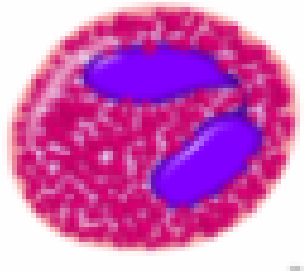
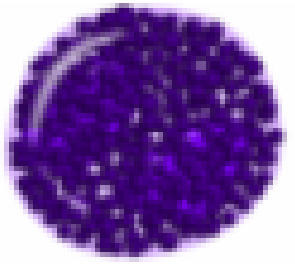
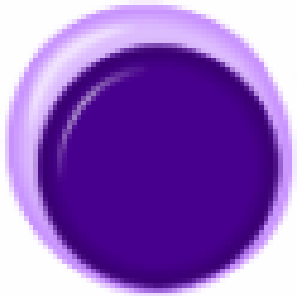
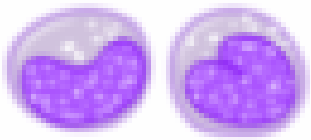
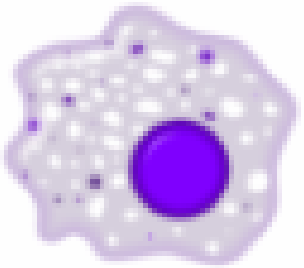
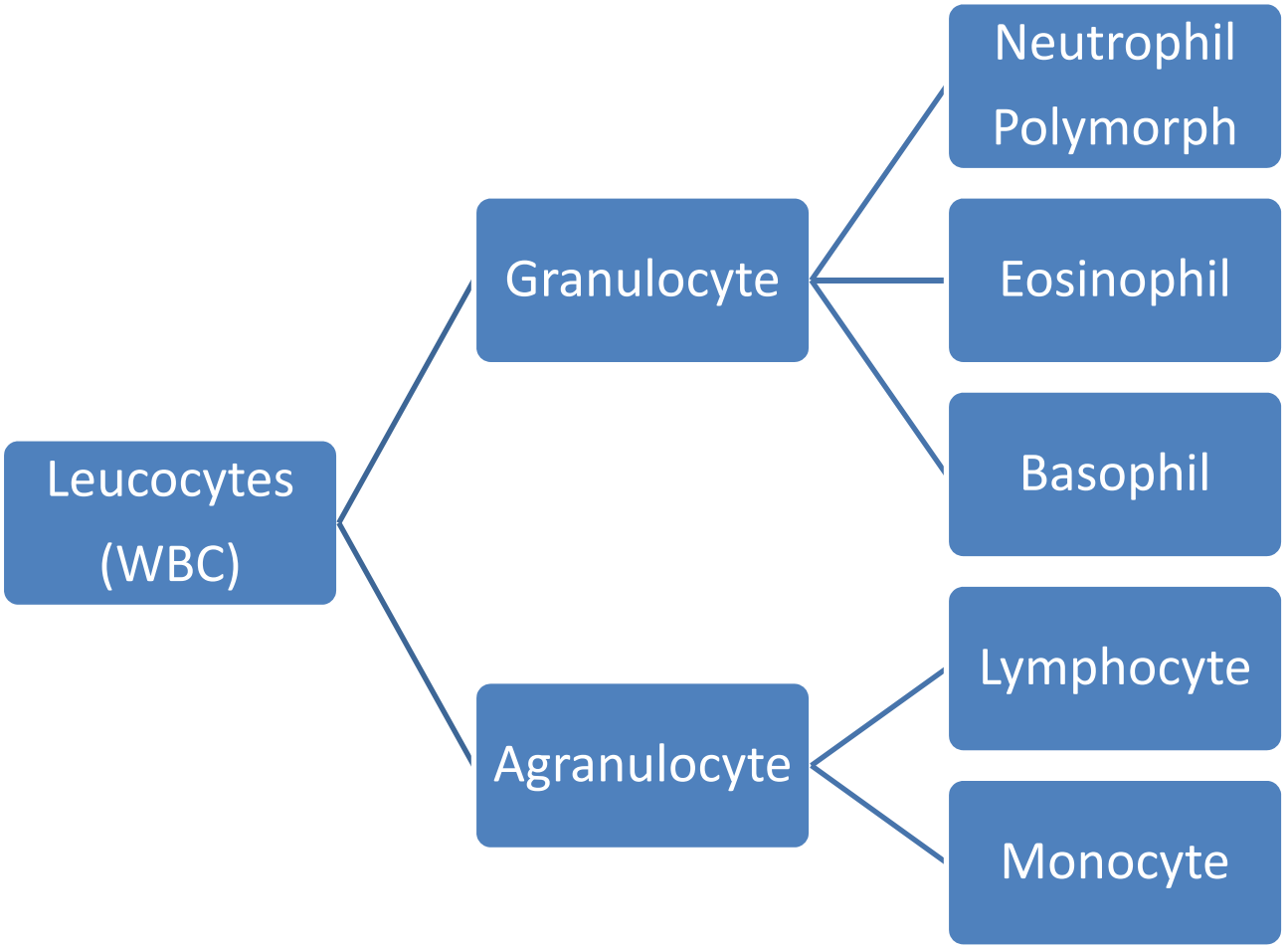
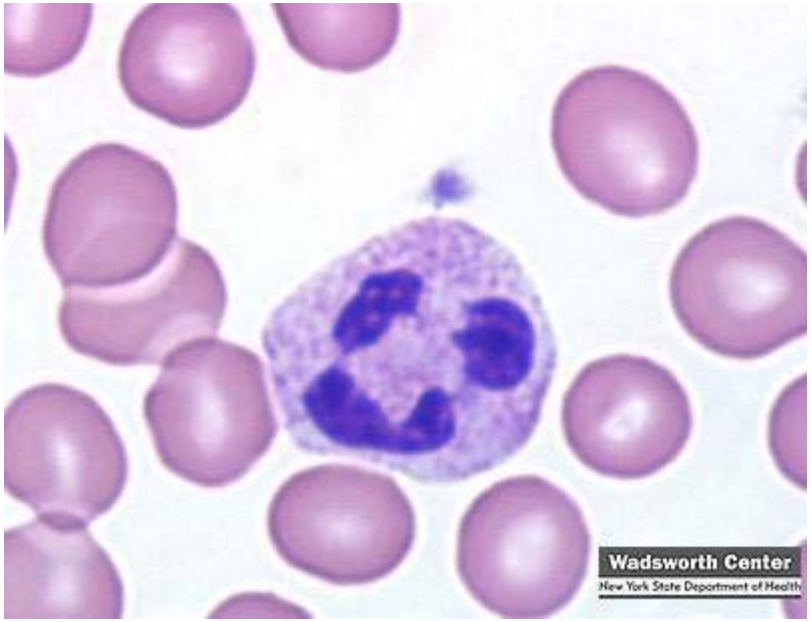
Leucocytes

Neutrophil	Eosinophil	Basophil
		
Lymphocyte	Monocyte	Macrophage
		

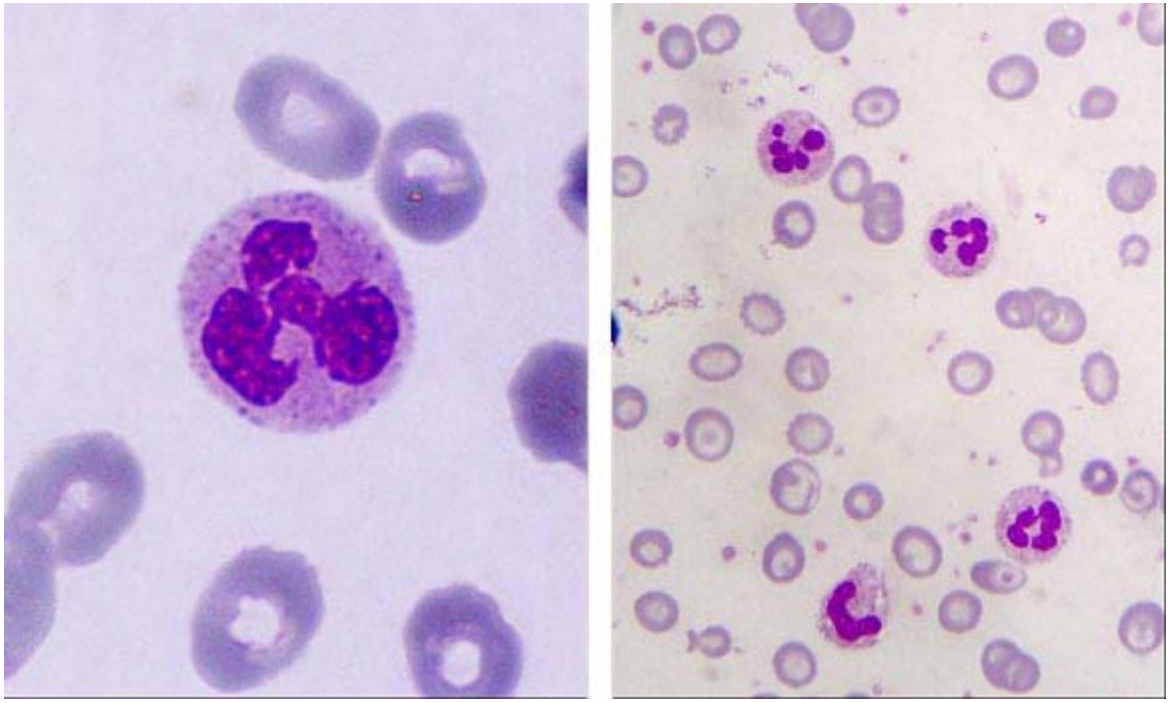
Classification



Neutrophil



Neutrophil



Neutrophil

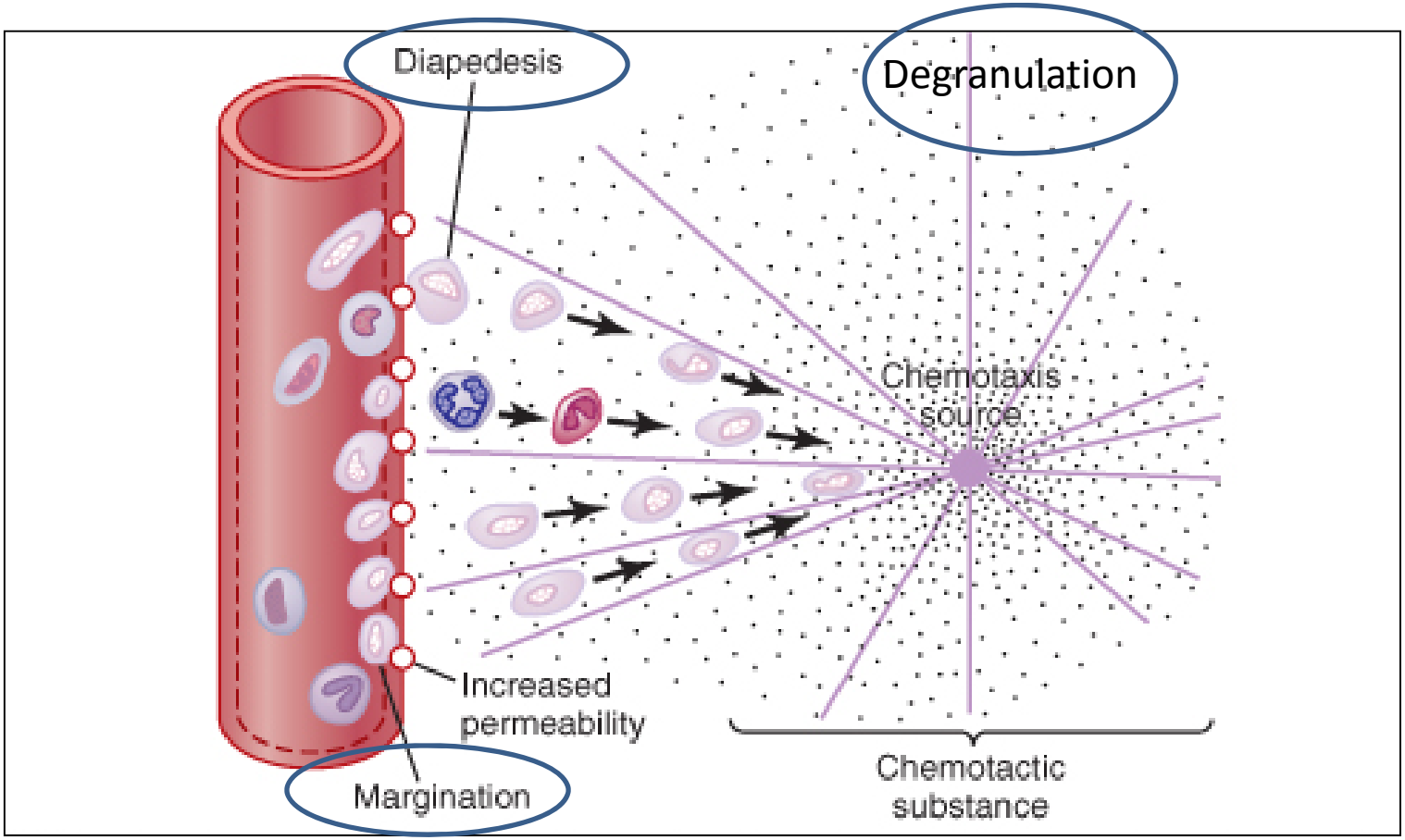
Cell type	Diameter (µm)	Nucleus	Cytoplasm	Cytoplasmic granules
Granulocyte	10-14	Blue violet 2-6 lobes, connected by chromatin thread Seen clearly through cytoplasm	Blue	Fine, closely packed, violet-pink, not seen separately Do not cover nucleus

Neutrophil granules

- Proteases: Cathepsin, phosphatases, nucleases, nucleotidases, beta glucuronidases elastase, metalloproteinase
- Lysozymes
- Myeloperoxidases: Catalyses conversion of Cl, Br, I to corresponding acids
- NADPH oxidase: superoxide, singlet oxygen, hydrogen peroxide
- Defensins: Antimocrobial antibiotics
- Oxidizing agents: hydroxide, halide, hypochlorite

Functions
Neutrophils & macrophages

- Defend against infection



Chemotactic substances

- Bacterial or viral toxins
- Degenerative products of inflammed tissues
- Reaction products of the complement complex

Phagocytosis

Selection of a substance for phagocytosis

- Rough surface
- Absence of protein coat
- Opsonization

Steps in phagocytosis

- Attachment to the particle
- Projecting pseudopodia all around it
- Pseudopodia on opposite side fuse
- Phagocytic vesicle / phagosome formed

Eosinophil

Cell type	Diameter (µm)	Nucleus	Cytoplasm	Cytoplasmic granules
Granulocyte	10-15	Blue –violet 2 lobes Lobes connected by thick chromatin strand Seen clearly through cytoplasm	Light pink-red	Large, coarse Uniform sized Brick red –orange Seen separately Do not cover nucleus

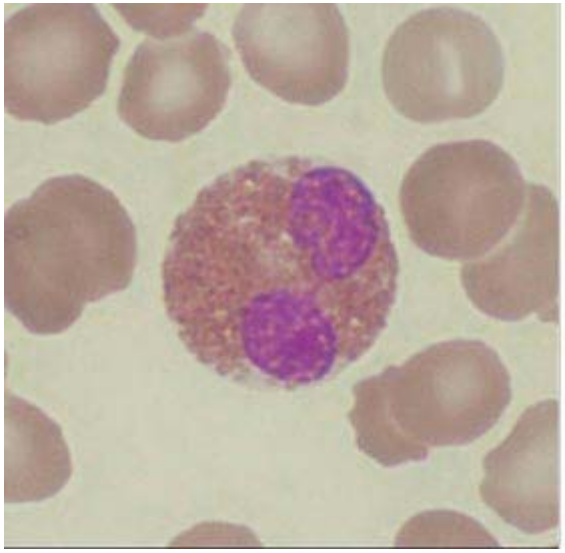
Composition of Eosinophil granules

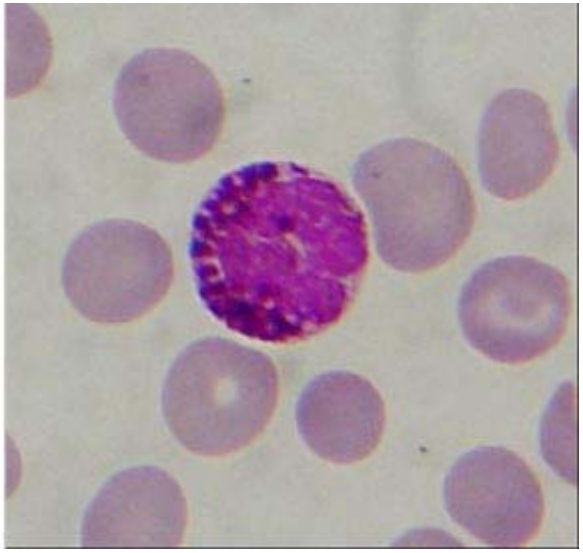
- MBP: Major basic protein: Disrupts the membrane of parasites&
- induces histamine release from
- Basophils& mast cells
- ECP: Eosinophilic cationic protein: Binds to heparin & neutralises its
- anticoagulant activity
- EDN: Eosinophil derived neurotoxin: Neurotoxin acting on myelinated nerves
- EPO: Eosinophil peroxidase: A sticky protein : adheres to host cells & mast cells

