IMMUNOPATHOLOGY

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Immunity refers to protection against infections, and the immune system is the collection of cells and molecules that are responsible for defending the body against the countless pathogenic microbes in the environment.

Deficiencies in immune defenses result in an increased susceptibility to infections, which can be life-threatening if the deficits are not corrected.

On the other hand, the immune system is itself capable of causing great harm and is the root cause of some of the most vexing and intractable diseases of the modern world.

Thus, diseases of immunity range from those caused by “too little” to those caused by “too much or inappropriate” immune activity

INNATE AND ADAPTIVE IMMUNITY

Innate immunity (also called natural, or native, immunity) is mediated by cells and proteins that are always present and poised to fight against microbes, being called into action immediately in response to infection.

The major components of innate immunity are epithelial barriers of the skin, gastrointestinal tract, and respiratory tract, which prevent microbe entry; phagocytic leukocytes (neutrophils and macrophages); a specialized cell type called the natural killer (NK) cell; and several circulating plasma proteins, the most important of which are the proteins of the complement system

The innate immune response is able to prevent and control many infections.

However, many pathogenic microbes have evolved to overcome the early defenses, and protection against these infections requires the more specialized and powerful mechanisms of adaptive immunity (also called acquired, or specific, immunity).

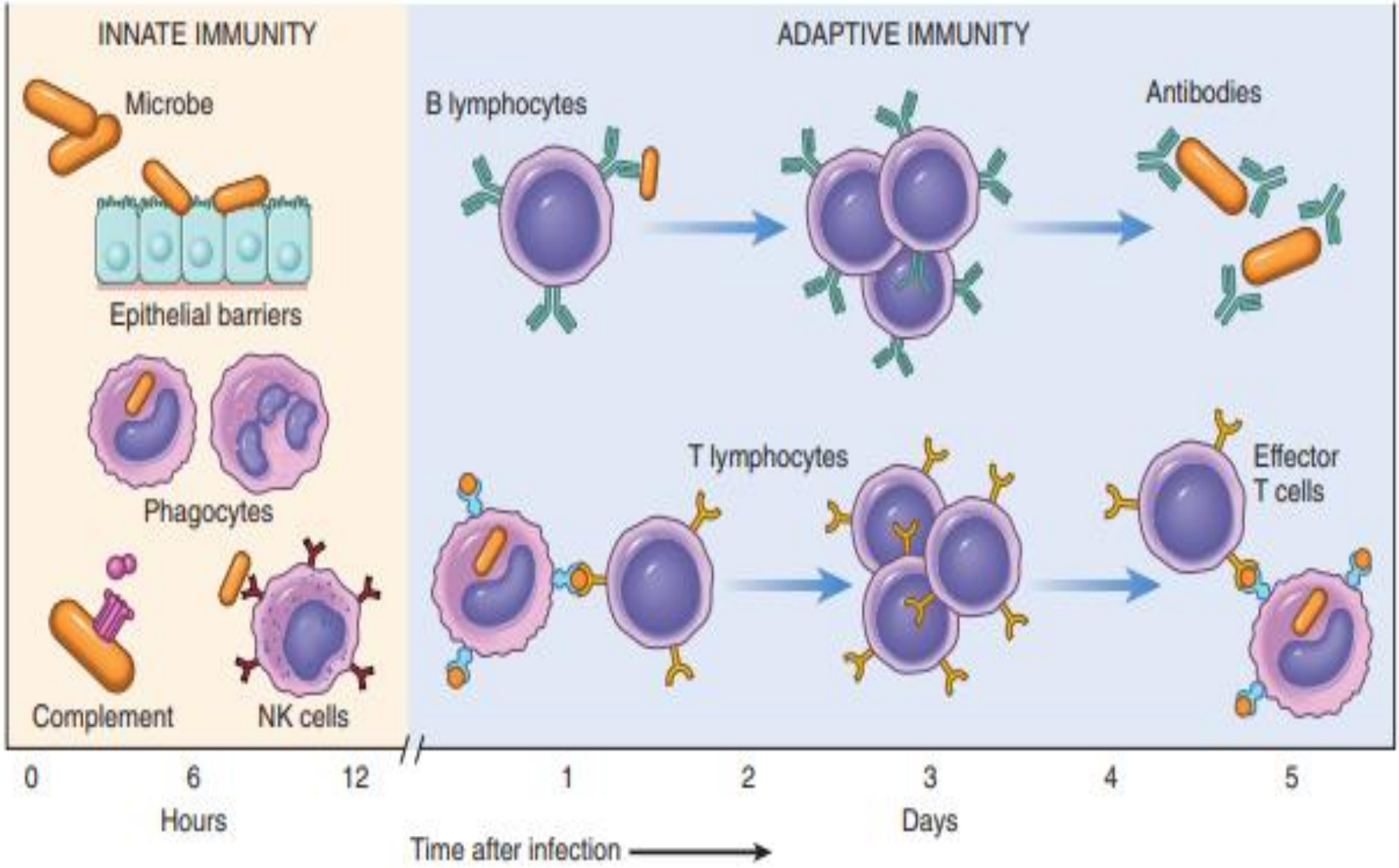


Figure 4–1 The principal mechanisms of innate immunity and adaptive immunity. NK, natural killer.

