 3. Cell surface antigens
 4. Antigens of blood elements
- Antinuclear antibodies (ANAs) include
 1. Antibodies to DNA
 2. Antibodies to histones
 3. Antibodies to nonhistone proteins bound to RNA
 4. Antibodies to nucleolar antigens

Pathogenesis of SLE

• Genetic factors

- Increased risk in family members and concordance in monozygotic twins noted
- MHC genes are thought to regulate the production of autoantibodies (specific polymorphisms of HLA-DQ are linked to the production of anti-ds DNA, anti-Sm and AP antibodies)
- Non-MHC genes may also contribute
- Lupus patients may have inherited deficiency of early complement components; eg, C2 (lack of complement impairs removal of circulating immune complexes)
- The genome-wide association studies have indicated the involvement of several genetic loci. These loci encode proteins which are responsible for lymphocyte activation and cytokine (IFN) responses.

- **Environmental factors**

- **Drugs** such as hydralazine and procainamide are known to induce an SLE-like response.

- **Ultraviolet light** may bring about changes in DNA such that it becomes immunogenic.

- **Sex hormones** are thought to be involved in the pathogenesis (since females are affected more than males).

- **Immunologic factors**

- **Susceptibility genes** interfere with normally existing self-tolerance. Environmental insults induce apoptosis and defective clearance of the nuclei of the apoptotic bodies which in turn increases the burden of nuclear antigens.

- **Self-nucleic acids** may mimic their microbial counterparts to activate TLRs which send signals to B cells specific for nuclear antigens as well as dendritic cells resulting in production of antinuclear antibodies. Dendritic cells produce type 1 IFN which stimulates B cells.

- **Tissue damaging antibodies** are driven against self-antigens (results from an antigen-specific helper T cell-dependent B cell response). The lesions of SLE are mainly caused by **immune complexes** (type III HS).

TABLE 5.11.

Year 1997 revised criteria for the classification of SLE

1.	Malar rash	Fixed erythema, flat or raised over the malar eminences
2.	Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging
3.	Photosensitivity	Skin rash due to exposure to UV light
4.	Oral ulcers	Oral or nasopharyngeal ulceration
5.	Arthritis	Nonerosive arthritis involving two or more peripheral joints causing tenderness, swelling and effusion
6.	Serositis	Pleuritis (history of pleuritic pain or rub or effusion), pericarditis (ECG documentation or pericardial rub or effusion)
7.	Renal disorder	Persistent proteinuria ($>0.5\text{g/dl}$) and cellular casts (RBC, haemoglobin, granular, tubular or mixed)
8.	Neurological disorder	Seizures and psychosis (unexplained)
9.	Haematological disorder	Haemolytic anaemia with reticulocytosis, leucopenia ($<4 \times 10^9$ cells/L), lymphopenia ($<1.5 \times 10^9$ cells/L) and thrombocytopenia ($<100 \times 10^9$ cells/L)
10.	Immunologic disorder	Anti-ds DNA, anti-Sm antibody; positive findings of antiphospholipid syndrome (increased IgM or IgG anticardiolipin antibodies, positive test for lupus anticoagulant, false positive serologic test for syphilis confirmed by negative TPI or FTABS)
11.	Antinuclear antibodies	Positive antinuclear antibodies (in the absence of drugs known to be associated with drug-induced SLE)