Functions of Eosinophils

- Specialise in dealing with parasites which are too large to be phagocytosed
- Chemicals released by degranulation are toxic to larvae of parasites
- Also degrade histamine & inhibit mast cell degranulation. Thus they decrease the intensity of allergic reactions
- Show phagocytosis but are less efficient than neutrophils
- Especially abundant in the mucosa of GIT, respiratory & urinary tracts

Eosinophil and Basophil





Basophil

Cell type	Diameter (µm)	Nucleus	Cytoplasm	Cytoplasmic granules
Granulocyte	10-15	Blue-violet S shaped Not clearly seen because overlaid with granules	Bluish	Large Very coarse Variable sized Deep purple Seen separately Completely fill the center & cover the nucleus

Granules contain

- Heparin
- Histamine, bradykinin, serotonin, eosinophil chemotactic factor slow reacting substance

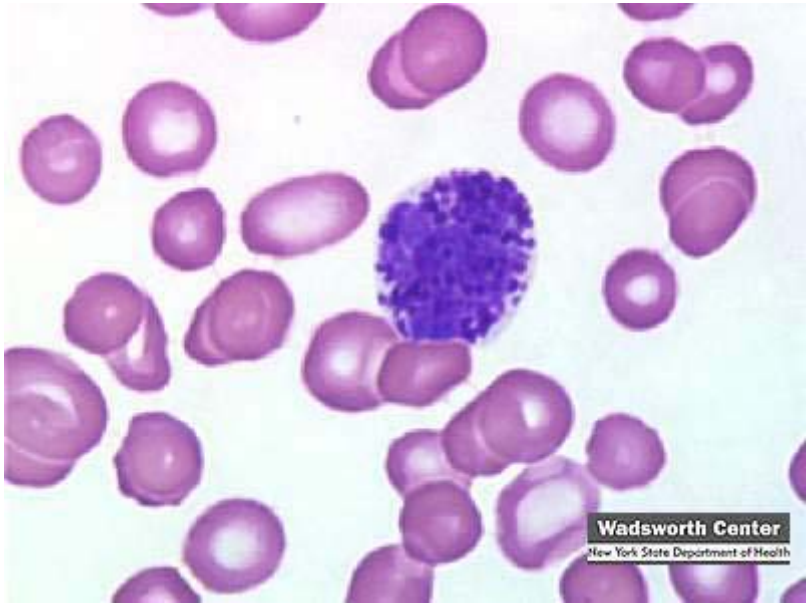
Functions of Basophils

- Essential for immediate type hypersensitivity reactions eg. Urticaria, rhinitis, anaphylactic shock
- IgE mediated allergies.

  They have receptors for the constant region of IgE molecules

  The allergen & the IgE molecule possibly form a complex with basophil which leads to allergic manifestations
- Protection from some parasitic infections eg Scabies
- Heparin release by basophils after a meal may facilitate post absorptive metabolism of dietary triglycerides by activating lipoprotein lipase

Basophil



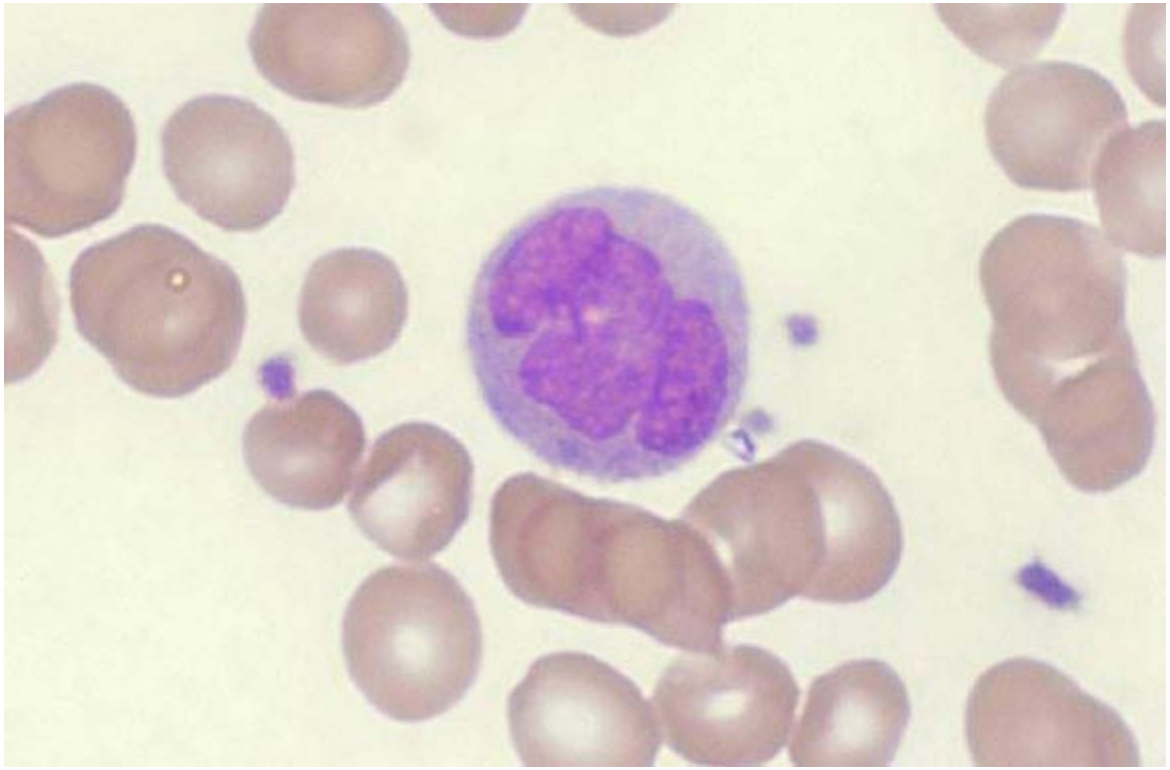
Monocyte

Cell type	Diameter (µm)	Nucleus	Cytoplasm	Cytoplasmic granules
Agranulocyte	12-20	Pale blue violet Large single Indented or horse shoe or kidney shaped	Abundant Frosty Slate blue Amount may be larger than that of nucleus	No visible granules

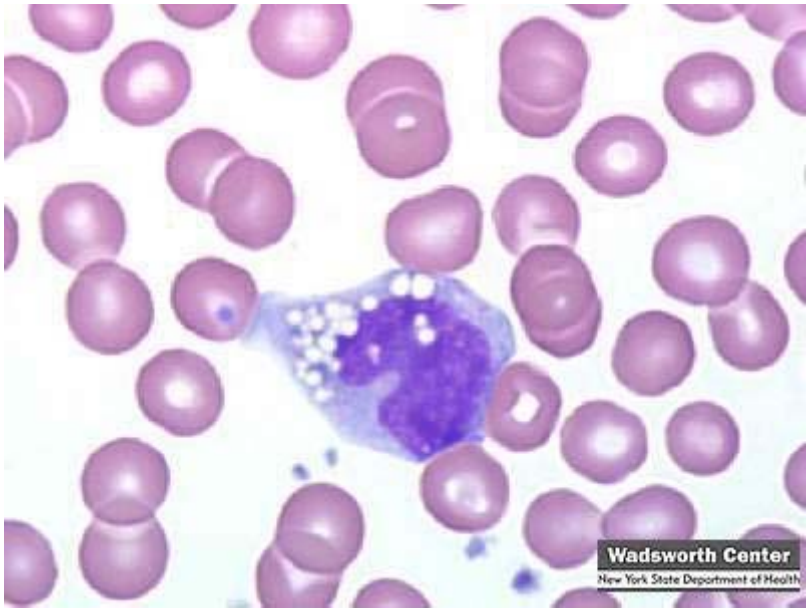
Functions of Moncytes/ Macrophages

- Major role in innate as well as acquired immunity. Become activated by lymphokines from T lymphocytes
- Phagocytose micro organisms as well as inert particles
- Secrete IL-1, TNF, G-CSF and M-CSF
- Process and present the antigen to immuno competent cells
- Destroy senescent RBCs and initiate catabolism of hemoglobin

Monocyte



Monocyte

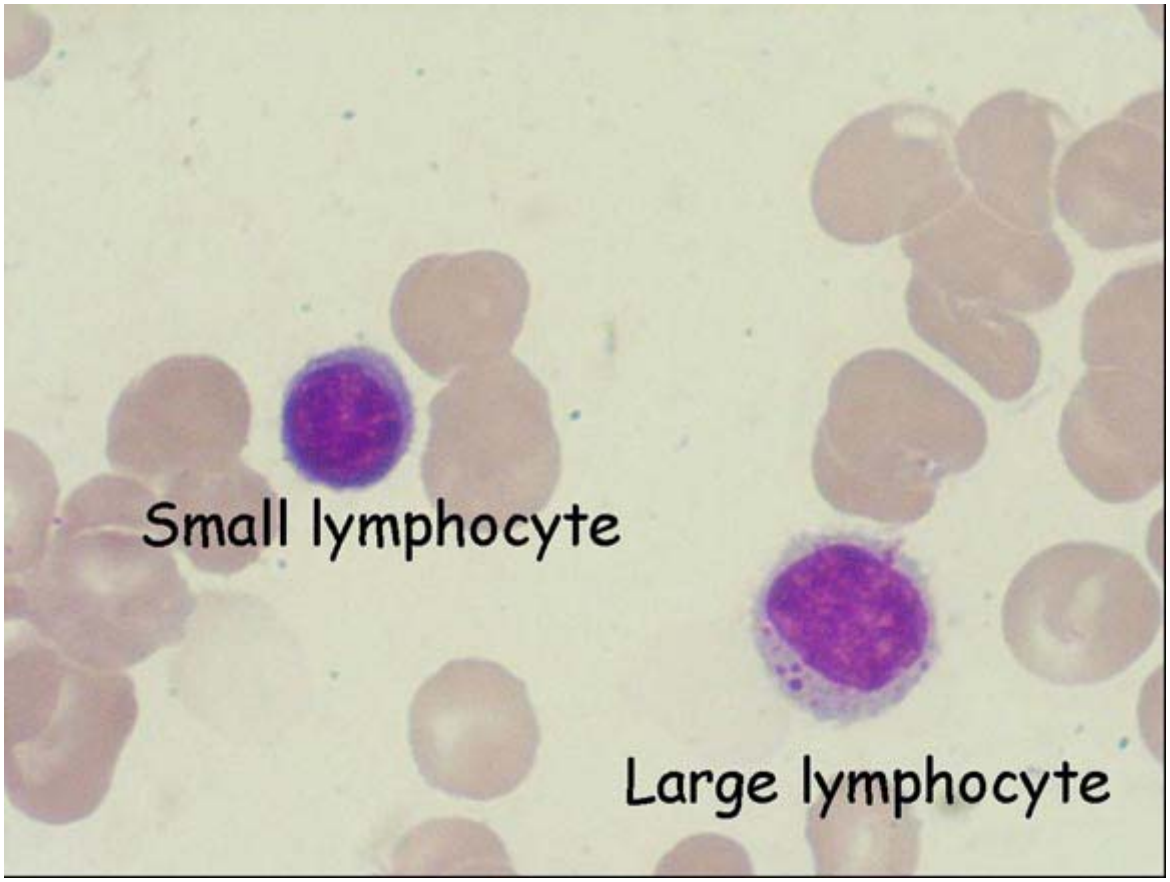


Lymphocyte

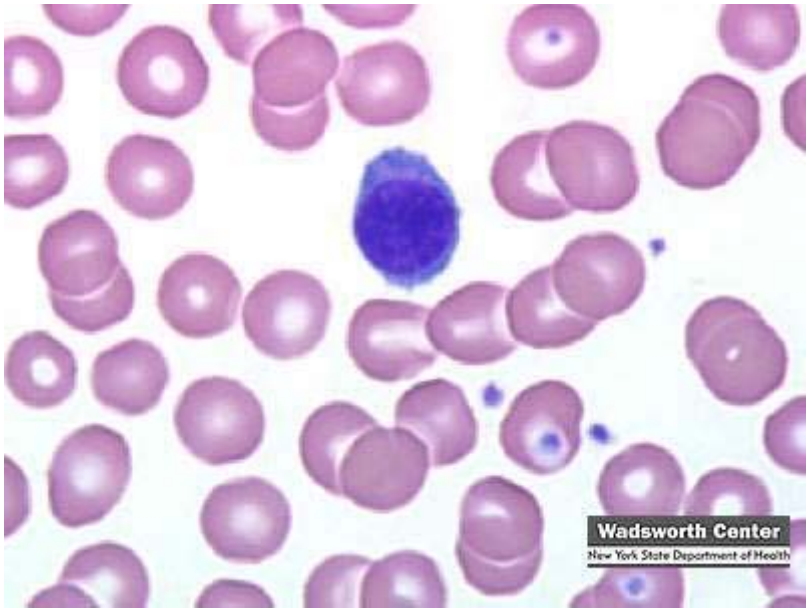
Cell type	Diameter (µm)	Nucleus	Cytoplasm	Cytoplasmic granules
Small Lymphocye Agranulocyte	7-9	Deep blue violet Single, large, round, almost fills the cell Condensed lumpy chromatin , gives ink spot appearance	Hardly visible Thin crescent of clear, light blue cytoplasm	No visible granules
Large lymphocyte Agranulocyte	10-15	Deep blue violet Single, large, round or oval Central or eccentric	Large crescent of clear, light blue cytoplasm Amount larger than in small lymphocyte	No visible granules

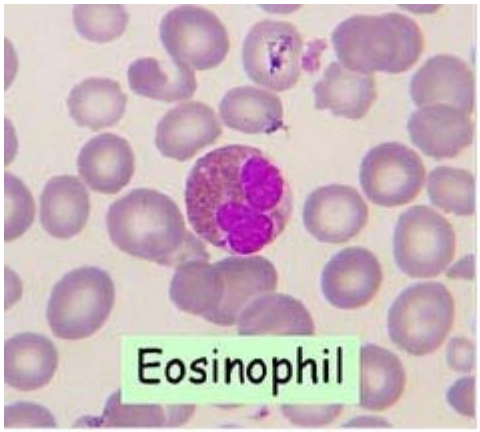
Functions of Lymphocytes

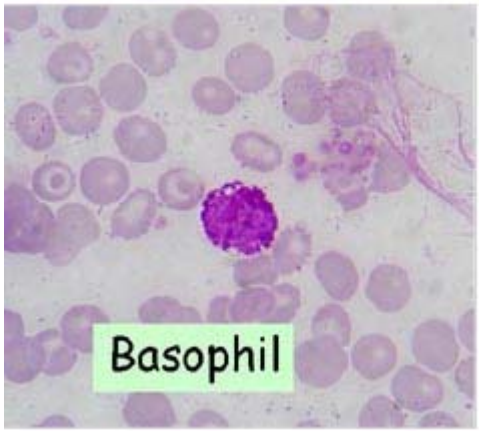
- Directly involved in specific acquired immunity
- T-lymphocytes: Cell mediated immunity
- B-lymphocytes: Humoral immunity