There are two types of adaptive immune responses: humoral immunity, mediated by soluble proteins called antibodies that are produced by B lymphocytes (also called B cells) and cell-mediated (or cellular) immunity, mediated by T lymphocytes (also called T cells)

CELLS AND TISSUES OF THE IMMUNE SYSTEM

The cells of the immune system consist of lymphocytes, which recognize antigens and mount adaptive immune responses; specialized antigen-presenting cells (APCs), which capture and display microbial and other antigens to the lymphocytes; and various effector cells, whose function is to eliminate microbes and other antigens.

Cells and Tissues of the Immune System

- Lymphocytes are the mediators of adaptive immunity and the only cells that produce specific and diverse receptors for antigens.
- T (thymus-derived) lymphocytes express TCRs that recognize peptide antigens displayed by MHC molecules on the surface of APCs.

- B (bone marrow–derived) lymphocytes express membrane-bound antibodies that recognize a wide variety of antigens. B cells are activated to become plasma cells, which secrete antibodies.
- NK cells kill cells that are infected by some microbes or are stressed and damaged beyond repair. NK cells express inhibitory receptors that recognize MHC molecules that are normally expressed on healthy cells, and are thus prevented from killing normal cells.
- APCs capture microbes and other antigens, transport them to lymphoid organs, and display them for recognition by lymphocytes. The most efficient APCs are DCs, which are located in epithelia and most tissues.
- The cells of the immune system are organized in tissues. Some of these tissues are the sites of mature lymphocyte production (the generative lymphoid organs, the bone marrow and thymus), while others are the sites of immune responses (the peripheral lymphoid organs, including lymph nodes, spleen, and mucosal lymphoid tissues).

Disorders of the immune system are divided into three broad categories

1. Hypersensitivity reactions (immunologically mediated tissue injury)
2. Autoimmune diseases
3. Immunodeficiency diseases

Hypersensitivity Reactions

The purpose of the immune response is to protect against invasion by foreign organisms, but they often lead to host tissue damage.

An exaggerated immune response that results in tissue injury is broadly referred to as a hypersensitivity reaction.

Classification

a. According to Gell and Comb's classification, hypersensitivity reactions can be divided into four types (type I, II, III, and IV) depending on the mechanism of immune recognition involved and on the inflammatory mediator system recruited.

b. Types – I II, and III reactions are dependent on the interaction of specific antibodies with the given antigen, whereas, in type IV reactions recognition is achieved by antigen receptors on T-cells.

Table 4–1 Mechanisms of Hypersensitivity Reactions

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Immediate (type I) hypersensitivity	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation	Anaphylaxis; allergies; bronchial asthma (atopic forms)
Antibody-mediated (type II) hypersensitivity	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury	Autoimmune hemolytic anemia; Goodpasture syndrome
Immune complex–mediated (type III) hypersensitivity	Deposition of antigen–antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Inflammation, necrotizing vasculitis (fibrinoid necrosis)	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction
Cell-mediated (type IV) hypersensitivity	Activated T lymphocytes → (1) release of cytokines, inflammation and macrophage activation; (2) T cell–mediated cytotoxicity	Perivascular cellular infiltrates; edema; granuloma formation; cell destruction	Contact dermatitis; multiple sclerosis; type 1 diabetes; tuberculosis

IgE, IgG, IgM, immunoglobulins E, G, M.

Type I hypersensitivity reaction

Immediate hypersensitivity is a tissue reaction that occurs rapidly (typically within minutes) after the interaction of antigen with IgE antibody that is bound to the surface of mast cells in a sensitized host.

The reaction is initiated by entry of an antigen, which is called an allergen because it triggers allergy. Many allergens are environmental substances that are harmless for most persons on exposure. Some people apparently inherit genes that make them susceptible to allergies. T