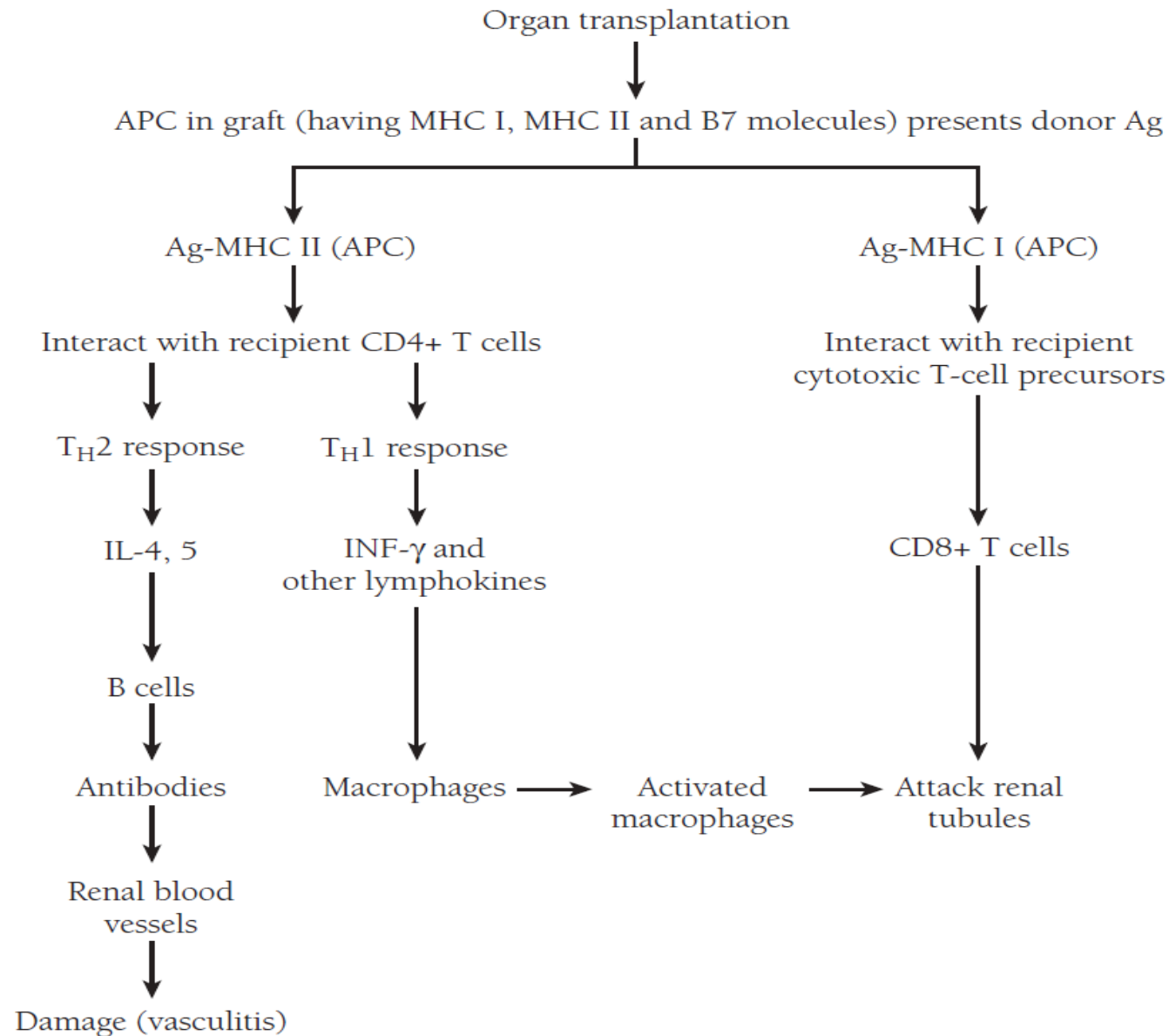
Q. Define transplant rejection. Describe the pathogenesis, clinical features and morphology of acute and chronic rejection.

Transplant rejection is defined as **recognition** by the **host of the grafted tissue as foreign**. Rejection is a complex process in which both **CMI** and **circulating antibodies** play a role.

T cell-mediated reactions (cellular rejection):

Occurs due to cytotoxic CD8+ T lymphocytes-mediated killing of grafted cells or delayed hypersensitivity, triggered by activated CD4+ T helper cells, and is mediated by two main pathways:

1. Direct pathway



FLOWCHART 5.10. Direct pathway of cellular rejection.

2. Indirect pathway

(a) Recipient T lymphocytes recognize antigens of the graft donor after they are presented by the recipient's own antigen-presenting cells.

(b) Uptake and processing of MHC molecules shed from the grafted organ by host antigen-presenting cells.