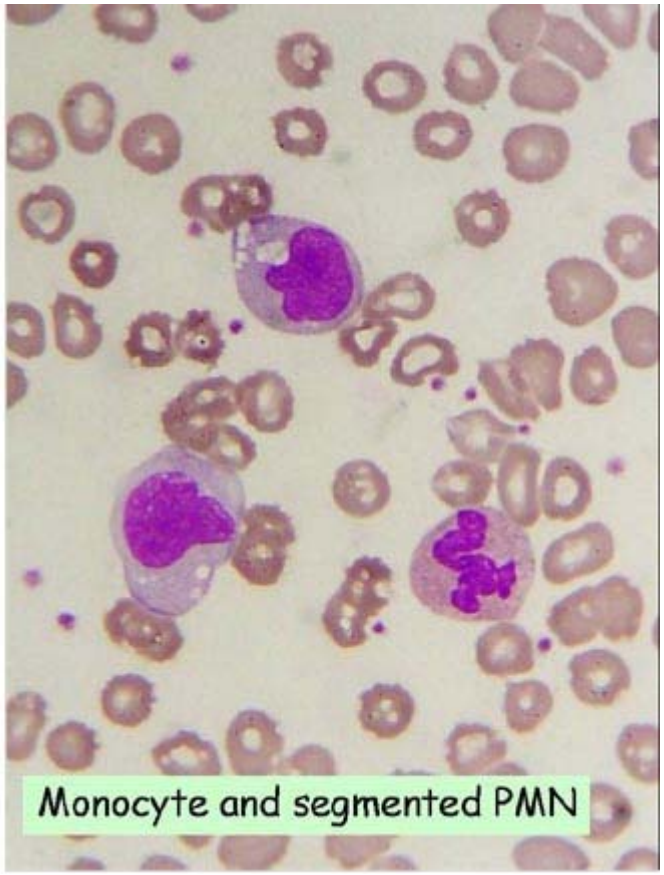

Small lymphocyte
Large lymphocyte

Lymphocyte

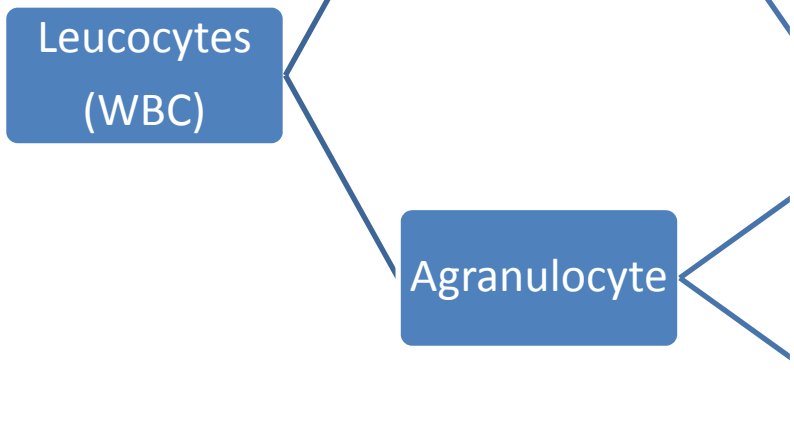



Eosinophil


Basophil

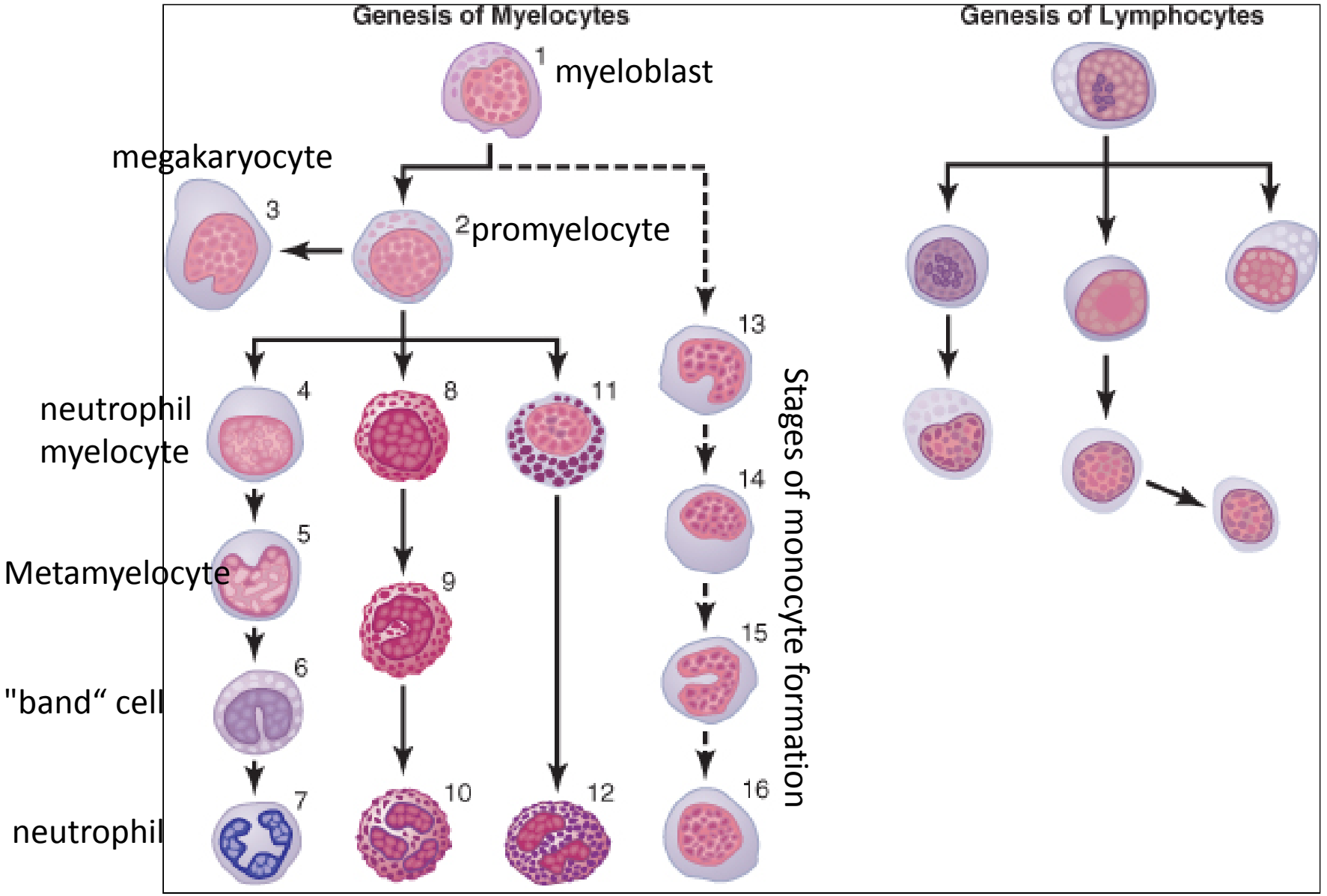

Monocyte and segmented PMN

Normal counts



DLC	Absolute counts
50-70%	3000-6000
1-4%	150-300
0-1%	0-100
20-40%	1500-4000
2-8%	300-600

Development



Factors affecting granulopoiesis

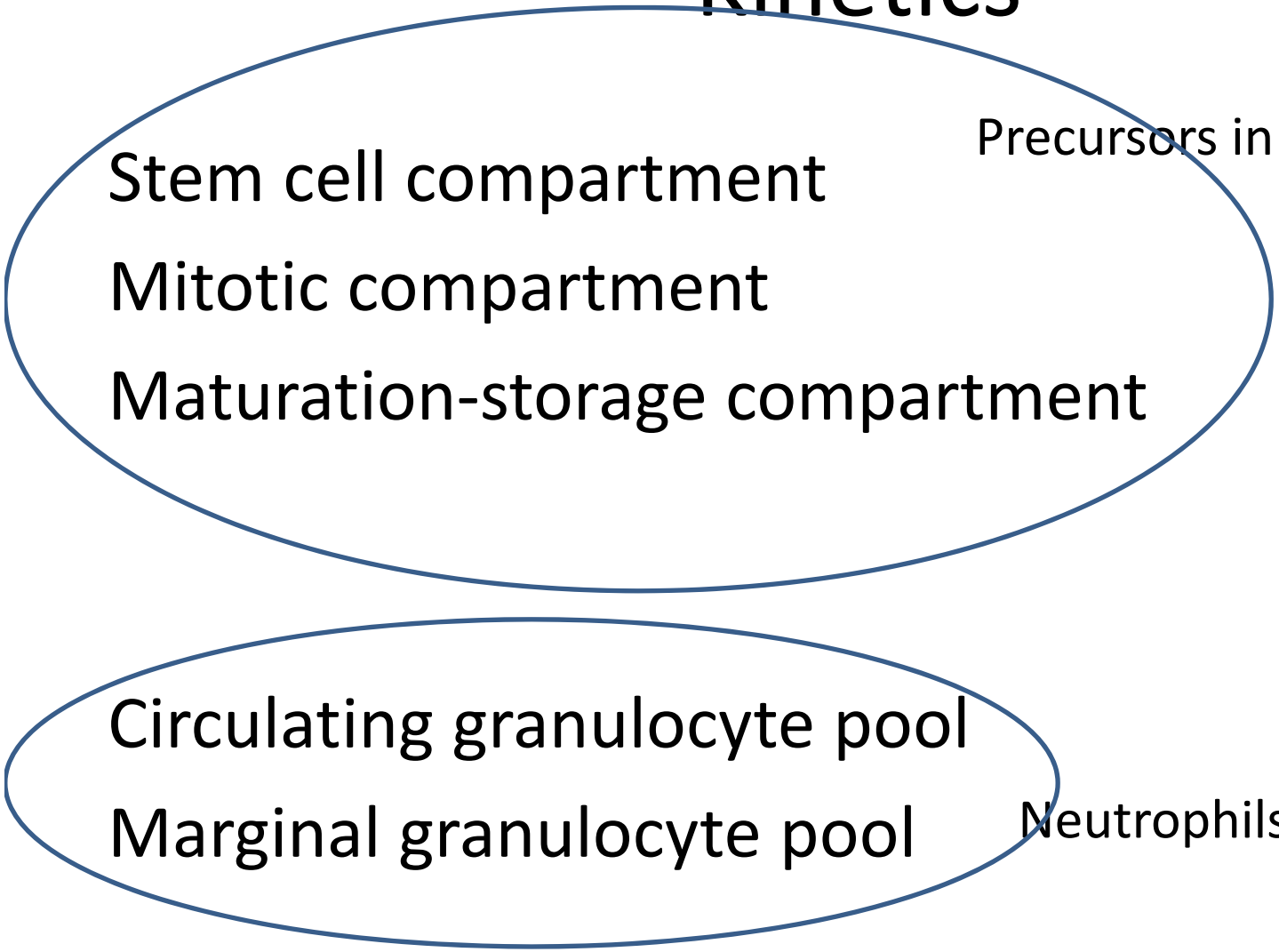
- Interleukin-1(IL-1): Produced by Macrophages. Acts on early progenitor cells to stimulate their proliferation, & also enhances the effector function of all types of leukocytes.
- Tumour necrosis factor: Produced by macrophages & has same function as IL-1
- Granulocyte-macrophage colony stimulating factor(GM-CSF): Produced by fibroblasts, vascular endothelial cells & T-lymphocytes

Factors affecting granulopoiesis

- Interleukin-3(IL-3)/ Multi-CSF: Produced by T lymphocytes. Stimulates the proliferation of all peripheral blood cells
- Granulocyte-Colony stimulating factor(G-CSF): Produced by monocytes, fibroblasts & endothelial cells.

  Stimulates proliferation of precursor cells of only ganulocyte series
- Macrophage-Colony stimulating factor(M-CSF): Produced by macrophages, fibroblasts & endothelial cells. Specifically stimulates the proliferation of precursors of macrophages.

Kinetics


Stem cell compartment
Mitotic compartment
Maturation-storage compartment
Precursors in the bone marrow
Circulating granulocyte pool
Marginal granulocyte pool
Neutrophils in blood

Life span

- Granulocytes: 4-8 hours in circulation

  Another 4-5 d in tissues where they are needed
- Monocytes: 10-20 hours in blood

  Months –years in tissues as macrophages
- Lymphocytes: weeks-months

  Recirculate from the lymph nodes & other lymphoid areas to blood and back again

Reticulo endothelial system/ Monocyte-macrophage cell system

- Tissue macrophages in the skin & subcutaneous tissue(Histiocytes)
- Macrophages in lymph nodes
- Alveolar macrophages in the Lung
- Macrophages in the Liver sinusoids(Kupffer cells)
- Macrophages of the Spleen & Bone marrow(Littoral cells)

Function of RES

The RES acts as a physiological unity

- Ingest & destroy RBCs and form & release blilrubin
- Also destroy leukocytes & platelets
- Ingest bacteria
- Ingest & process antigen which then stimulates antibody formation in the plasma cells

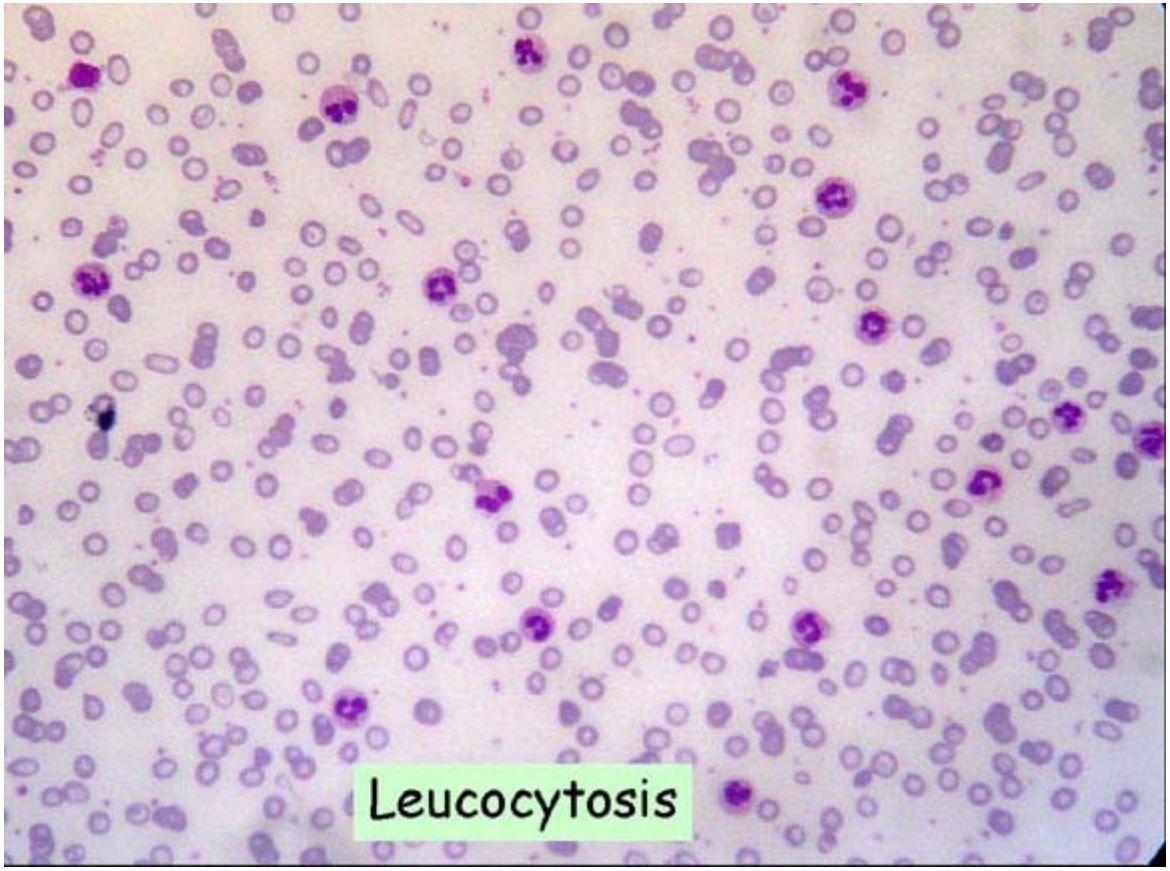
Inflammation: Role of Neutrophil & Macrophages

- First line of defence: Tissue macrophage, within first hour or so
- Second line of defence: Neutrophil invasion, within few hours & increase in the number of neutrophils in blood
- Third line of defence:Secondary macrophage invasion, within days
- Fourth line of defence: Increased production of granulocytes & monocytes

Feedback control of Macrophage & Neutrophil response

- TNF α
- IL-1
- GM-CSF
- G-CSF
- M-CSF

Leukocytosis



Physiological causes of Leukocytosis

- Newborn infants
- Food intake
- Exercise
- Pregnancy
- Sun exposure

Neutrophilia

- Acute infections: Especially localised infections due to Cocci(Streptococci, Staphylococci)
- Burns, acute hemorrhage, hemolysis, trauma, surgery
- Tissue necrosis: Myocardial infarction, pulmonary infarction
- Drugs: glucocorticoids
- Physiological causes: Muscular exercise, stress, after meals, pregnancy

Eosinophilia

- Allergic conditions: Asthma, urticaria, eczema, hay fever, food sensitivity
- Parasitic infections: hook worm, tape worm
- Drugs: Aspirin
- Tropical pulmonary eosinophilia

Basophilia

- Viral infections: Influenza
- Alllergic diseases

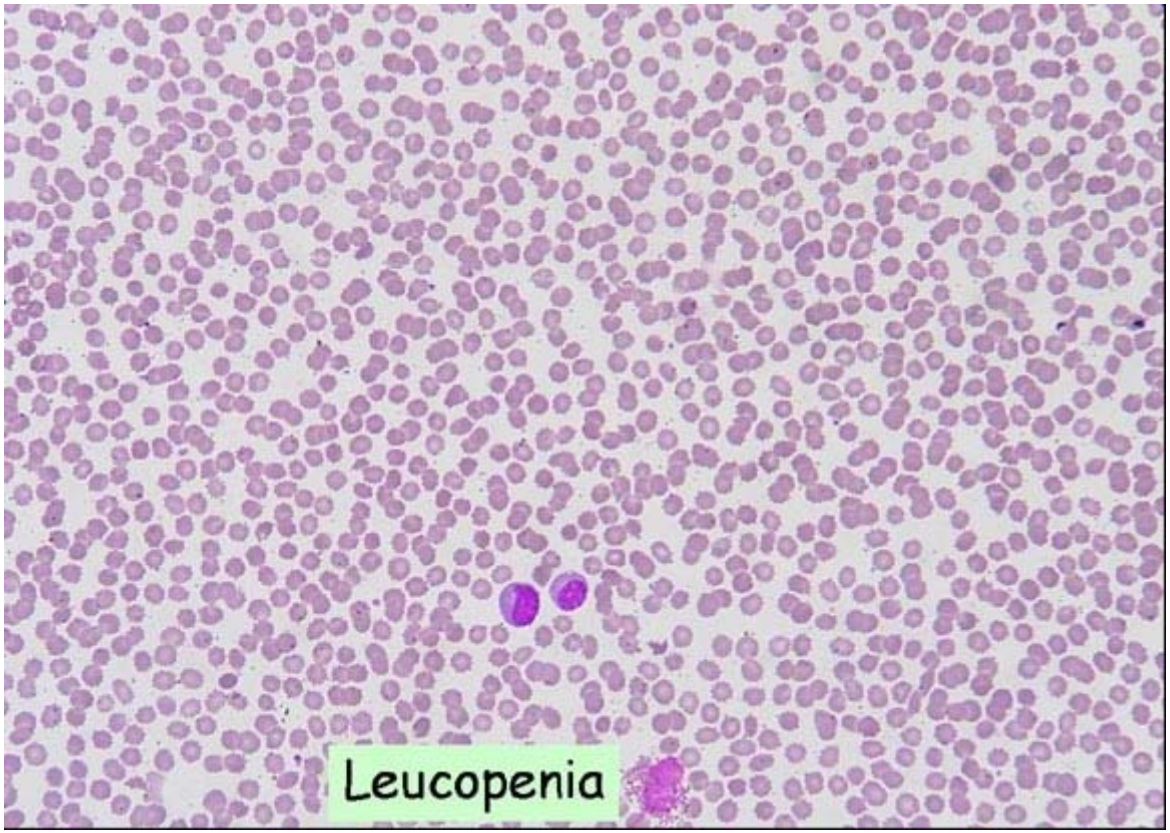
Monocytosis

- Malaria, kala azar, Rheumatoid arthritis, Leukemia

Lymphocytosis

- Infants &children, whooping cough, viral infections, autoimmune diseases
- Chronic infections: TB, Hepatitis, chronic cholecystitis, chronic pancreatitis