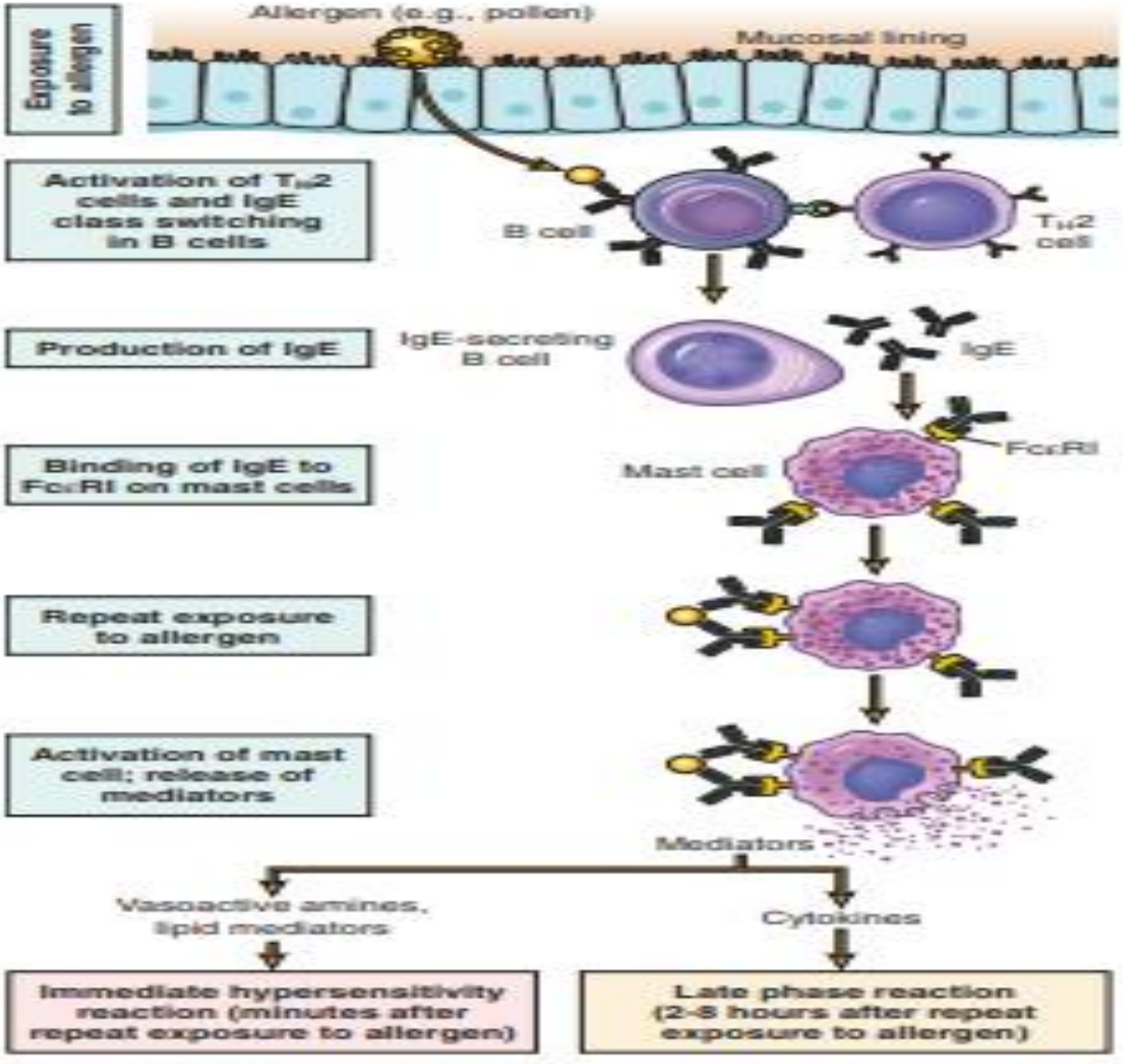
Sequence of Events in Immediate hypersensitive Reactions

Most hypersensitivity reactions follow the same sequence of cellular responses

• Activation of TH2 cells and production of IgE antibody. Allergens may be introduced by inhalation, ingestion, or injection.

- Sensitization of mast cells by IgE antibody. Mast cells are derived from precursors in the bone marrow, are widely distributed in tissues, and often reside near blood vessels and nerves and in subepithelial locations

- Activation of mast cells and release of mediators. When a person who was sensitized by exposure to an allergen is reexposed to the allergen, it binds to multiple specific IgE molecules on mast cells, usually at or near the site of allergen entry


Exposure to allergen
Allergen (e.g., pollen)
Mucosal lining
Activation of T_H2 cells and IgE class switching in B cells
B cell
T_H2 cell
Production of IgE
IgE-secreting B cell
IgE
Binding of IgE to FcεRI on mast cells
Mast cell
FcεRI
Repeat exposure to allergen
Activation of mast cell; release of mediators
Mediators
Vasoactive amines, lipid mediators
Cytokines
Immediate hypersensitivity reaction (minutes after repeat exposure to allergen)
Late phase reaction (2-8 hours after repeat exposure to allergen)

Type I reactions have two well-defined phases

Initial phase (response)

Characterized by vasodilatation, vascular leakage, and depending on the location, smooth muscle spasm or glandular secretions.

Late phase

As it is manifested for example in allergic rhinitis and bronchial asthma, more intense infiltration of eosinophiles, neutrophiles, basophilic, monocytes and CD4 + T cells are encountered and so does tissue destruction (epithelial mucosal cells).

Immediate (Type I) Hypersensitivity

- Also called allergic reactions, or allergies
- Induced by environmental antigens (allergens) that stimulate strong T_H2 responses and IgE production in genetically susceptible individuals
- IgE coats mast cells by binding to Fcε receptors; reexposure to the allergen leads to cross-linking of the IgE and FcεRI, activation of mast cells, and release of mediators.
- Principal mediators are histamine, proteases, and other granule contents; prostaglandins and leukotrienes; and cytokines.
- Mediators are responsible for the immediate vascular and smooth muscle reactions and the late-phase reaction (inflammation).
- The clinical manifestations may be local or systemic, and range from mildly annoying rhinitis to fatal anaphylaxis.

Type II hypersensitivity reaction

Antibody-mediated (type II) hypersensitivity disorders are caused by antibodies directed against target antigens on the surface of cells or other tissue components. The antigens may be normal molecules intrinsic to cell membranes or in the extracellular matrix, or they may be adsorbed exogenous antigens (e.g., a drug metabolite).

Antibody-mediated abnormalities are the underlying cause of many human diseases. In all of these disorders, the tissue damage or functional abnormalities result from a limited number of mechanisms

Mechanisms of Antibody-Mediated Diseases

Antibodies cause disease by targeting cells for phagocytosis, by activating the complement system, and by interfering with normal cellular functions.

The antibodies that are responsible typically are high-affinity antibodies capable of activating comp

Opsonization and phagocytosis.

When circulating cells, such as erythrocytes or platelets, are coated (opsonized) with autoantibodies, with or without complement proteins, the cells become targets for phagocytosis by neutrophils and macrophages

Inflammation.