Antibody-mediated reactions

These are due to preformed antibodies, (eg, hyperacute rejection)

Morphology of rejection

(a) Hyperacute rejection

- (i) Occurs minutes or hours after transplantation and leads to a cyanotic, mottled and flaccid kidney excreting a few drops of bloody urine.
- (ii) There is a rapid accumulation of neutrophils within arterioles, glomeruli and peritubular capillaries along with deposits of immunoglobulins and complement in the vessel wall. EM shows endothelial injury with fibrin-plated thrombi.

(b) Acute rejection

(i) Occurs days, months or even years after transplant.

(ii) Both cellular and humoral responses involved.

Features of acute cellular rejection:

- Increased serum creatinine
- Clinical signs of renal failure
- Extensive interstitial mononuclear infiltrate, oedema and haemorrhage
- Mononuclear cells in the glomerular and peritubular capillaries, which may invade tubules to induce tubular necrosis
- Vascular endothelial injury mediated by CD8+ T cells

Features of acute humoral rejection:

- Mediated primarily by the antidonor antibodies
- Characterized by the necrotizing vasculitis, endothelial cell necrosis, neutrophilic infiltrate and deposition of immunoglobulins along with complement and fibrin

(c) Chronic rejection

(i) Progressive rise of serum creatinine over a period of 4–5 months is the hallmark.

(ii) It is dominated by vascular changes (dense intimal fibrosis), interstitial fibrosis, glomerular loss, tubular atrophy, shrinkage of renal parenchyma, interstitial infiltrate of plasma cells and eosinophils.

Q. Write briefly on transplantation of hematopoietic cells.

Indications

- Haematological malignancies
- Nonhaematological cancers
- Aplastic anaemia
- Immunodeficiency states

Problems With Bone Marrow Transplantation (BMT)

- GVHD (graft-versus-host disease)
- Transplant rejection
- Immunodeficiency

Common Congenital Immune Deficiency Disease

1. XLA (X-linked agammaglobulinaemia or Bruton disease)

(a) Failure of B cell maturation and absence of antibodies (due to mutations in BTK gene, which encodes B cell tyrosine kinase, required for delivering maturation signals from pre-B cells and B cell receptors)

(b) Absence of gammaglobulin in the blood

(c) Manifests by about 6 months of age, when there is depletion of maternal immunoglobulins

(d) Patients are susceptible to recurrent bacterial or viral infections and infections with *Giardia lamblia*

2. Common variable immunodeficiency

- (a) Heterogeneous group of disorders characterized by hypogammaglobulinaemia, impaired immune response and increased susceptibility to infections
- (b) Onset in second decade
- (c) Defects in antibody production due to unknown cause
- (d) Plasma cells are absent, perhaps due to a block in antigen-stimulated B cell differentiation
- (e) These patients are also prone to develop autoimmune diseases as well as lymphoid tumours.

3. Selective IgA deficiency:

(a) Most common of all primary immunodeficiencies.

(b) Failure of IgA production due to unknown cause (seemingly caused by a block in the terminal differentiation of IgA-secreting B cells to plasma cells)

(c) Since IgA is the most common immunoglobulin in mucosal surfaces, its deficiency leads to recurrent sinonasal and pulmonary infections as well as diarrhoea.

4. X-linked SCID (severe combined immunodeficiency):

Failure of both T cell and B cell maturation due to the mutation in the common γ chain of the cytokine receptor, leading to failure of IL-7 signalling and defective haemopoiesis (IL-7 is the growth factor responsible for stimulating survival and expansion of B and T cell precursors).

5. Autosomal SCID:

Failure of T cell development and a secondary defect in antibody responses, which are due to a defect in the gene coding for ADA (adenosine deaminase), leading to accumulation of toxic metabolites, which hamper lymphocyte maturation and proliferation. ADA is an enzyme involved in purine metabolism.

6. X-linked hyper-IgM syndrome:

- (a) In normal individuals, IgM is the first antibody to be produced by the body followed sequentially by IgG, IgA and IgE.
- (b) This orderly appearance of different antibody types is called heavy chain class isotype switching.
- (c) IgM-producing cells turn on the transcription of genes that encode for other isotypes, depending on the contact-mediated signals provided by the interaction between CD40 molecule on B cells and CD40L on activated T cells.
- (d) The most common genetic abnormality is mutation in the gene coding for CD40L (on X chromosome). Patients with this syndrome produce normal or even supernormal levels of IgM antibodies to antigens but lack the ability to produce IgG, IgA and IgE isotypes.