Leukopenia



Physiological causes of leukopenia

- Exposure to extreme cold

Neutropenia

- Typhoid & Paratyphoid infections
- Viral: Influenza
- AIDS
- Kala azar
- Bone marrow depression: Chloremphenicol, aspirin & radiations
- Autoimmune disease

Eosinopenia

- Acute stressful illness
- ACTH & glucocorticoid treatment
- Acute pyogenic conditions

Basopenia

- Acute pyogenic infections
- Glucocorticoid treatment

Monocytopenia

- Bone marrow depression

Lymphocytopenia

- Steroid treatment

Leukemia

Uncontrolled production of WBCs caused by cancerous mutation of a myelogenous or lymphogenous cell

Types

- Lymphocytic
- Myelogenous

Effects of leukemia on the body

- Metastatic growth of leukemic cells in abnormal areas of the body

Eg bone invasion leading to pain, easy fractures

- Spread to spleen, lymph nodes, liver & other vascular regions
- Infections
- Severe anemia
- Bleeding tendency

Host defense system

- Immune mechanisms
  - Antigen specific response
  - Generally takes several days
  - Key feature is memory for the antigen and a subsequent fulminant response
- Non immune mechanisms(Inflammation)
  - Not antigen specific
  - Immediate response beginning within minutes of an insult
  - No memory

Immunity

- Innate immunity
- Acquired(adaptive) immunity

    B cell mediated (Humoral)immunity

    T cell mediated(Cellular) immunity

Innate immunity

- Barriers
- Phagocytosis
- Activation of complement system
- Release of interferons
- Production of antibacterial peptides
- Other proteolytic cascades

Complement system

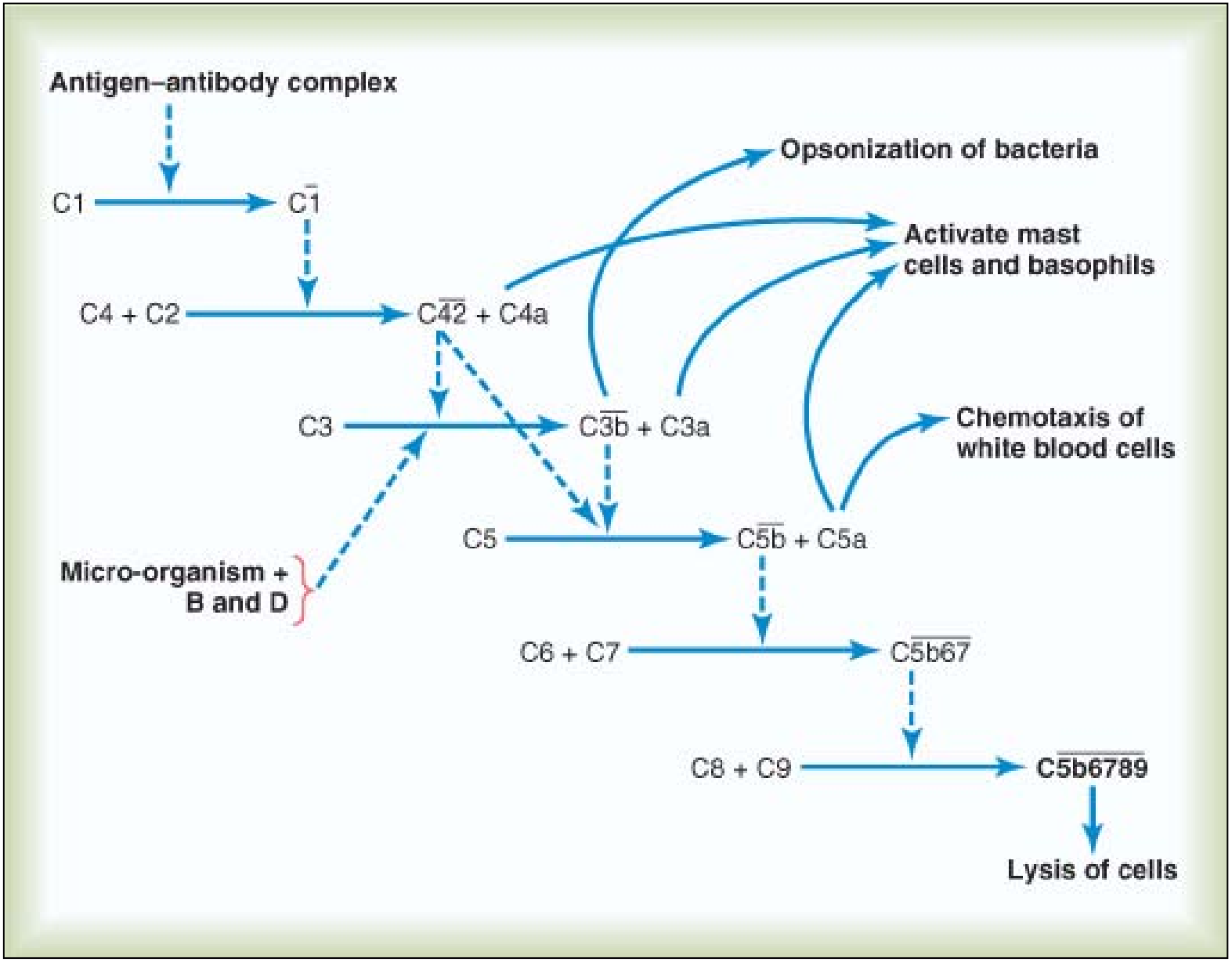
- Consists of about 20 proteins
- Activation via 3 different pathways
- **Classical pathway**: Triggered by immune complexes
- Mannose binding lectin pathway: Triggered when lectin binds mannose group in the bacteria
- Alternative/ Properdin pathway: Triggered by various viruses, bacteria, fungi & tumour cells

Complement system

Causes microbial destruction by 3 mechanisms

- ✓ Forming a coating over microorganisms which can then be easily phagocytosed since the phagocytes have receptors for the same complement components which coat the microorganisms
- ✓ Release of histamine by mast cells & basophil granules
- ✓ Membrane attack complex which punches holes (perforins) in the microbial wall

Classical pathway of complement activation



Interferons

- Released by virally infected cells

Functions

- Form a protective ring of uninfected cells thereby limiting the spread of infection
- Inhibit protein synthesis by interfering with translation and degradation of mRNA

Interferons….

Interferon	Cellular source	Major activity
Alpha	Virally infected cells	Induction of resistance of cells to viral infection
Beta	Virally infected cells	Induction of resistance of cells to viral infection
Gama	Helper T cells NK cells	Used to enhance killing of phagocytosed bacteria in chronic granulomatous disease

Cells mediating innate immunity

- Neutrophils
- Macrophages
- Natural killer cells(NK cells): Large lymphocytes that are not T cells but are cytotoxic

Natural killer cells

- Kill virally infected and tumour cells
- They have receptors for certain glycoproteins which appear on the surface of some virally infected cells
- Surface receptor KIR (Killer Inhibitory Receptor) interacts with HLA class I molecules on the surface of normal cells.
- Cancerous cells have modified ligands which do not bind properly with the receptor therefore the NK cells kill them

Major histocomptibility complex(MHC)

MHC gene is situated in a cluster of loci on chromosome 6

Its products the cell surface molecules are of 2 classes I &II

Term MHC is given because antigenic determinants on these 2 classes determine whether the organ or tissue transplants are recognised as self or foreign and thus are accepted or rejected

Human leukocyte antigen(HLA)

- In humans the MHC is referred to as HLA because it was first recognized by analyzing patterns of reactions of peripheral blood lymphocytes with sera containing antibodies to leukocytes
- HLA class I: Comprises A, B, C loci
- HLA class II: Comprises DR, DQ, DP loci
- HLA class III: Comprises complement region containing genes for complement components C2 & C4 of classical pathway, properdin factor B of alternate pathway & TNF alpha & beta

Acquired immunity

- Cytokines released from the cells mediating innate immunity activate cells of the acquired immune system

- Cellular immunity

  Mediated by T lymphocytes

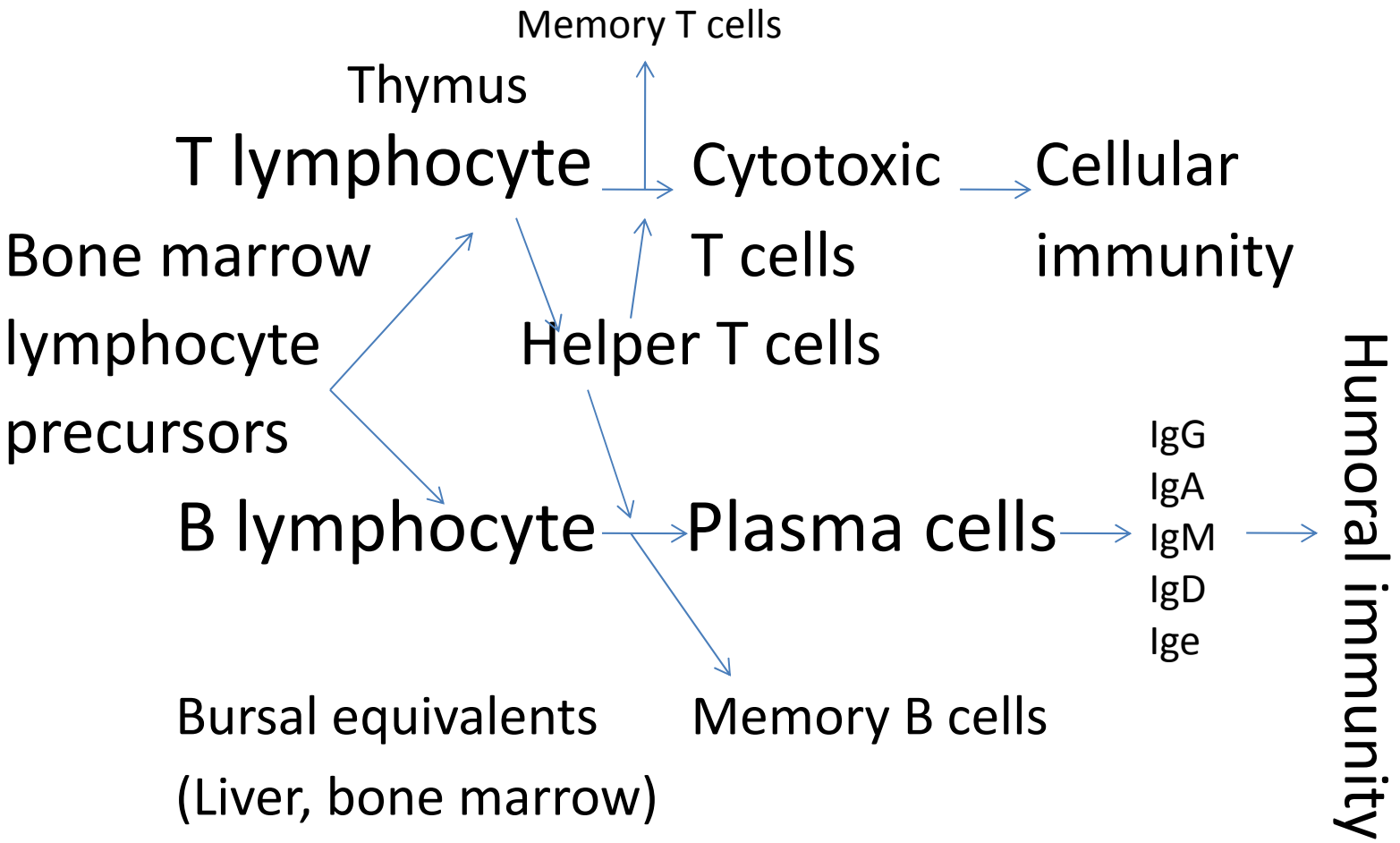
  Responsible for delayed allergic reactions and rejection of transplants of foreign tissue

- Humoral immunity

  Mediated by circulating immuglobulin antibodies in the gamma globulin fraction of plasma proteins

  Major defense against bacterial infections

Development of the immune system



“Self recognition process” - Burnet

- All potentially antigenic material encountered in fetal life whether ‘self’ or ‘not self’ elicits no response either then or subsequently.

Clonal selection theory- Burnet

- It proposes that certain lymphocytes known as immunologically competent are genetically endowed with the capacity to respond to one or very few molecules of specific antigenic pattern by making antibodies against that pattern
- Antigenic stimulation thus produces a “clone” of cells , all of similar specific reactivity

Immune tolerance

- Ehrlich: First to emphasize that animals do not usually make any immunological response to their own plasma proteins or tissue cells although they are excellent antigens in other species
- Burnet & Fenner: Proposed an explanation

  In utero during the period of immunological immaturity all the potential antigens that the lymphocytes come in contact are recognized as “self”

T lymphocyte : Ontogeny & functions

T cell precursors(Bone marrow)

Extreme high rate of division(Thymic Cortex)

Early thymocyte (Majority die within thymic cortex)

Minority migrate to medulla of thymus & undergo differentiation

Possess a T cell surface antigen receptor which has following recognition properties

T lymphocyte : Ontogeny & functions…

Properties of T cell surface antigen

- Distinguishes between foreign MHC proteins & self MHC proteins reacting with the former and tolerating the latter
- The receptor does not react with a self MHC protein in the absence of antigen but it recognizes & reacts with a complex made up of an antigen derived peptide bound to a self MHC protein
- The receptor of each T cell will be clonotypic, i.e. will recognize only a single specific immunological determinant (epitope) of an antigen derived peptide bound to an MHC protein

Antigen recognition & T cell activation

T cells released from thymus

Each cell programmed to recognize a specific antigenic determinant

T cell

Activated by antigen

Antigen activated cell

Receptors for IL-2

Proliferation of clones of daughter cells

Macrophages

Il-1/IL-6

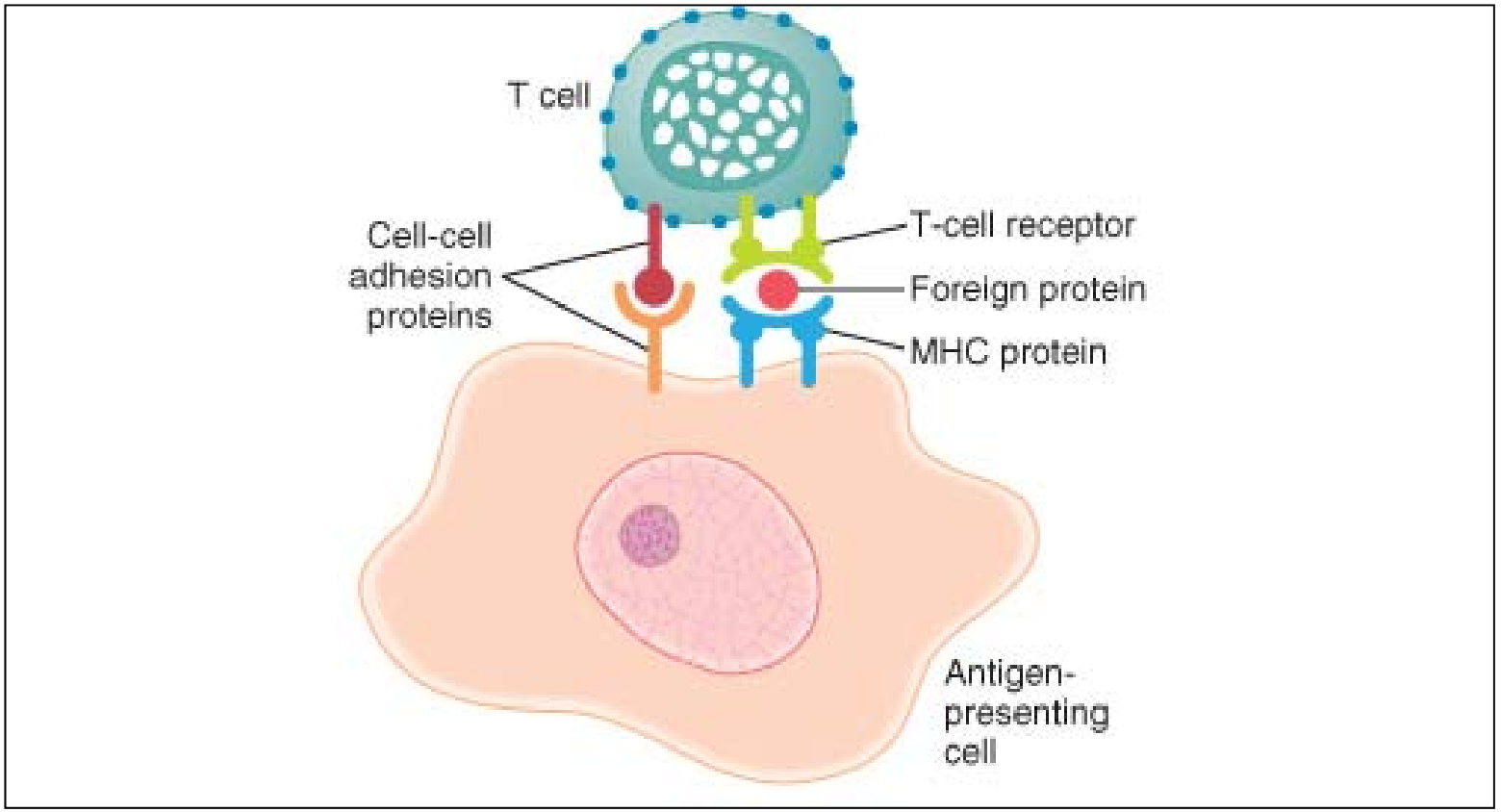
T lymphocyte : Ontogeny & functions…

Effector functions

- Helper T cells help B cells to secrete antibody
- Helper T cells mediate delayed hypersensitivity reactions
- Suppressor T cells keep immune responses from escaping control by damping the proliferation & differentiation of antibody producing B cells & cytotoxic T cells
- Activated T cells secrete lymphokines