Antibodies bound to cellular or tissue antigens activate the complement system by the “classical” pathway

Antibody-mediated cellular dysfunction

In some cases, antibodies directed against cell surface receptors impair or dysregulate cellular function without causing cell injury or inflammation

Type III hypersensitivity / immune complex-mediated

Antigen–antibody (immune) complexes that are formed in the circulation may deposit in blood vessels, leading to complement activation and acute inflammation.

The antigens in these complexes may be exogenous antigens, such as microbial proteins, or endogenous antigens, such as nucleoprotein

Table 4–4 Examples of Immune Complex–Mediated Diseases

Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	Nuclear antigens	Nephritis, skin lesions, arthritis, others
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Polyarteritis nodosa	Hepatitis B virus antigens in some cases	Systemic vasculitis
Reactive arthritis	Bacterial antigens (e.g., *Yersinia*)	Acute arthritis
Serum sickness	Various proteins (e.g., foreign serum protein such as horse antithymocyte globulin)	Arthritis, vasculitis, nephritis
Arthus reaction (experimental)	Various foreign proteins	Cutaneous vasculitis

Pathogenesis of Diseases Caused by Antibodies and Immune Complexes

- Antibodies can coat (opsonize) cells, with or without complement proteins, and target these cells for phagocytosis by macrophages, which express receptors for the Fc tails of IgG molecules and for complement proteins. The result is depletion of the opsonized cells.
- Antibodies and immune complexes may deposit in tissues or blood vessels, and elicit an acute inflammatory reaction by activating complement, with release of breakdown products, or by engaging Fc receptors of leukocytes. The inflammatory reaction causes tissue injury.
- Antibodies can bind to cell surface receptors or essential molecules, and cause functional derangements (either inhibition or unregulated activation) without cell injury.

Type IV hypersensitivity (Cell-mediated) reaction

Several autoimmune disorders, as well as pathologic reactions to environmental chemicals and persistent microbes, are now known to be caused by T cells. The occurrence and significance of T lymphocyte–mediated tissue injury have been increasingly appreciated as the methods for detecting and purifying T cells from patients' circulation and lesions have improved.

This group of diseases is of great clinical interest because many of the new, rationally designed biologic therapies for immune-mediated inflammatory diseases have been developed to target abnormal T cell reactions.

Two types of T cell reactions are capable of causing tissue injury and disease: (1) cytokine-mediated inflammation, in which the cytokines are produced mainly by CD4+ T cells, and (2) direct cell cytotoxicity, mediated by CD8+ T cells

Table 4–5 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 T_H17 (and T_H1?) cytokines; role of antibodies and immune complexes?	Chronic arthritis with inflammation, destruction of articular cartilage and bone
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by T_H1 and T_H17 cytokines, myelin destruction by activated macrophages	Demyelination in CNS with perivascular inflammation; paralysis, ocular lesions
Type I diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation, destruction of islet cells by CTLs	Insulitis (chronic inflammation in islets), destruction of β cells; diabetes
Hashimoto thyroiditis	Thyroglobulin, other thyroid proteins	Inflammation, CTL-mediated killing of thyroid epithelial cells	Hypothyroidism
Inflammatory bowel disease	Enteric bacteria; self antigens?	Inflammation mediated mainly by T_H17 cytokines	Chronic intestinal inflammation, ulceration, obstruction
Autoimmune myocarditis	Myosin heavy chain protein	CTL-mediated killing of myocardial cells; inflammation mediated by T_H1 cytokines	Cardiomyopathy
Contact sensitivity	Various environmental chemicals (e.g., urushiol from poison ivy or poison oak)	Inflammation mediated by T_H1 (and T_H17?) cytokines	Epidermal necrosis, dermal inflammation with 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 on the basis of similarity to experimental animal models of the diseases.
CNS, central nervous system; CTL, cytotoxic T lymphocyte.

Mechanisms of T Cell–Mediated Hypersensitivity Reactions

- Cytokine-mediated inflammation: CD4+ T cells are activated by exposure to a protein antigen and differentiate into T_H1 and T_H17 effector cells. Subsequent exposure to the antigen results in the secretion of cytokines. IFN-γ activates macrophages to produce substances that cause tissue damage and promote fibrosis, and IL-17 and other cytokines recruit leukocytes, thus promoting inflammation.
- T cell–mediated cytotoxicity: CD8+ CTLs specific for an antigen recognize cells expressing the target antigen and kill these cells. CD8+ T cells also secrete IFN-γ.

Immunologic Tolerance

Immunologic tolerance is a state in which an individual is incapable of developing an immune response to specific antigens.

Self-tolerance refers to lack of responsiveness to an individual's antigens.

Tolerance can be broadly classified into two groups: central and peripheral tolerance.

Immunodeficiency Diseases

The term immunodeficiency covers a group of disorders of specific immune responses, neutrophil, macrophage and natural killer cells functions, as well as defects in the compliment system that lead to impaired resistance to microbial infections.

Classification

These diseases are crudely classified into primary and secondary types.

Primary immunodeficiency diseases (exceedingly rare)

These disorders usually manifest in early childhood and are almost always genetically determined. Though, some overlap exists primary immunodeficiency diseases are further divided into:

Deficiencies of antibody (B – cells) immunity.

Eg. Infantile X-linked agammaglobinmea

Transient hypogammaglobulinmea of infancy

Deficiencies of cell mediated (T-cell) Immunity

T-cell deficiencies are difficult to trace as T-cells affects B cell functions Eg. Di George's syndrome:

Combined T-cell and B-cell deficiencies Eg Severe combined immunodeficiency disease (SCID).