7. Wiskott–Aldrich syndrome

(a) X-linked recessive disorder characterized by thrombocytopenia, eczema and a marked susceptibility to recurrent infections

(b) Associated with a progressive age-related depletion of T lymphocytes in the peripheral blood and lymph nodes

(c) Also, there is inability to synthesize antibodies to polysaccharide antigens and increased susceptibility to encapsulated pyogenic organisms.

Q. Write in detail on the etiopathogenesis of acquired immunodeficiency syndrome (AIDS).

AIDS is a disease caused by a retrovirus, human immunodeficiency virus (HIV).

Two genetically different but related forms of HIV, namely HIV-1 and HIV-2, are implicated. Infection is characterized by depletion of CD4+ T cells (fewer than 200/mL in number).

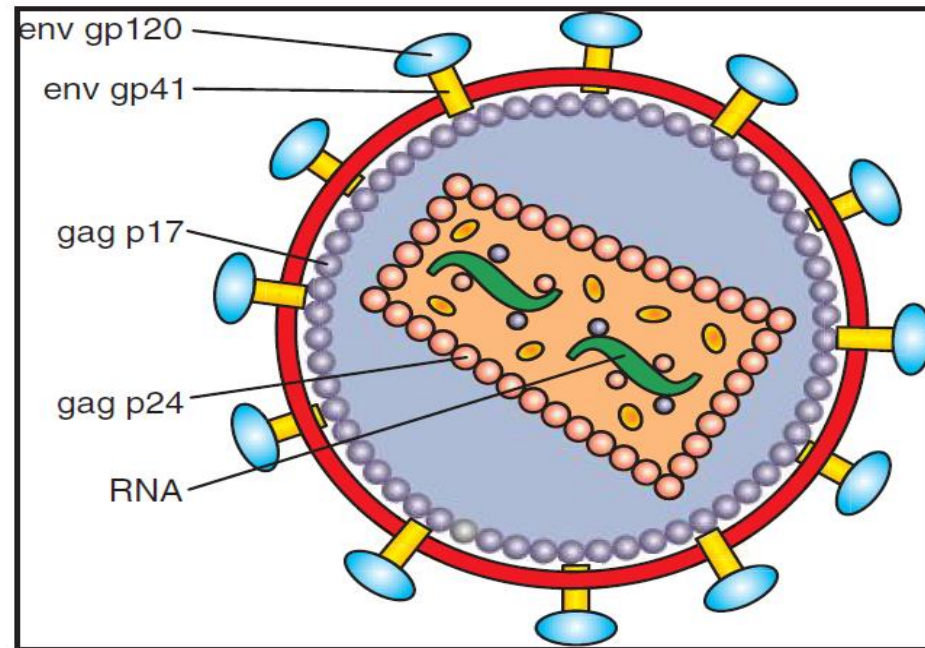


FIGURE 5.5. Structure of HIV virus.

Structure of HIV Virus (Fig. 5.5)

- HIV virus is spherical in shape and contains an electron-dense, cone-shaped core which further contains:
 - Major capsid protein p24
 - Nucleocapsid proteins p7/p9
 - Two copies of genomic RNA
 - Three viral enzymes (protease, reverse transcriptase and integrase)
- The viral core is surrounded by a matrix protein called p17.
- The viral envelope is studded with two glycoproteins, gp120 and gp 41, critical for infection.
- HIV proviral genome contains nonstructural and regulatory genes like LTR, vif, vpr, vpu, nef and rev, which code for different viral proteins.