Types and functions of T lymphocytes

- Cytotoxic T cells: Destroy transplanted & other foreign cells
- Helper T cells: Help in the development of the former
- ✓ TH1 cells: secrete IL-2 & gamma interferon, concerned primarily with cellular immunity
- ✓ TH2 cells: Secrete IL-4 & IL-5, interact primarily with B cells in relation to humoral immunity
- Memory T cells: Produce an accelerated response to a second exposure of antigen
- Suppressor T cells: Help in immune tolerance



Activation of T cells requires interaction of T-cell receptors with an antigen (foreign protein) that is transported to the surface of the antigen-presenting cell by a major histocompatibility complex (MHC) protein. Cell-to-cell adhesion proteins enable the T cell to bind to the antigen-presenting cell long enough to become activated.

MHC restriction

- T cells respond to antigen on the macrophages & other cells only when they are presented along with the self MHC antigen
- CD4 positive lymphocyte(Helper T cells) recognize class II antigen
- CD 8 positive lymphocytes(Cytotoxic T cells) recognize class I antigen

HLA antigens and their role

- HLA class I

Found on the surface of virtually all nucleated cells

Principal antigens responsible for graft rejection & cell mediated cytolysis

- HLA class II

  Found only on cells of immune system- macrophages, dendritic cells, activated T cells & B cells

  Responsible for graft vs host response & immediate leukocyte reactions

- HLA class III

Heterogenous

HLA antigens and their role…

- The MHC system was originally identified in the context of transplantation which is an artificial event
- In the natural state they serve as

✓ Cell surface markers: that help infected cells to signal cytotoxic & helper T cells

✓ Enormous polymorphism of MHC gene helps maximize protection against mirobial infections

✓ Increase the specificity of the self antigen thus it prevents microbes with similar genetic makeup to sneak past by molecular mimicry

B cell ontogeny & functions

B cell differentiation from precursor to plasma cell occurs in 2 phases

- Non antigen driven phase: Occurs within central lymphoid tissue

Very rapid cell division & rapid cell death also

- Rearranement of a functional gene for the heavy chain(IgM)
- Synthesis of a heavy chain of IgM
- Rearrangement of a gene for light chain synthesis
- Synthesis of light chain
- Next a second class of heavy chain (IgG) is also made

B cell ontogeny & functions…

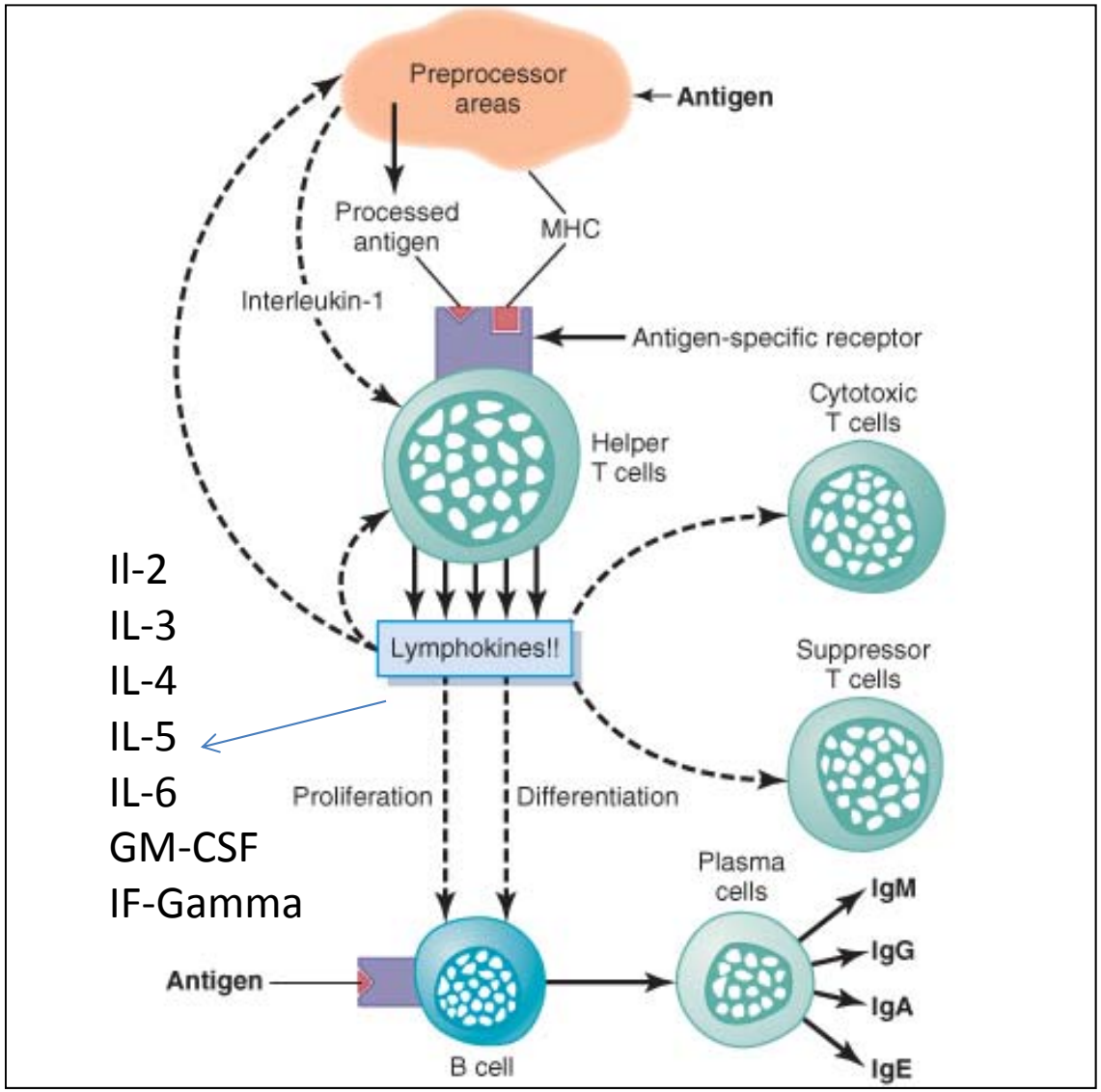
- Antigen dependent phase

Occurs in peripheral lymphoid tissue

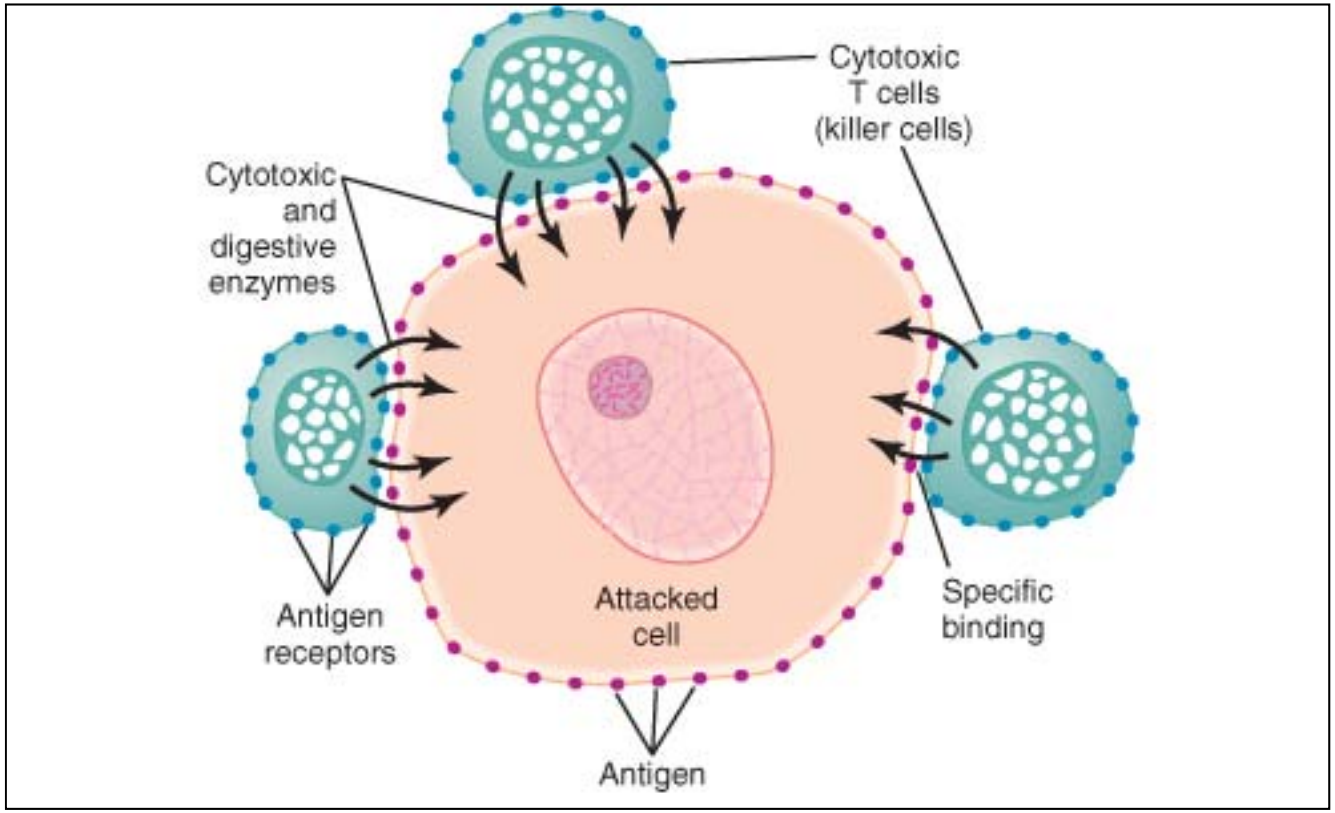
Programmed to recognize antigen in the presence of cytokines from activated T cells and macrophages

This leads to formation of

- IgM secreting cell
- Another B cell whose surface IgM &IgD are replaced with surface IgG, IgA or IgE
- B cell memory pool



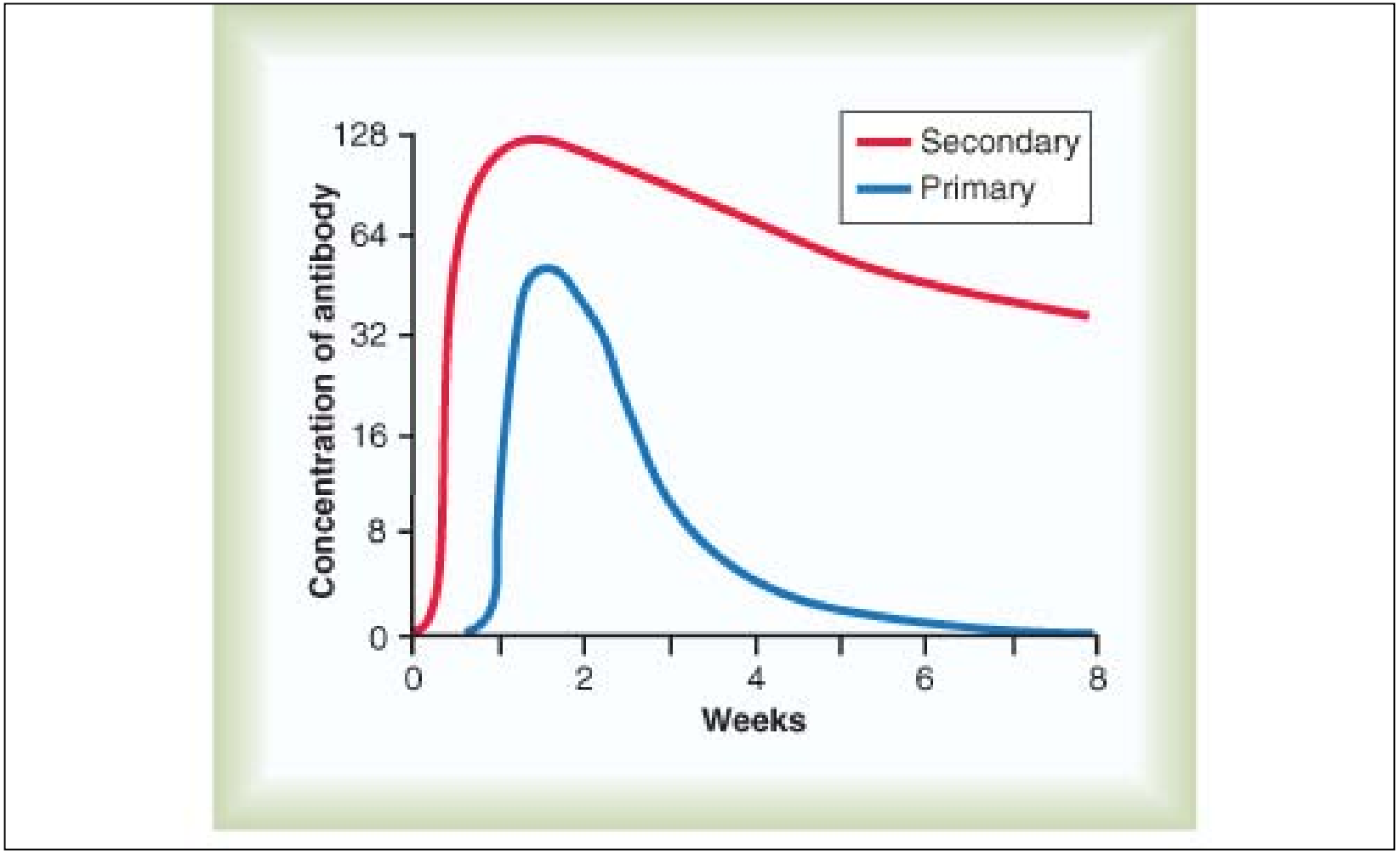
Regulation of the immune system, emphasizing a pivotal role of the helper T cells



Direct destruction of an invading cell by sensitized lymphocytes (cytotoxic T cells).