Secondary immunodeficiencies States

These immunodeficiency states may be acquired secondary to various disease processes or drug effects for example

Protein deficiency

Lack of protein leads to cell mediated immunity and hypocomplementamia

Hematologic malignancies

Leukemia and lymphomas where normal functioning cell replaced by neoplastic ones here both humeral and cell mediated immunity are impaired

Acute viral infection

Especially infectious mononucleosis and misels cause temporary impairment of cell mediated immunity

Chronic renal failure

Probably due to toxic effects of accumulated metabolites that affects both B and Tcell functions

Iatrogenic

Steroids etc for organ transplants, cytotoxic drugs or radiotherapy for the treatment of malignancies.

Splenctomy

After staging operations of lymphomas or traumatic spleen rupture Splenectomy leads to a characteristic immunodeficiency in which the patient is susceptible to infections by phylogenic bacteria especially pneumococal pneumonia.

Acquired Immunodeficiency Syndrome (AIDS)

AIDS is a retroviral disease characterized by profound immuno suppression that leads to opportunistic infections, secondary neoplasms and neurological manifestations

Modes of transmission

Sexual activities 75% of all world-wide transmission is heterosexual transmission

Parenteral transmission In intravenous drug abusers, hemophiliacs who received factor viii concentrates and random recipients of blood transfusion

Mother to child transmission

About 25 –30% HIV, positive mother will transmit HIV to their infants. About 60% of this infection is transmitted during child- birth 25% during pregnancy and 15% during breastfeeding.

Needle Pricking Accidental needle struck injury or exposure to non-intact skin to infected blood in laboratories accounts for about 0.3% risk of stereovision as compared to a 30% risk of accidental exposure to hepatitis B infected blood.

Pathogenesis

Targets of HIV infections are: The immune system and Central nervous system

Target cells are those having CD4 receptors include

CD4 + T helper cells

Monocytes /macrophages

Tissue cells such as dendritic cells present in genital tracts and anorectal region and Certain brain cells (glial cells)

The life cycle of HIV virus after internalization

This include

DNA Synthesis- the uncoated viral RNA is copied into double stranded DNA by reverse transcriptase

Viral integration-the DNA derived from the viruses in integrated into host genome by the viral integrate enzyme, thereby producing the latest proviral form of HIV-I.

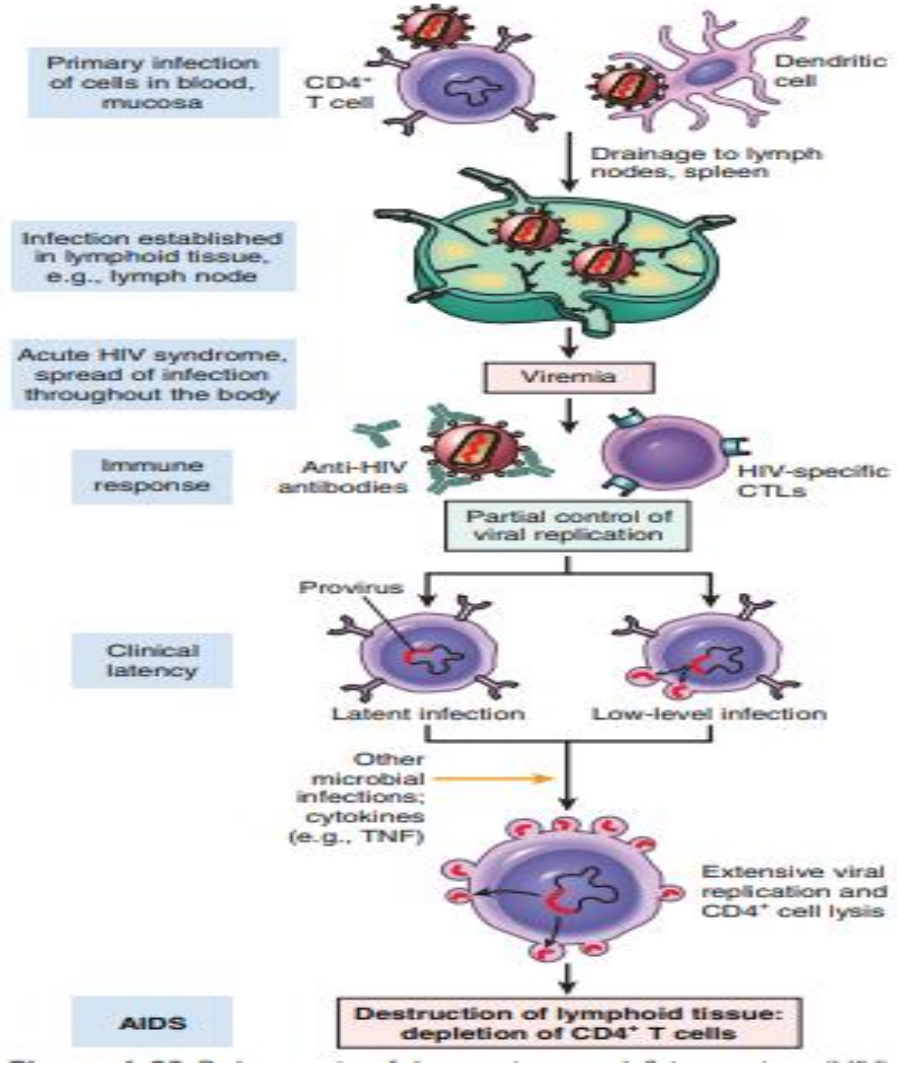
Viral replication- viral RNA is reproduced by transcriptional activation of the integrated HIV provirus

Viral dissemination- to complete the life cycle, nascent viruses assembled in the cytoplasm and disseminate to other target cells after directly lysing the cell (direct cytopathic effect of the virus).