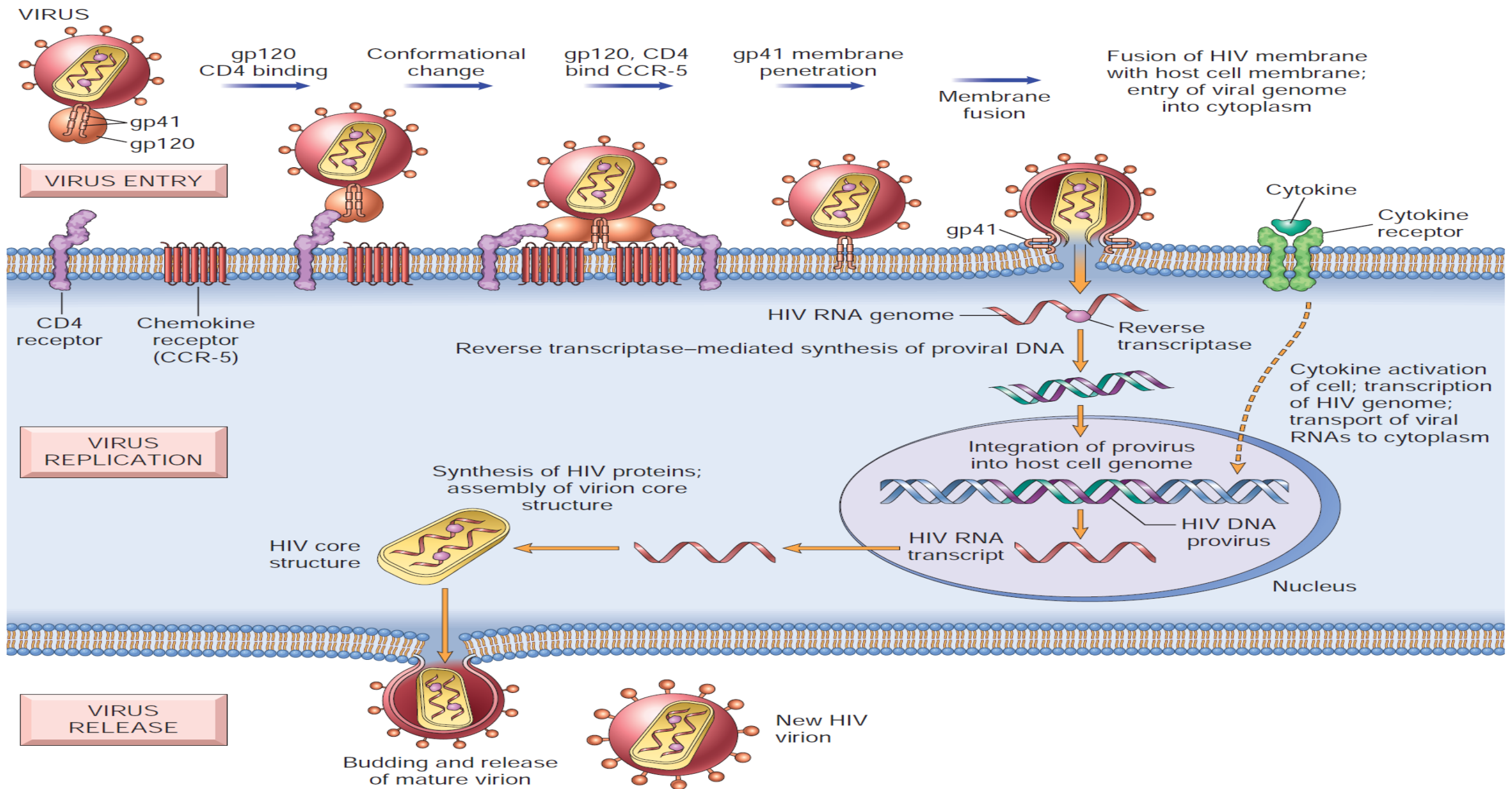


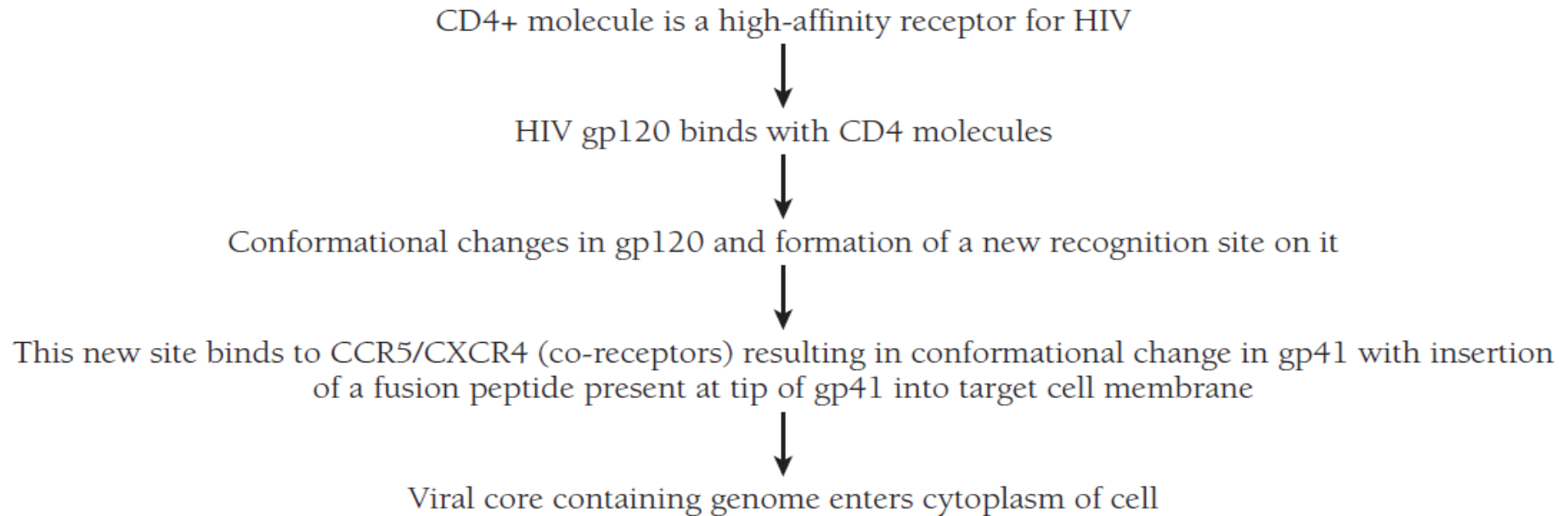
Figure 6.41 The life cycle of HIV showing the steps from viral entry to production of infectious virions. (Modified with permission from Wain-Hobson S: HIV. One on one meets two, *Nature* 384:117, 1996. Copyright 1996, Macmillan Magazines Limited.)

Pathogenesis of HIV

Targets

1. **Immune system**: CD4+ T cells, macrophages/monocytes and dendritic cells/Langerhans cells

CD4+ T lymphocyte (Flowchart 5.14)



FLOWCHART 5.14. Steps in the binding of HIV virus to CD4+ T lymphocyte.

Macrophages

- Act as a factory and reservoir for the virus and a vehicle for HIV to be transported to other organs
- Provide a site for viral replication in late phase of the disease, when CD4+T cell count is greatly decreased
- HIV may be macrophage tropic (R5 virus strains) or CD4+ T cell tropic
- CCR5 (β -chemokine) receptors are present on monocytes/macrophage and freshly isolated peripheral blood T cells (not in vitro propagated T cell line)
- T cell tropic-CXCR4 (α -chemokine) receptors are present on T cells, both freshly isolated and culture retained
- M-tropic viruses are more efficient in transmitting AIDS but T-tropic HIV gradually accumulates and cause the final rapid phase of disease (being more virulent)
- On internalization, viral genome undergoes reverse transcription to form cDNA
- cDNA may remain in episomal form in quiescent T cells but may be integrated into host genome in dividing cells
- After integration, provirus may remain silent or may transcribe and form viral particles in activated T cell on exposure to antigen/cytokines (clinical latency/chronic infection)
- Release of viral particles results in CD4+ T cell lysis
- Qualitative defects in T cells are observed in T cells even in asymptomatic patients (leading to clinical symptoms)