Types and functions of B lymphocytes

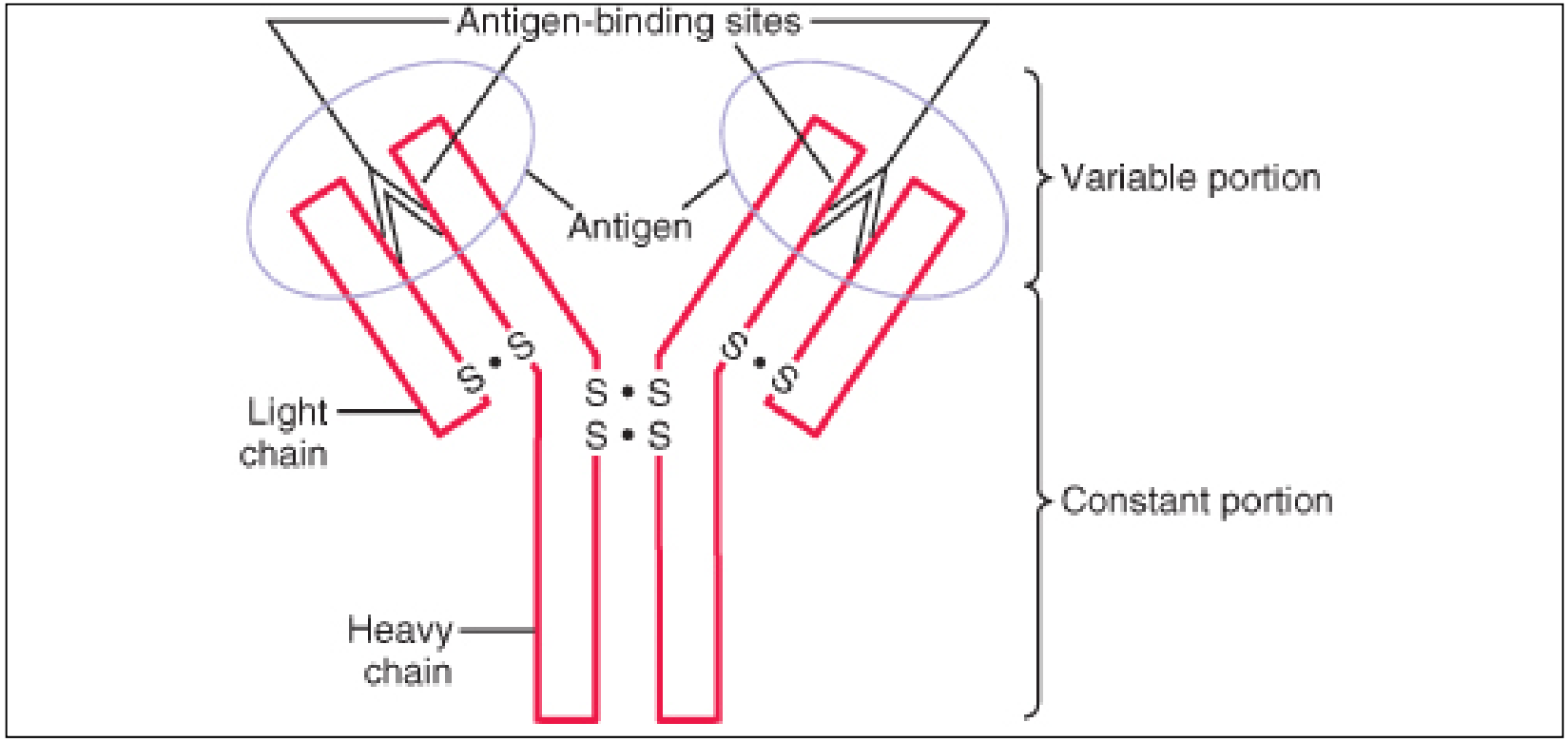
- Plasma cells which form antibodies
- Memory B cells



Time course of the antibody response in the circulating blood to a primary injection of antigen and to a secondary injection several months later.

Nature of antibodies

- Gamma globulins
- Molecular weight: 160,000 – 970,000
- Constitute 20% of all plasma proteins



Structure of antibody

Structure of immunoglobulins

- Monomer:Basic unit : 2light+2 heavy chains
- Polymers: 2-5 basic units + J chain that holds the units together
- Amino acids of L and H chains form loops known as domains
- Variable region : NH2 terminal
- Hypervariable region: amino acid sequences unique to that polypeptide chain
- Constant portion: carboxy terminal

Structure of immunoglobulins….

- Two types of light chains: kappa and lambda
- Five types of heavy chains
- Ig G: Subtypes γ 1, γ2, γ3, γ4
- Ig A: Subtypes α1, α2
- Ig M: Subtypes μ1, μ2
- Ig D: δ
- Ig E: ε

Structure of antibody

Constant portion determines:

- Diffusivity of the antibody
- Adherence to specific structures within tissues
- Attachment to complement complex
- Passage through membranes

Variable portion determines:

- Specificity to a particular type of antigen

Specificity of antibodies

- Due to unique structural organization of amino acids in the variable portion of both the light & heavy chain
- The amino acid organization has a different stearic shape for each antigen
- A highly specific antibody is strongly held to the antigen by several bonds

✓ Hydrophobic bond

✓ Hydrogen bond

✓ Ionic bond

✓ Van der Waals forces

Cytokines

- Hormone like molecules
- Secreted by: Lymphocytes, macrophages, endothelial cells, neurons, glial cells
- Eg. IL1, IL2, IL4, IL5, IL6, Il8, IL11, IL12, TNF-alpha
- Actions

  Autocrine

  Paracrine

  Endocrine

Emperical categorization

Emperical categorization

- Immunoregulatory cytokines: Involved in activation growth & differentiation of Lymphocytes & Monocytes

  Eg. IL-2, IL-4, TGF-beta
- Proinflammatory cytokines: Produced predominantly by mononuclear phagocytes in response to infectious agents

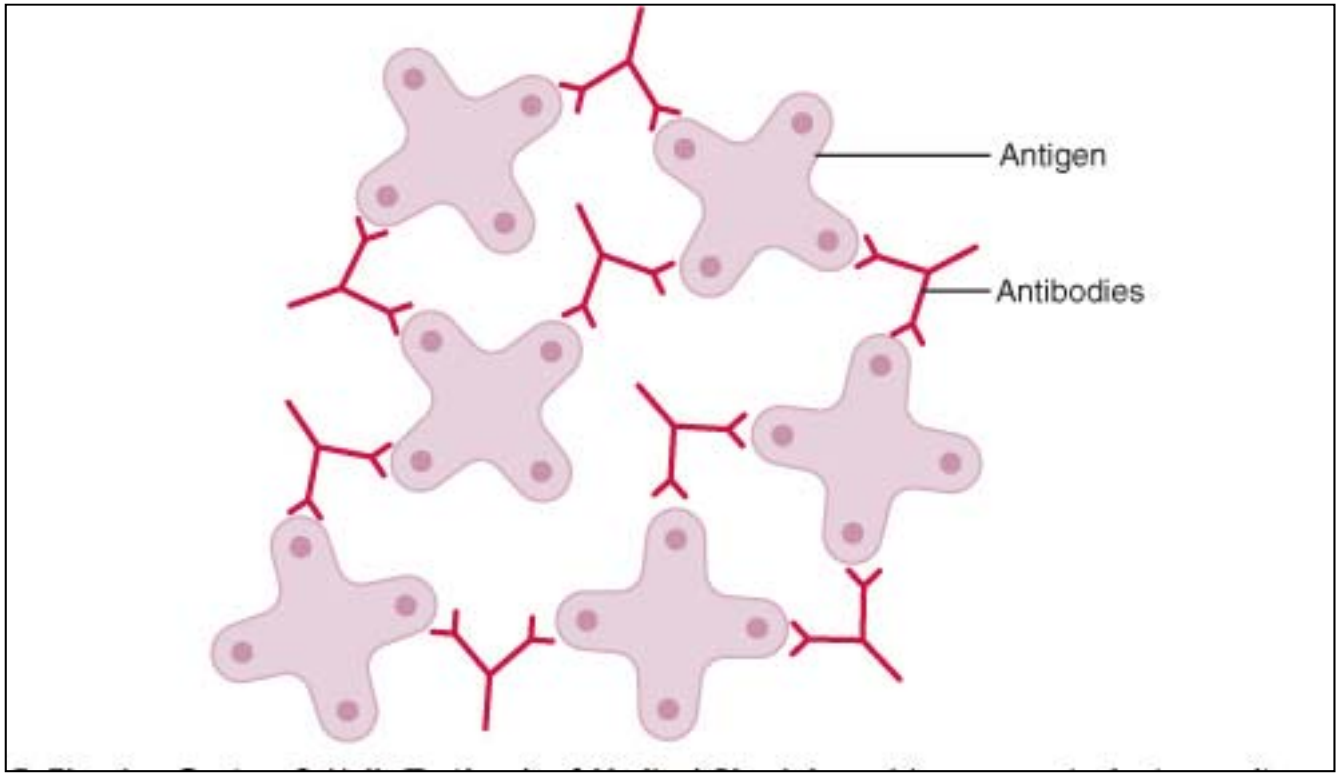
  Eg. IL-1, TNF alpha, IL-6, IL-8
- Regulating immature leukocyte growth & differentiation

  Eg. IL-3, IL-7, GM-CSF

Who name	Function	Heavy Chain (Sub classes)	Structure	Properties
IgG	Complement activation	γ 1, γ2, γ3, γ4	Monomer	Can cross placenta Secreted in milk, saliva, nasal, lacrimal secretions Not in CSF Appear late in response to infection
Ig A	Localized protection in external secretions	α1, α2	Monomer, Dimer	Mucosal defense
IgM	Complement activation	μ1, μ2	Pentamer	Intravascular Appears early in response to infection Much more effective than IgG

Who name	Function	Heavy chain	Structure	Properties
Ig D	Antigen recognition by B cells	δ	Monomer	Found in trace amounts in plasma Function unknown Acts as antigen recognition site on the surface of B cells
Ig E	Reagin activity Release histamine from basophils & mast cells	ε	Monomer	Secreted in helminthic infections Atopic allergy Can invoke mast cell triggered immediate hypersensitivity reactions

Mechanism of action of antibodies



Direct action of antibody on invading agent

Direct action

- Agglutination: Multiple large particles with antigen on their surface are bound together in a clump
- Precipitation: Complexes of antigen & antibody become so large that they become insoluble
- Neutralization: The antibody covers the toxic site of antigen
- Lysis: Potent antibodies are capable of directly attacking membranes of pathogens and thus causing rupture of the organism

Complement system for antibody action

Classical pathway effects

- Opsonization & phagocytosis
- Lysis
- Agglutination
- Neutralization
- Chemotaxis
- Activation of mast cells & basophils
- Inflammatory effects

Antigen presenting cells(APC)

- Specialized cells in the lymph nodes, spleen & Langerhan's cells in the skin
- In APC the products of antigen digestion are complexed to products of MHC (Major Histocompatibility Gene) and presented on the surface of the cell
- MHC gene – chromosome 6
- Its product is a glycoprotein
- Class I antigen is found in all nucleated cells
- Class II antigen is found on APC, B & T lymphocytes

Lymphoid tissue

Embryological development

Lymphopoiesis first appears at 3 months of IUL in the fetal liver & thymus

At birth

Thymus weighs 10-12 g

Cell mediated immunity is well developed so that graft rejection can occur

Peripheral lymphoid tissue(lymph nodes, spleen, gut associated lymphoid tissue) is very slightly developed

IgA & IgE: Traces

IgM: Formed before birth & present in significant amounts

IgG: High amount but is maternally derived

Lymphoid tissue…

Central lymphoid tissue: Thymus & bone marrow

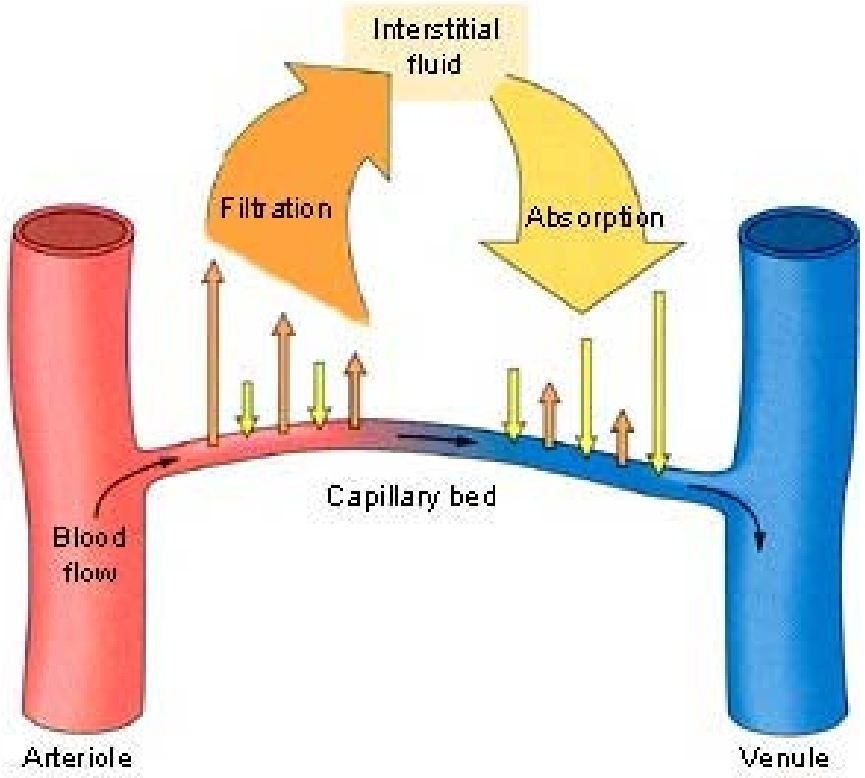
Peripheral lymphoid tissue

- Lymph nodes
- Spleen
- Ring of tonsillar tissue in oropharynx
- Submucosal accumulation of lymphocytes in the respiratory tract, urinary tract & gut(Peyer's patches)

Small lymphocytes: Quiescent lymphocytes of the peripheral lymphoid tissue

Large lymphocytes: After exposure to antigen

Lymphatic system



Proteins exert colloidal osmotic pressure of 25 mmHg

Lymphatic system

Function

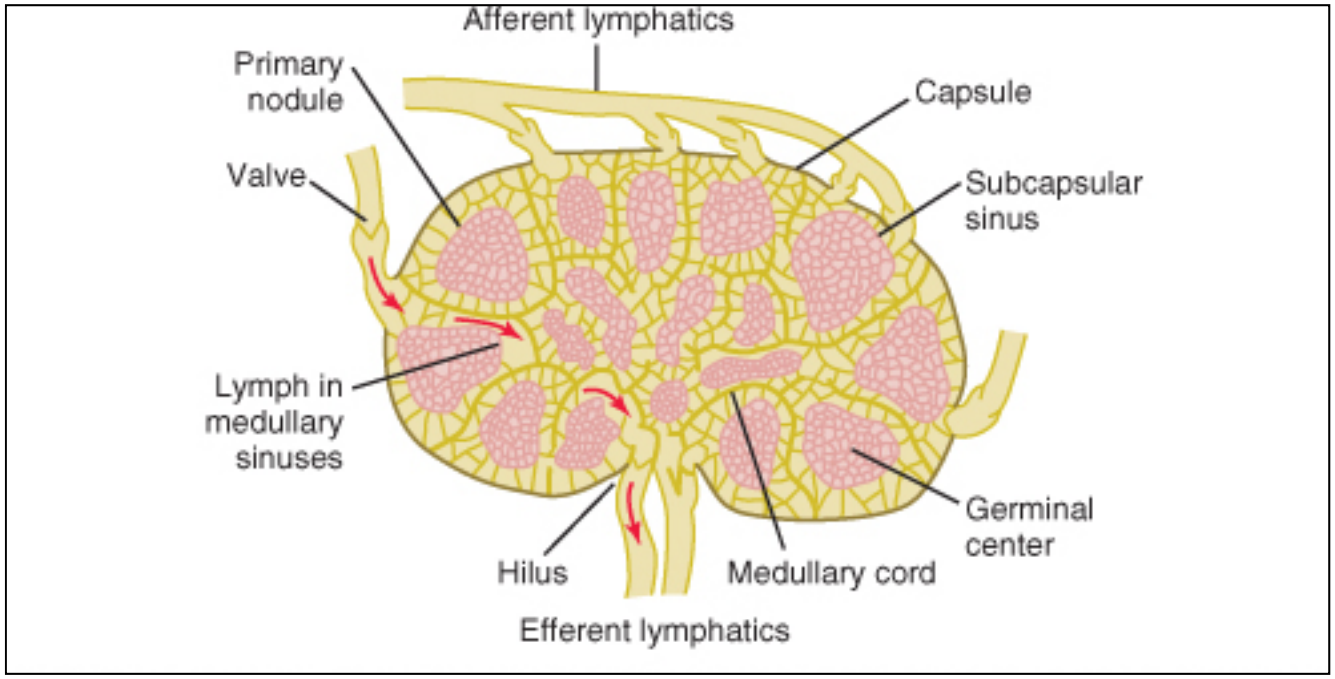
- To return excess tissue fluid and protein to the intravascular compartment by pinocytosis
- As a transport mechanism to remove RBCs, bacteria
- Filtering system in the lymph nodes

Endothelium of the lymphatic capillaries is similar to that of blood capillaries with little or no basement membrane

Diameter variable depending on state of function and the organ

Lymph pump (for anterograde flow)

- Arteriolar vasocinstriction
- Arteriolar pulsation
- Muscle contraction
- Retrograde flow is prevented by lymph valves


Afferent lymphatics
Primary nodule
Capsule
Valve
Subcapsular sinus
Lymph in medullary sinuses
Germinal center
Hilus
Medullary cord
Efferent lymphatics

Lymph node

Location of T & B lymphocytes in adults

	T cells	B cells
Peripheral blood	60-80%	20-30%
Thoracic duct	85-90%	10-15%
Lymph nodes	Paracortical	Subcapsular Germinal center Medullary cords
Spleen	Periarteriolar sheath	Germinal centers Red pulp Around periarteriolar sheath

- Lymphatics are most abundant on the undersurface of the diaphragm
- Lymphatic system exists in all organd except