The HIV virus after internalization assumes two forms of infectivity such as latent infection and productive infections.

In latent infections, the virus may be lacked in the cytoplasm (preintegration latency) or after being integrated into host DNA (Post integration latency). Hereafter the highlight of HIV productive infection is surfaced

Pathogenesis of human immunodeficiency virus (HIV) infection.



This productive infection predominantly occur in lymphoid tissues, within macrophages, dendritic cells and CD4+T CELLS.

- Viremia after 8 weeks of infection supervene

- Viremia is subsequently cleared by the development of an anti viral immune response effected by CD8+cytotoxic T cells

Major Abnormalities of Immune Function in AIDS

Lymphopenia
Predominantly caused by selective loss of the CD4+ helper T cell subset; reduced CD4+/CD8+ ratio
Decreased T Cell Function in vivo
Preferential loss of activated and memory T cells Decreased delayed-type hypersensitivity Susceptibility to opportunistic infections Susceptibility to neoplasms
Altered T Cell Function in vitro
Decreased proliferative response to mitogens, alloantigens, and soluble antigens Decreased cytotoxicity Decreased helper function for B cell antibody production Decreased interleukin-2 and interferon-γ production
Polyclonal B Cell Activation
Hypergammaglobulinemia and circulating immune complexes Inability to mount de novo antibody response to a new antigen Poor responses to normal signals for B cell activation in vitro
Altered Monocyte or Macrophage Functions
Decreased chemotaxis and phagocytosis Decreased HLA class II antigen expression Diminished capacity to present antigen to T cells Increased spontaneous secretion of interleukin-1, tumor necrosis factor, interleukin-6

HLA, human leukocyte antigen.

This results in transient decrease in CD4+T cells and an apparent rise in CD8+T cells

- As viremia declines, the HIV disseminates into lymphoid tissues and undergoes clinical latency but not viral latency

- Finally the flows of the CD4+T cells count with variable time results in AIDS.