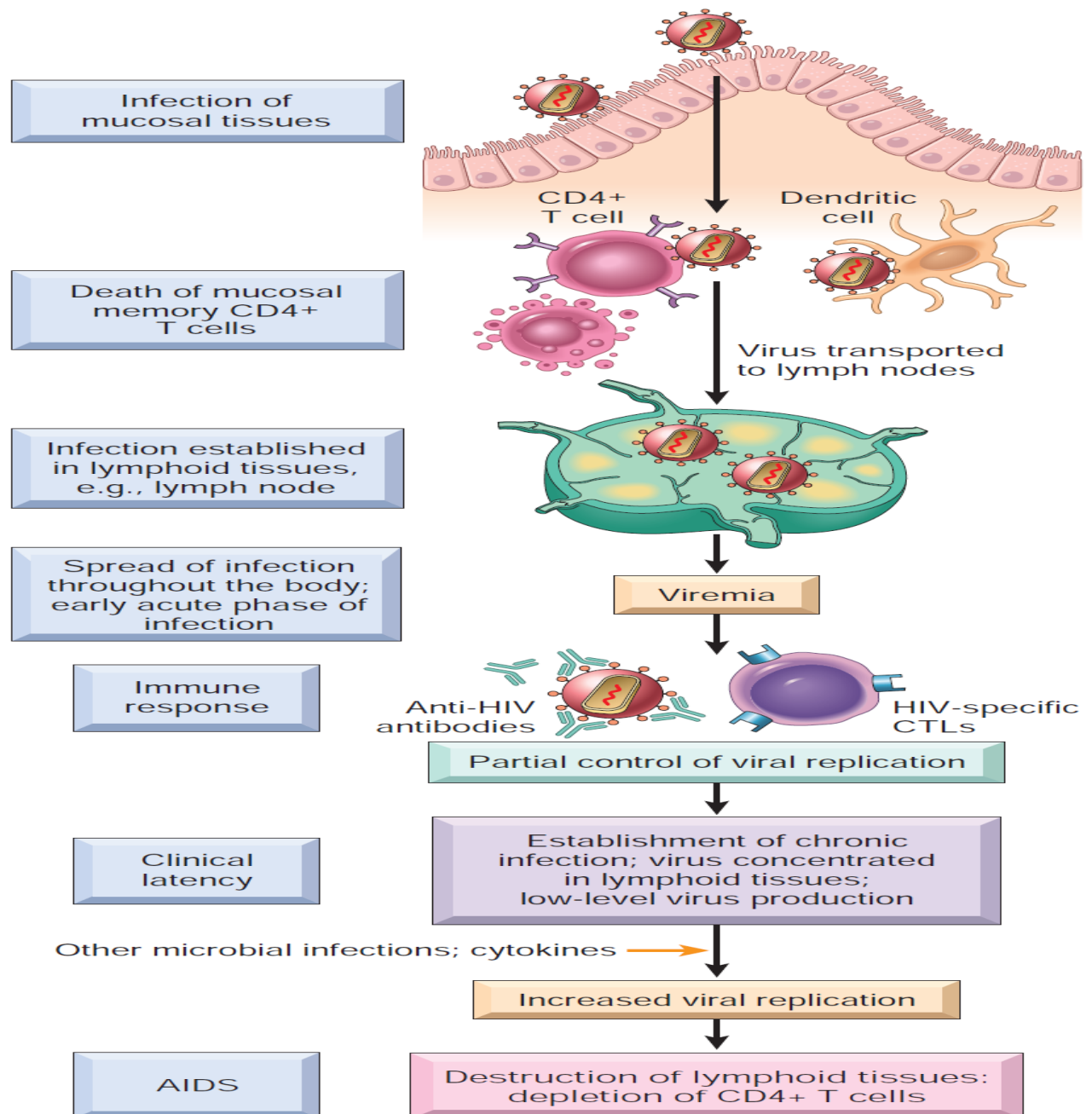
Dendritic cells

- Mucosal Langerhans cells capture the virus and transport it to regional lymph nodes.
- Follicular dendritic cells in germinal centre of lymph nodes are reservoirs of HIV.

2. CNS

- Viruses are carried to circulation by infected monocytes.
- Viruses infect macrophages and microglia (HIV does not infect neurons).
- Neurological deficit is due to direct effect of gp 120 or may be caused indirectly by viral products and soluble factors (IL-1, TNF- α , IL-6) produced by macrophages/

Figure 6.42 Pathogenesis of HIV-1 infection. The initial infection starts in mucosal tissues, involving mainly memory CD4⁺ T cells and dendritic cells, and spreads to lymph nodes. Viral replication leads to viremia and widespread seeding of lymphoid tissue. This corresponds to the early acute phase of HIV infection. The viremia is controlled by the host immune response, and the patient then enters a phase of clinical latency. During this phase, viral replication in both T cells and macrophages continues unabated, but there is some immune containment of virus (not illustrated). There continues a gradual erosion of CD4⁺ cells, and ultimately CD4⁺ T-cell numbers decline, and the patient develops clinical symptoms of full-blown AIDS. CTL, Cytotoxic T lymphocyte.