  CNS

  Cornea

Composition of lymph

- Protein concentration lower than plasma
- All clotting factors present , some synthesised by the liver are in higher concentration in the Hepatic lymph
- Antibodies
- Electrolyte concentration : Positive ions are slightly less and negative ions are slightly more
- Lipids: Chylomicrons will be higher after a fatty meal
- Cells: Lymphocytes, monoctye/macrophage, granulocyte

- Clonal anergy/ immunological silence:

  When B and T lymphocytes in fetal life are exposed to potentially antigenic materials in the tissues, they are subsequently unable to make a specific immune response to these material i.e. B and T lymphocytes enter a prolonged hyporesponsive phase

- Clonal abortion/ negative selection

  Many of the not/anti self lymphocytes are eliminated in the thymus during their early development. Suppressor T cells keep the development of such not self antibodies in check

Autoimmunization

- It can occur when new antigenic material are formed after the period of immunological immaturity

  Eg spermatozoa
- Breakdown of the barrier which anatomically segregates the potential antigen from the immuno competent cell

  Eg Brain constituents, heart, pancreas, thyroglobulin
- Breakdown of acquired tolerance and appearance of immune reactive cells “forbidden clones” in the blood
- Deficiency of suppressor T cells

Criteria for the presence of autoimmune disease

- Mere presence of auto antibodies or even of sensitization does not establish the autoimmune nature of disease
- It is necessary to show in addition that the administration of serum antibodies or immunologically potent cells from the lymph node to normal animals can reproduce the disease

Autoimmune diseases

They can be B/ T cell mediated and organ specific/ tissue specific

Eg

- Acquired hemolytic anemia: Antibody against RBC
- Diabetes mellitus(Type I): Pancreatic B cell antibody
- Myasthenia gravis: Antibody against nicotinic cholinergic receptor
- Grave's disease: Antibody against TSH receptor

Autoimmune diseases…

- Molecular mimicry

Rheumatic fever following Streptococcal throat infection

A portion of the cardiac myosin resembles Streptococcal M protein

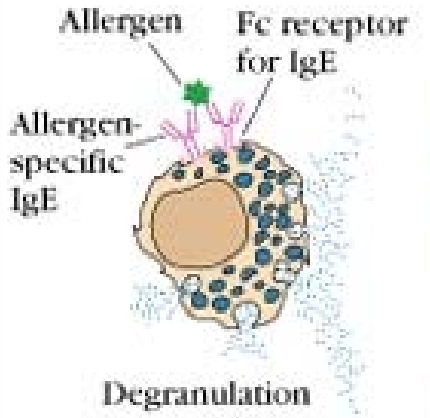
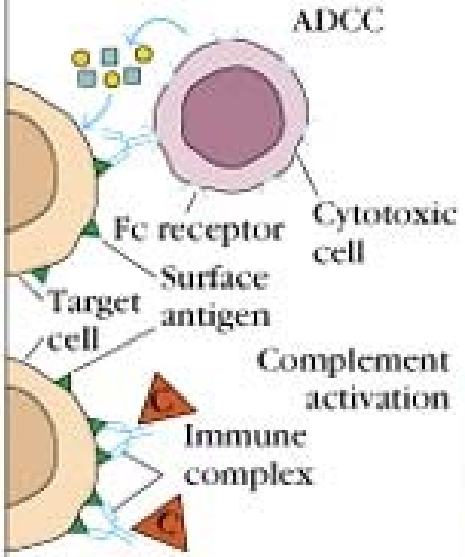
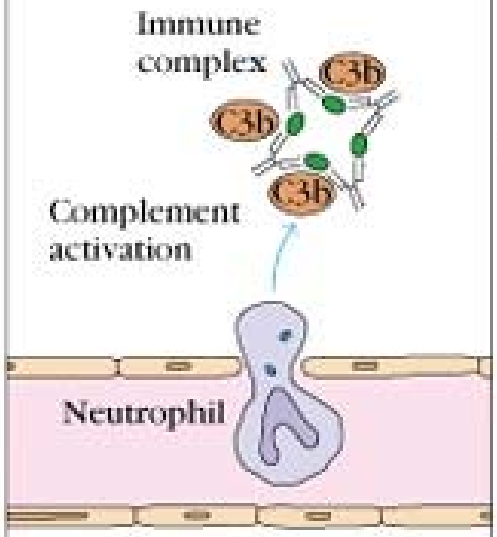
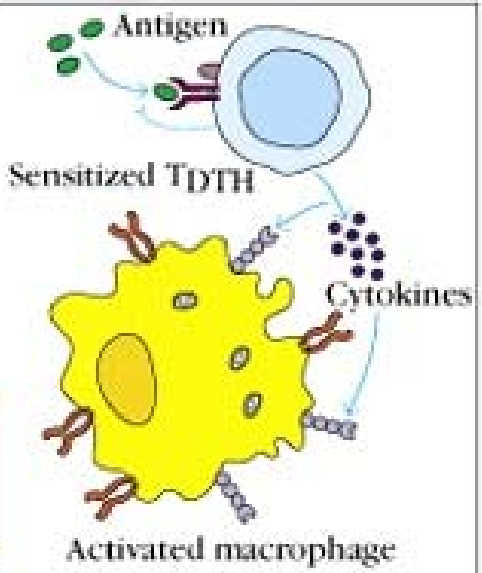
Active vs passive immunity

- Active immunity: Ones own body develops either antibodies or activated T cells in response to invasion of the body by foreign antigen
- Passive immunity: Develops by infusing preformed antibodies or activated T cells or both

Immunization by injections

Hypersensitivity reactions

- Anaphylactic type (Immediate)
- Cytotoxic type
- Complex mediated
- Cell mediated (delayed type)

 **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 meditates 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 T_{DTH} cells release cytokines that activate macrophages or T_C 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, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

TYPE I Hypersensitivity
Classic allergy

- Mediated by IgE attached to Mast cells.

- The symptoms resulting from allergic responses are known as **anaphylaxis**.
    - Includes: Hay fever, asthma, eczema, bee stings, food allergies.

Allergens

- Allergens are nonparasite antigens that can stimulate a type I hypersensitivity response.

- Allergens bind to IgE and trigger degranulation of chemical mediators.

Allergens

Proteins
- Foreign serum
- Vaccines

Plant pollens
- Rye grass
- Ragweed
- Timothy grass
- Birch trees

Drugs
- Penicillin
- Sulfonamides
- Local anesthetics
- Salicylates

Foods
- Nuts
- Seafood
- Eggs
- Peas, beans
- Milk

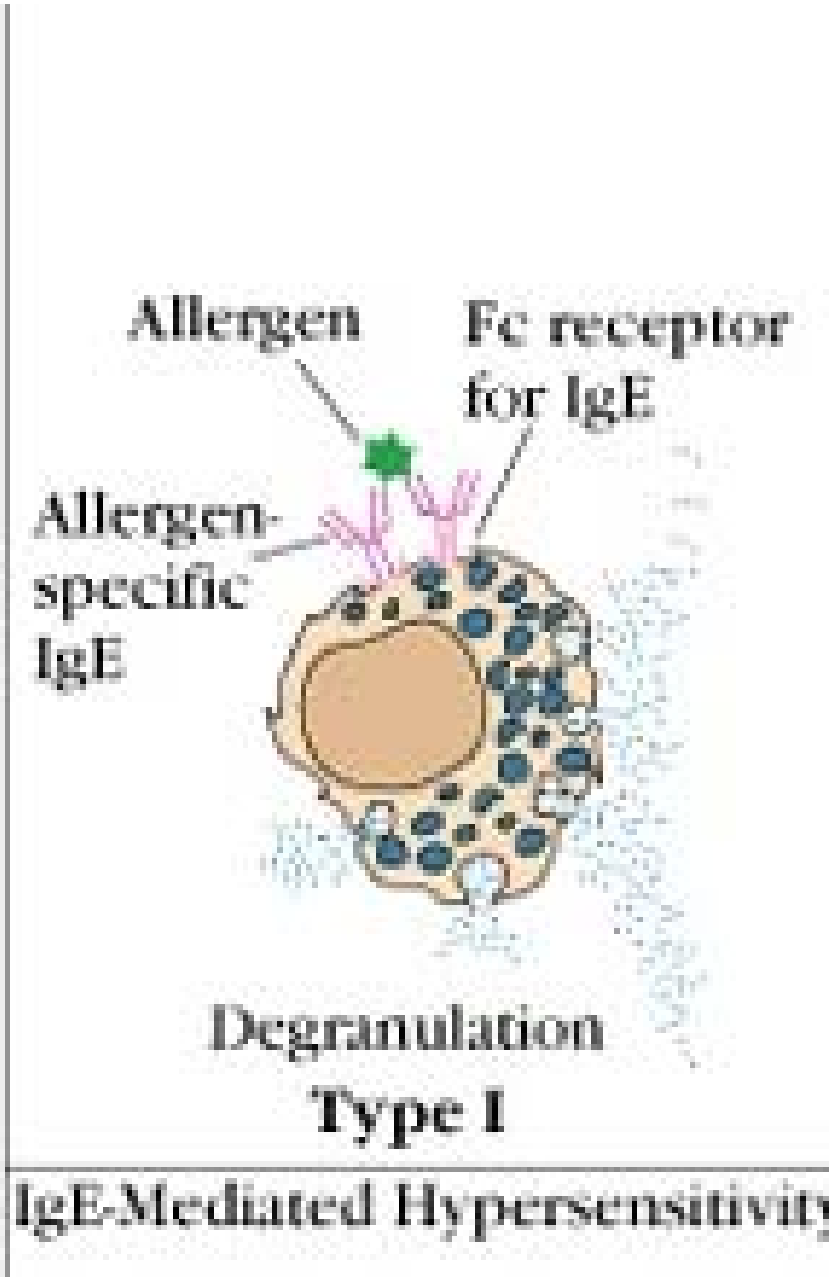
Insect products
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Dust mites

Mold spores

Animal hair and dander

Characteristics of allergens

- Small 15-40,000 MW proteins.
- Specific protein components
  - Often enzymes.
- Low dose of allergen
- Mucosal exposure


Allergen
Fc receptor for IgE
Allergen-specific IgE
Degranulation
Type I
IgE-Mediated Hypersensitivity

Mechanisms of allergic response

Sensitization

- The IgE can attach to Mast cells by Fc receptor, which increases the life span of the IgE.
- Half-life of IgE in serum is days whereas attached to FcεR it is increased to months.

Immediate hypersensitivity Anaphylactic type

- Introduction of specific antigens in previously sensitized persons can produce immediate reactions in skin and mucous membranes
- Skin: wheal & flare
- Nasal mucosa: swelling & irritation leading to sneezing(Hay fever, allergic rhinitis)
- Bronchi & bronchioles: mucosal swelling & increased smooth muscle tone producing bronchial asthma characterized by great difficulty in breathing & signs of hypoxia

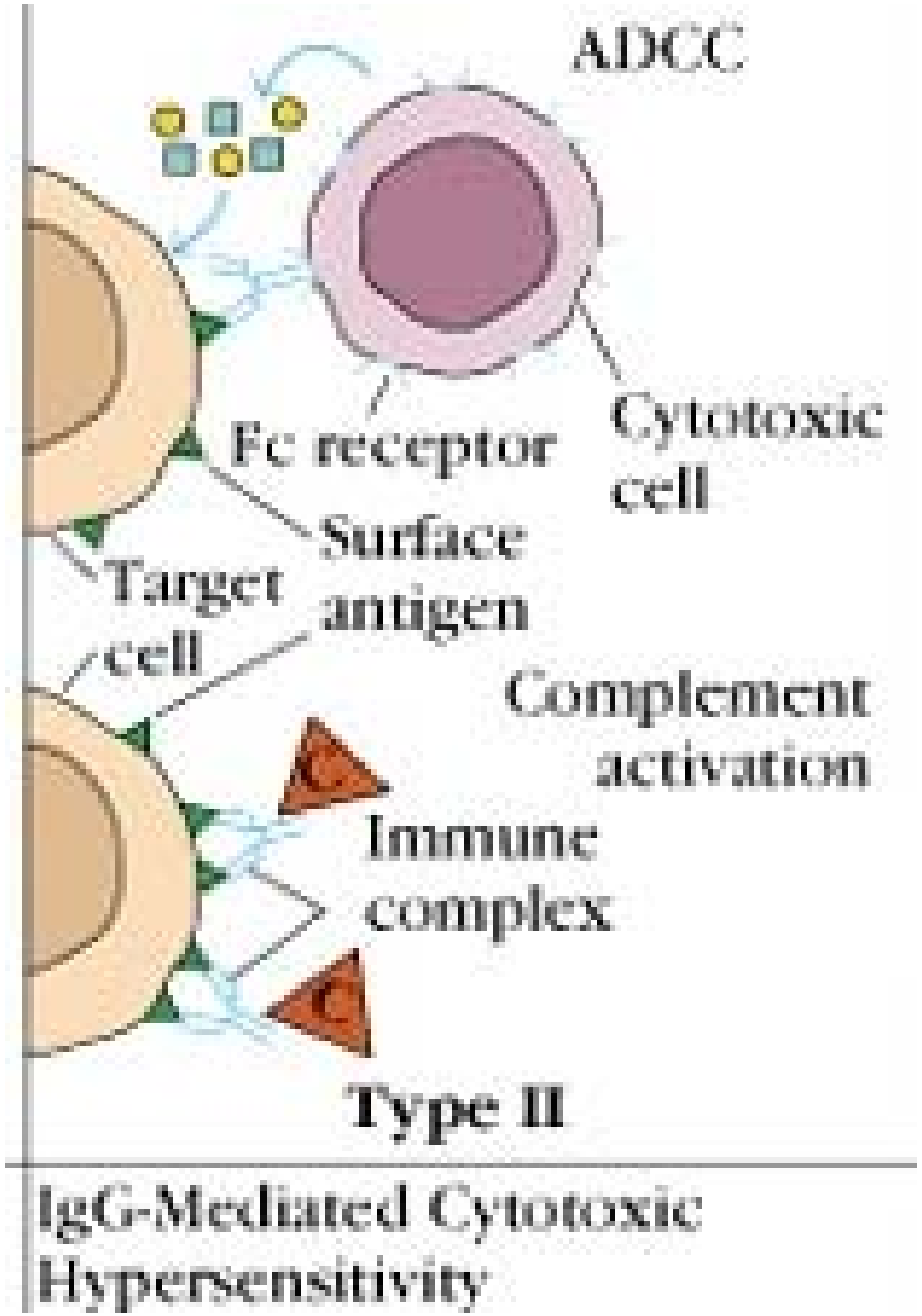
Immediate hypersensitivity
Anaphylactic type

- IgE immunoglobulins strongly attach to mast cells/ basophils
- On combining with antigen the mast cells/ basophils rupture and release

➢ Histamine
➢ Proteases
➢ Slow reacting substance of anaphylaxis
➢ Eosinophil chemotactic factor
➢ Heparin
➢ Platelet activating factor

Immediate hypersensitivity: Anaphylactic type… Influence of cAMP

- Increased cAMP reduces all chemical mediators of immediate hypersensitivity reaction
- Drugs which raise cAMP levels antagonize effects of antigen-IgE interactions eg. Isoprenaline, salbutamol, theophylline

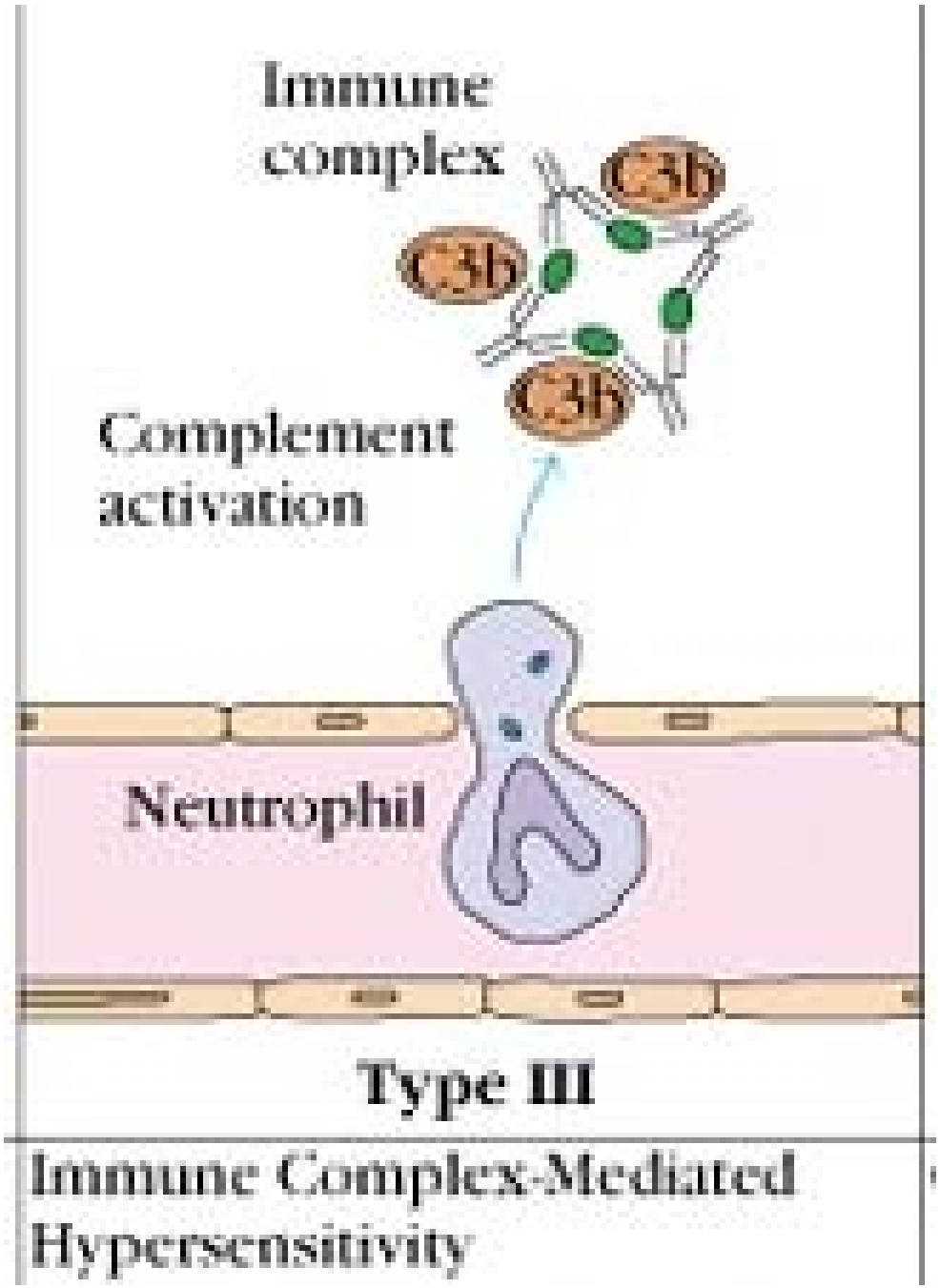

ADCC
Fc receptor
Cytotoxic cell
Surface antigen
Target cell
Complement activation
Immune complex
C
C
Type II
IgG-Mediated Cytotoxic Hypersensitivity

Cytotoxic type hypersensitivity

In this type antibodies bind to antigen on a cell surface

This promote contact with phagocyte by

- Reducing electrical charge on the surface
- Opsonic adherence
- Immune adherence in which C3 component of complement promotes phagocytosis


Immune
complex
C3b
C3b
C3b
Complement
activation
Neutrophil
Type III
Immune Complex-Mediated
Hypersensitivity

TYPE III
Antigen antibody immune complexes.
IgG mediated

Immune Complex Disease

- Large amount of antigen and antibodies form complexes in blood.