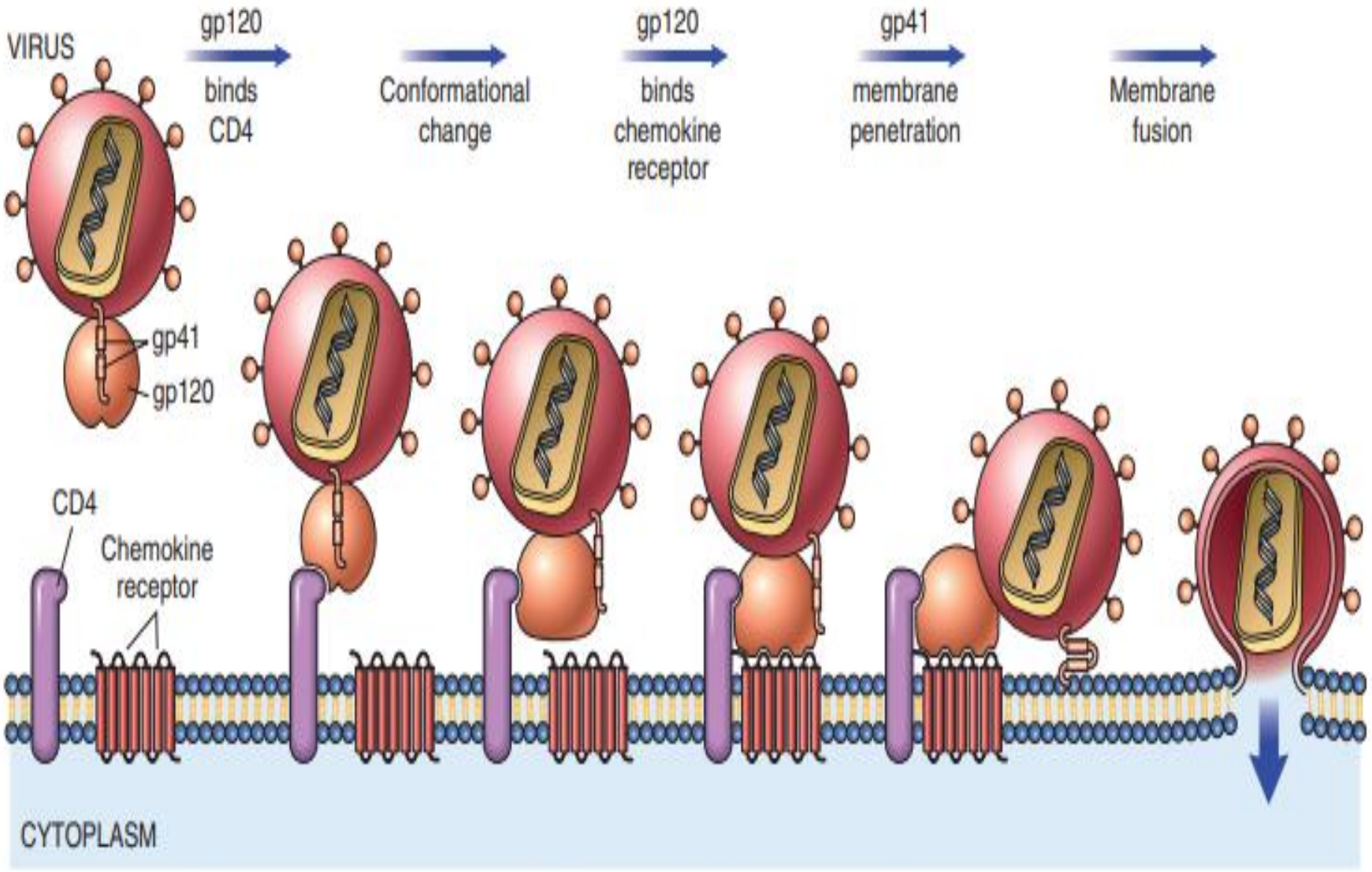


Figure 4–27 Molecular basis of entry of human immunodeficiency virus (HIV) into host cells. Interactions with CD4 and a chemokine receptor ("coreceptor").

Natural history of HIV infection

Three phases reflecting the dynamics of virus – host interaction are recognized

Early acute phase

High level of viral production, viremia and widespread seeding of lymphoid tissues.

Its spread is controlled by immune system and the virus is mainly swept into the lymph nodes

The decline in HIV viral load usually coincides with the time of sero-conversion and the primary or early HIV infection. Acute phase occurs 4 – 8 weeks after acquiring the virus

There may be a short (1 – 2 weeks) seroconversion illness which cause the following in about 50-70% individuals: fever, rash sore throat, muscle and joint pain and some lymph node swelling.

The level of viral load in early acute phase of the disease is called the set point and anti retroviral therapy can reduce this set point thus, early detection especially in cases of needle stick injuries, rape and other known risky exercises can benefit from it.

The middle chronic phase

Relative containment of the viruses with a period of clinical latency (not viral latency). Patients develop asymptomatic infections.

Persistent generalized lymph adenopathyes (PGL) develops and PGL is defined as palpable lymphadenopathy at two or more extra – inguinal sites, persisting for more than 3 months in persons infected with HIV.

Minor opportunistic infections such as trush, herpes zoster etc.

The final, crisis phase

Characterized by breakdown of host defences with increased plasmal viral load and clinical disease. Typically the patient presents with

Prolonged fever > 1/12

Fatigue, weight loss and diarrhea

CD4 + T cells < 500 /µl

After a variable period:

(i) Serious opportunistic infections, (Bacterial, Fungal, Viral

(ii) Secondary neoplasms: Kaposi sarcoma, Non Hodgkin's lymphoma, Cervical carcinoma

(iii) Clinical neurological diseases (AIDS defining disease)

AIDS-Defining Opportunistic Infections and Neoplasms Found in Patients with Human Immunodeficiency Virus (HIV) infection

Infections
Protozoal and Helminthic Infections
Cryptosporidiosis or isosporidiosis (enteritis) Pneumocystosis (pneumonia or disseminated infection) Toxoplasmosis (pneumonia or CNS infection)
Fungal Infections
Candidiasis (esophageal, tracheal, or pulmonary) Cryptococcosis (CNS infection) Coccidioidomycosis (disseminated) Histoplasmosis (disseminated)
Bacterial Infections
Mycobacteriosis ("atypical," e.g., *Mycobacterium avium-intracellulare*, disseminated or extrapulmonary; *Mycobacterium tuberculosis*, pulmonary or extrapulmonary) Nocardiosis (pneumonia, meningitis, disseminated) *Salmonella* infections, disseminated
Viral Infections
Cytomegalovirus (pulmonary, intestinal, retinitis, or CNS infections) Herpes simplex virus (localized or disseminated infection) Varicella-zoster virus (localized or disseminated infection) Progressive multifocal leukoencephalopathy
Neoplasms
Kaposi sarcoma Primary lymphoma of brain Invasive cancer of uterine cervix

SUMMARY

Human Immunodeficiency Virus Life Cycle and the Pathogenesis of AIDS

- Virus entry into cells: requires CD4 and co-receptors, which are receptors for chemokines; involves binding of viral gp120 and fusion with the cell mediated by viral gp41 protein; main cellular targets: CD4+ helper T cells, macrophages, DCs
- Viral replication: integration of provirus genome into host cell DNA; triggering of viral gene expression by stimuli that activate infected cells (e.g., infectious microbes, cytokines produced during normal immune responses)
- Progression of infection: acute infection of mucosal T cells and DCs; viremia with dissemination of virus; latent infection of cells in lymphoid tissue; continuing viral replication and progressive loss of CD4+ T cells

- Mechanisms of immune deficiency:
  - Loss of CD4+ T cells: T cell death during viral replication and budding (similar to other cytopathic infections); apoptosis occurring as a result of chronic stimulation; decreased thymic output; functional defects
  - Defective macrophage and DC functions
  - Destruction of architecture of lymphoid tissues (late)

Autoimmune Diseases

Autoimmunity implies that an immune response has been generated against self-antigens /Autoantigens/.

Central to the concept of autoimmune diseases is a breakdown of the ability of the immune system to differentiate between self and non-self antigens.

The presence of circulating autoantibodies does not necessarily indicate the presence of autoimmune disease. Thus, pathologic autoimmunity is characterized by

- The autoimmune response is not secondary to tissue injury but it has primary pathologic significance

- Absence of other well-defined cause of disease.