Q. Enumerate the abnormalities of immune functions in AIDS.

1. Lymphopenia

Selective loss of CD4+ T helper-inducer cells with reversal of CD4:CD8 ratio

2. Altered T cell functions in vitro

- (a) Decrease Lymphocyte proliferative response to mitogens and antigens
- (b) Decrease Specific cytotoxicity
- (c) Decrease T helper cell function for B cells (decreased antibody production)

3. Decreased T cell functions in vivo

- (a) Loss of activated and memory T cells
- (b) Decreased type IV hypersensitivity
- (c) Susceptibility to opportunistic infections and neoplasms

4. Altered monocyte/macrophage functions

- (a) Decrease Chemotaxis and phagocytosis
- (b) Decrease HLA-II expression
- (c) Decrease antigen presentation

5. Polyclonal B cell activation

- (a) Hypergammaglobulinaemia and circulating immune complexes
- (b) Decreased ability to mount an antibody response to a new antigen
- (c) Loss of control/signals for B cell function in vitro

Q. Enumerate the AIDS-defining opportunistic infections and Neoplasms

AIDS-defining opportunistic infections

Protozoal and Helminthic

- Cryptosporidiosis or isosporidiosis (enteritis)
- Toxoplasmosis (pneumonia or CNS infection)

Fungal

- Candidiasis (oesophageal, tracheal and pulmonary infections)
- Cryptococcosis (CNS infection)
- Coccidioidomycosis (disseminated infection)
- Histoplasmosis (disseminated infection)
- Pneumocystosis (pneumonia or disseminated infection)

Bacterial Infections

- Mycobacteriosis (atypical and Mycobacterium tuberculosis; pulmonary and extrapulmonary)
- Nocardiosis (pneumonia, meningitis and disseminated infections)
- Salmonella infection

Viral

- Cytomegalovirus (pulmonary, intestinal, retinal or CNS infections)
- Herpes simplex virus (localized or disseminated infection)
- Varicella zoster virus (localized or disseminated infection)
- Progressive multifocal leukoencephalopathy

AIDS-Defining Neoplasms

- Kaposi sarcoma
- B cell non-Hodgkin lymphoma
- Primary lymphoma of the brain
- Invasive cancer of the uterine cervix

Q. Write briefly on the laboratory diagnosis of AIDS.

Laboratory diagnosis of AIDS includes:

1. Nonspecific tests

(a) Decreased TLC

(b) Decreased lymphocyte count ($<2000/\text{mm}^3$)

(c) Decreased CD4⁺ T cell count (<200 CD4⁺ T cells/ μL) and reversal of T4:T8 ratio

(d) Thrombocytopenia

(e) Increased β_2 microglobulin level

2. Specific tests

(a) Antigen detection

(i) Acute illness/seroconversion stage:

p24 antigenaemia and viraemia, also appearance of IgM thereafter

(ii) Asymptomatic phase: decreased or absent free p24, but antibody-bound p24 antigen may be seen

(iii) Clinical disease: increased free p24 antigen

Method: Antigen-capture ELISA

In the first few weeks after infection and in terminal phase, the test is uniformly positive.

(b) Antibody detection

(i) Simplest and most widely used method

(ii) Negative in window period that follows infection (time taken for antibodies to appear); IgM appears first followed by IgG

(iii) ELISA:

- Sensitive but not so specific

- Types used: 'Direct solid phase antiglobulin ELISA' and 'Capture ELISA specific for IgM antibody'

(iv) Western blot test: more specific than ELISA

(v) PCR: Now 'new gold standard' test for diagnosis in all stages of HIV

(c) Direct virus isolation and culture in neoplastic T cell line

END