- If not eliminated can deposit in capillaries or joints and trigger inflammation.

TYPE III
Immune Complexes

- PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes.

BUT

- If unable to phagocytize the immune complexes can cause inflammation via C’ activation ---> C3a C4a, C5a and "frustrated phagocytes".

TYPE III
Immune Complex Disease
"Frustrated Phagocytes"

- If neutrophils and macrophages are unable to phagocytize the immune complexes these cells will degranulate in the area of immune complex deposition and trigger inflammation.
- Unable to eat -------try to digest outside cell.

TYPE III
Immune Complex Disease

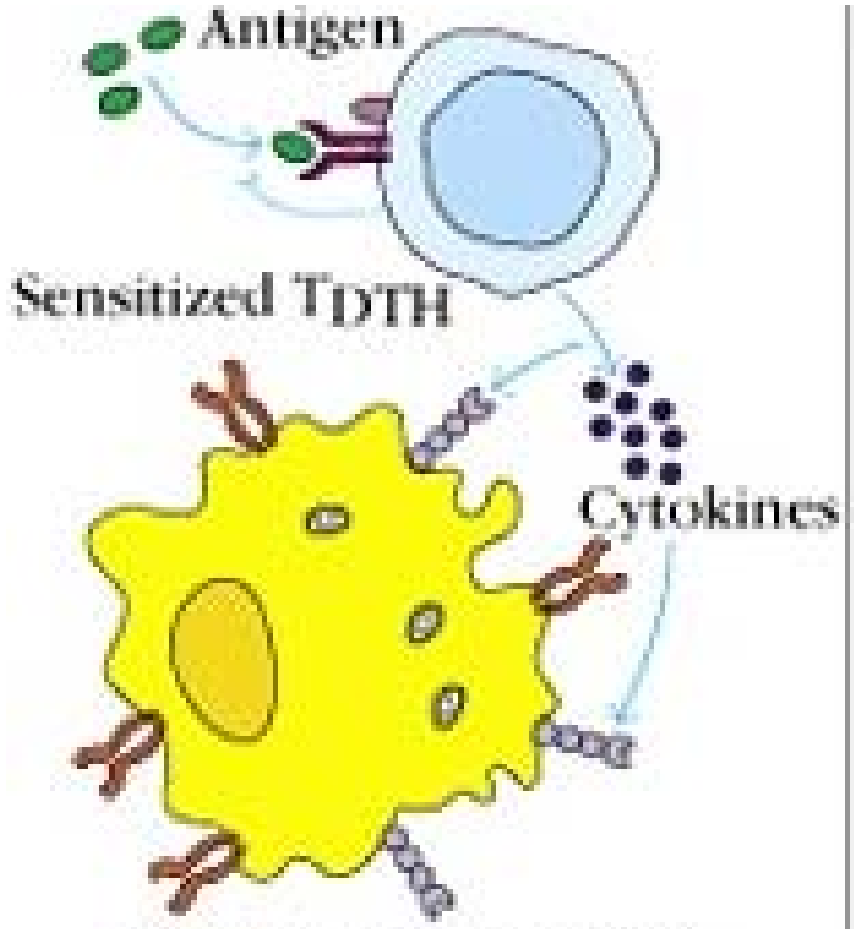
Localized disease

- Deposited in joints causing local inflammation = arthritis.
- Deposited in kidneys = glomerulonephritis.

TYPE III
Immune Complex Disease

- Serum sickness from large amounts of antigen such as injection of foreign serum.

  Serum sickness is usually transient immune complex disease with removal of antigen source.



Type IV

Cell-Mediated Hypersensitivity

Delayed type hypersensitivity
Th1 cells and macrophages

- DTH response is from:
  - Th1 cells release cytokines to activate macrophages causing inflammation and tissue damage.
  - Continued macrophage activation can cause chronic inflammation resulting in tissue lesions, scarring, and granuloma formation.
- Delayed is relative because DTH response arise 24-72 hours after exposure rather than within minutes.

Stages of Type IV DTH

Sensitization stage

- Memory Th1 cells against DTH antigens are generated by dendritic cells during the sensitization stage.
- These Th1 cells can activate macrophages and trigger inflammatory response.

Stages of Type IV DTH
Effector stage

- Secondary contact yields what we call DTH.
- **Th1** memory cells are activated and produce cytokines.
  - IFN-γ, TNF-α, and TNF-β which cause tissue destruction, inflammation.
  - IL-2 that activates T cells and CTLs.
  - Chemokines- for macrophage recruitment.
  - IL-3, GM-CSF for increased monocyte/macrophage

Stages of Type IV DTH

Effector stage

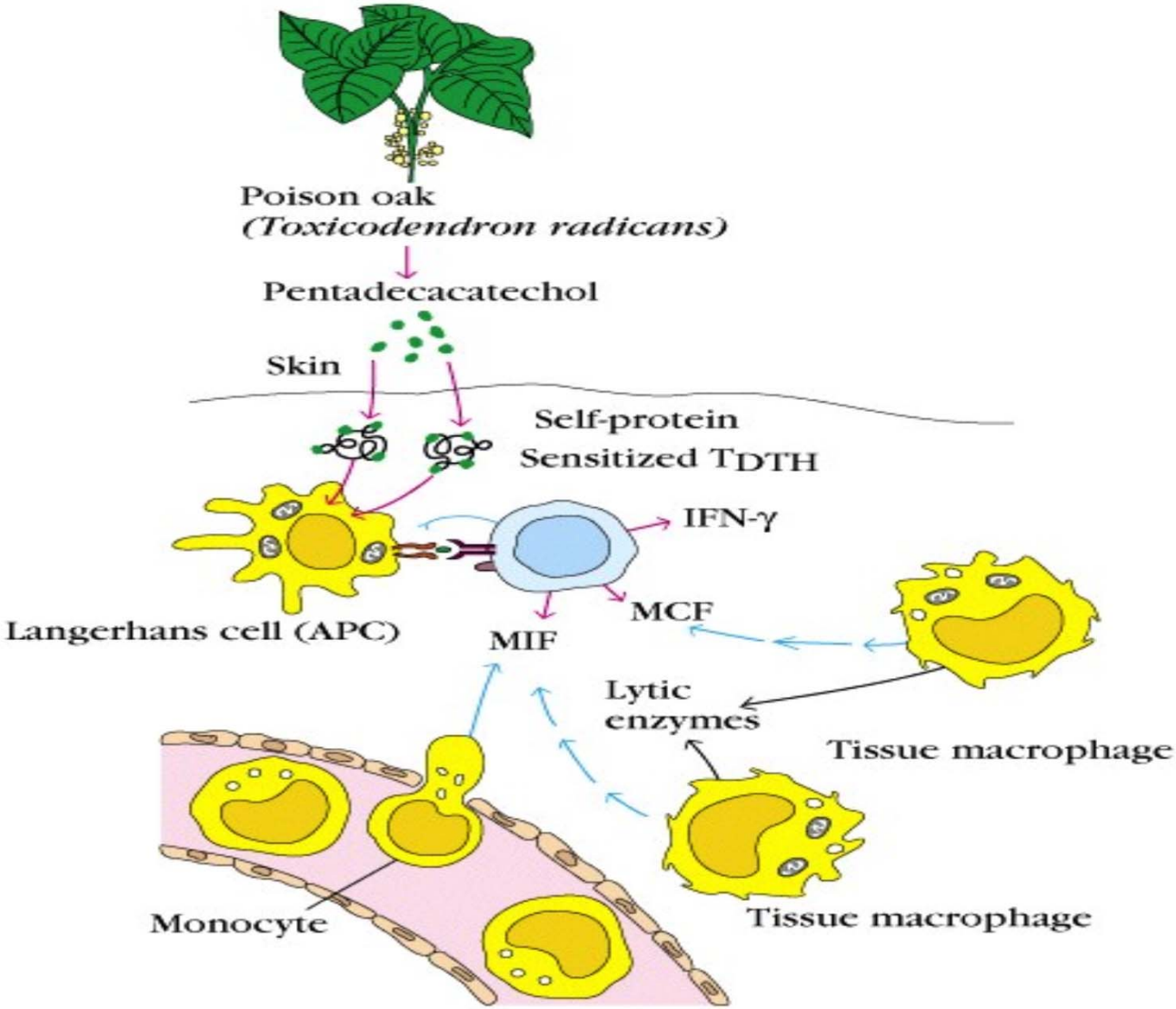
Secondary exposure to antigen

- Inflamed area becomes red and fluid filled can form lesion.
  - From tissue damage there is activation of clotting cascades and tissue repair.
- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation.

Type IV DTH
Contact dermatitis

- The response to poison oak is a classic Type IV.
  - Small molecules act as haptens and complex with skin proteins to be taken up by APCs and presented to Th1 cells to get sensitization.
  - During secondary exposure Th1 memory cells become activated to cause DTH.

Contact dermatitis



Delayed type hypersensitivity (DTH)

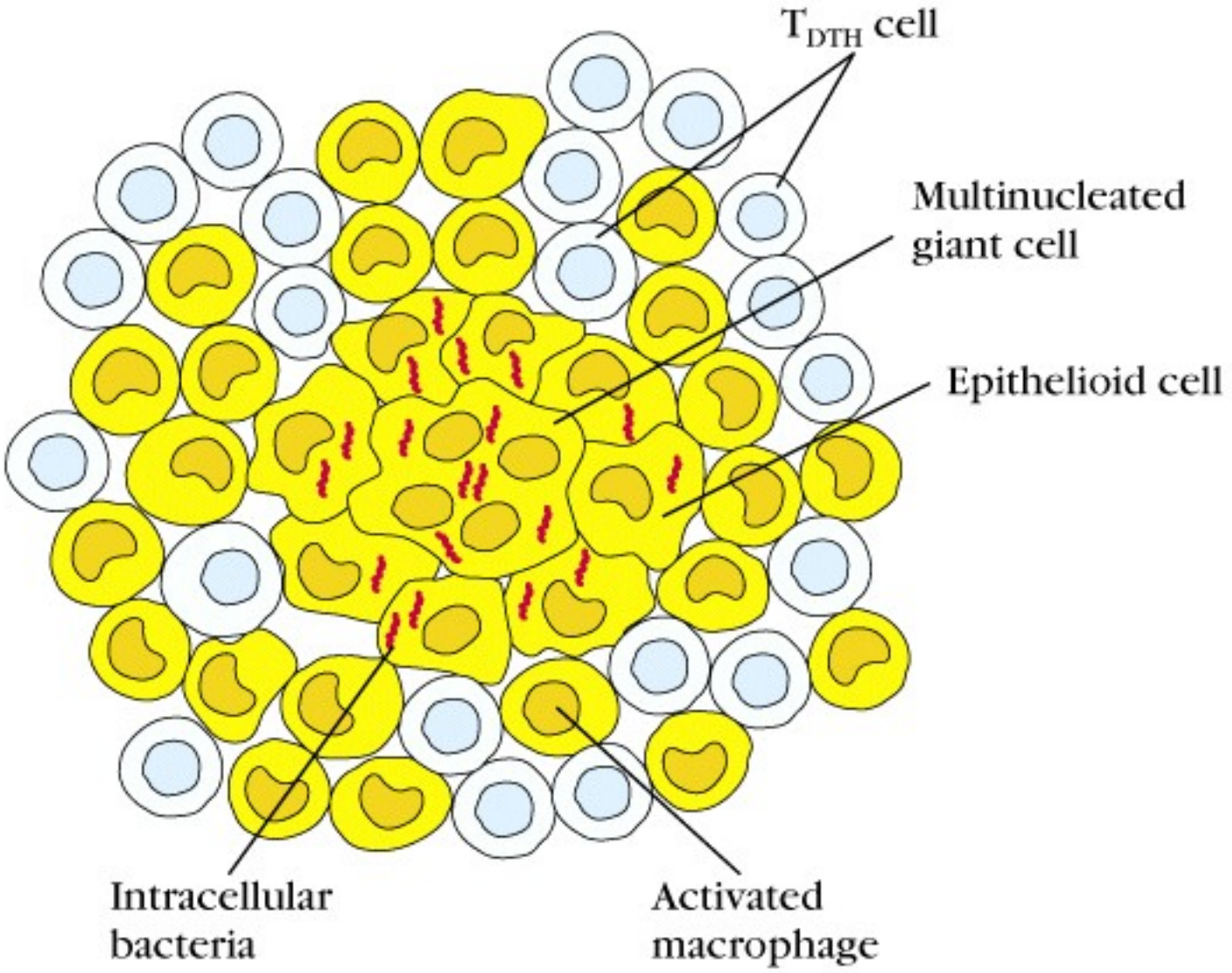
TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

Intracellular bacteria	Intracellular viruses
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Listeria monocytogenes	Measles virus
Brucella abortus	Contact antigens
Intracellular fungi	Picrylchloride
Pneumocystis carinii	Hair dyes
Candida albicans	Nickel salts
Histoplasma capsulatum	Poison ivy
Cryptococcus neoformans	Poison oak
Intracellular parasites	
Leishmania sp.	

DTH is a type of immune response classified by **Th1 and macrophage** activation that results in tissue damage.

DTH can be the result of Chronic infection or Exposure to some antigens.

Granuloma Formation from DTH Mediated by Chronic Inflammation



Human Immunodefficiency Virus(HIV)

- A retrovirus
- Virus binds to CD4 cells
- Decrease in CD 4 cells
- Failure of proliferation of CD8 & B lymphocytes
- Death from infections due to normally non pathogenic bacteria
- Normal ratio of CD4 to CD 8 cells is 1.2-3.0
- Permanent & progressive decrease in AIDS

Delayed hypersensitivity… (Examples)

- Tuberculin hypersensitivity: Classical reaction of skin induced by tuberculin

  Skin erythema and induration develops after several hours and is maximal at 24- 48.

  Histologically there is initial perivascular cuffing with mononuclear cells , then a more extensive exudation of monocytes and polymorphs within the dermis. The latter soon move away from the lesion leaving behind monocytes and lymphocytes
- Contact hypersensitivity: Extracts of plant poisons, Ivy

Tissue transplantation

- Allograft: Graft from one person to another
- Autograft: Skin from one part of a person to other
- Xenograft: An organ/ tissue transplant from one animal species to other
- Syngenic: Same genetic constitution
- Allogenic: Different genetic constitution

Allograft rejection

3 stages

Stimulus: Passenger leukocytes derived from the donor that leave the graft & reach regional lymph nodes

Afferent stage: Release of antigen from graft

Central stage: Activation of immune response

Efferent stage: Generation & release of humoral & CMI effectors that bring about destruction of graft

Allograft reaction

- An immunological response produced by the recipient against the transplant antigen of the graft
- For a few days: Allo & auto graft are normal
- After a week: Circulation to allograft decreases
- 2-3 weeks: Necrosis & sloughing off

Biological significance: Ability to reject occasional mutant cells formed during the normal course of cell division