Mechanisms of autoimmune diseases

1. Genetic: Evidences include

-Familial clustering of several diseases such as SLE, autoimmune hemolytic anemia, Hashimoto's thyroditis.

-linkage of several autoimmune diseases such as Hashimotos thyroditis, pernicious anemia, Addion's disease, primary hypothyroidism, etc so-called Schmidt's syndrome.

-Induction of autoimmune diseases with HLA especially class ll antigens exemplified by HLA-B27

Immunologic

Failure of peripheral tolerance: Breakdown of T-cell anergy .

T-cell anergy may be broken if the APC can be induced to express co-stimulatory molecules such as B7-1 and to secrete cytokines such as IL-12 that stimulate the generation of TH 1 cells.

This up regulation of co-stimulator molecule B7-1 has been noted in multiple sclerosis, Rheumatoid arthritis, psoriasis and Insulin dependant diabetes mellitus (IDD).

Failure of activation induced cell death defects in Fas – Fas ligand

System in generating apoptosis may allow persistence and proliferation of auto reactive T-cells in peripheral tissues. No known disease is incremented but SLE suggested only on experimental basis.

Failure of T-cell – mediated suppression

Loss of regulatory or suppressor T-cells can limit the function of auto reactive T and B cells and thus, can lead to autoimmunity.

There is evidence that patients with SLE have a deficiency of T-suppressor cells activity that would result in hypergamaglobinmea and the production of autoantibodies.

Molecular mimicry (cross – reacting antigens).

Some infectious agents share epitopes with self-antigens. An immune response against such microbes may produce tissue-damaging reactions against the cross reacting self-antigen.

The classic example is streptococcal pharyngitis, in which antibodies are produced to the streptococcal M – protein and cross-react with M – protein of the sarcolemma of cardiac muscle to produce the acute rheumatic fever.

Release of sequestrated antigens

Regardless of the exact mechanism by which self-tolerance is achieved (clonal deletion or anergy), it is clear that induction of tolerance requires interaction between the antigen and the immune system.

Thus, any self-antigen that is completely sequestrated during development is likely to be viewed as foreign if introduced into the circulation, and an immune response develops.

Microbial agents

Some bacteria, mycoplasm and viruses are implicated. Viruses and other microbes may share cross-reacting epitopes with self-antigens.

Example: Cross-reaction between certain coxsackieviruses and islet cells antigen glutamic acid decarboxylase.

Microbial infections with resultant tissue necrosis and inflammation can cause up regulation of co-stimulatory molecules on resting antigen-presenting cells in tissue, thus favouring a breakdown of T- cell anergy.

Classification of autoimmune diseases

The classification is based on the number of organs involved

Organ specific autoimmune diseases affect a single organ or tissue including Hashimoto's thyroiditis, Graves disease, 1o myxedema, Diabetes, chronic atropic gastritis, Myasthenia gravis

Organ nonspecific autoimmune diseases affect many organs and tissues including

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Systemic sclerosis
- Dermatomyositis
- Polymyositis

Systemic lupus erythematosis (SLE)

Systemic lupus erythematosis is a classic prototype of non-organ specific autoimmune disease characterized by a bewildering array of autoantibodies particularly antinuclear antibodies (ANAS).

It is a chronic remitting and relapsing often-febrile illness characterized principally by injury to the skin, joints, kidney and serosal membranes.

Each and very part of the body may be affected.

It is common among women of child bearing age and a female to male ratio of 9:1, pick on set 2nd to 4th decade

Pathogenesis

The fundamental defect in SLE is a failure of regulatory mechanism that sustains self tolerance

The cause of SLE remains unknown but it appears to be a complex disorder of multifactorial origin resulting from interactions including:

Genetic factors

There is an Increased familial risk

Hormonal factors

Estrogens confer increased risks (10 times more common in females than males) that accelerate during pregnancy and menses. Androgens however, confer decreased risk

Environmental factors

Drugs such as hydralazine, pencillin etc induce SLE – like illness) in which all acting in concert to cause activation of helper T-cells and B-cells that results in the secretion of several species of autoantibodies.

- **Ultraviolet rays**
- **Emotional stress**
- **Surgery**

Immunologic factors

i) B cell hyperactivity with hypergammaglobulinemia

ii) Autoantibodies present with reactivity to DNA, RNA, or phospholipids thus, antinuclear anti bodies (ANAS) are the ones that are directed against several nuclear antigen grouped into four categories

1. Antibodies to DNA
2. Antibodies to history
3. Antibodies to non-histone proteins bound to RNA
4. Antibodies to nucleolar antigens

Clinicopathologic features

Typically the patients young woman with a butterfly rash over the face. Generally the course of the disease is variable and almost unpredictable ANAs can be found in virtually 100% of patients but, not specific

The detection of antibodies against double stranded DNA and Some antigens are virtually diagnostic of SLE

Chronic discoid lupus erythmatosis is a disease where its skin involvement may mimic SLE.

SLE may affect almost any organ system in variable combinations; this vast heterogenicity in clinical presentation requires a clinical index of suspicion followed by laboratory confirmation.

Thus, criteria for the diagnosis of SLE are coined such as molar rash, photosensitivity, oral ulcer, arthritis, renal disorders, hematological disorder, immunologic disorder and antinuclear antibody.

A person is said to have SLE in any four or more of the criteria are present serially or simultaneously.

The End