White Blood Cells

WBCs

- White blood cells or leukocytes perform the defense functions of the body.
- The total leucocyte count in adult is 4,000 to 11,000 per cubic mm of blood.

CLASSIFICATION OF WBCs: Granulocytes and Agranulocytes.

  - **Granulocytes:** Neutrophils, Eosinophils and Basophils.
  - **Agranulocytes:** Monocytes and Lymphocytes.

- Leucocytes have three phases in their life: marrow phase, circulatory phase and tissue phase.
- In general, leukocytes after released into blood, circulate for few hours (4 – 8 hours) before entering into tissues where they live about 4 to 6 days.

NEUTROPHILS

- Neutrophils are most prevalent white blood cells in peripheral circulation, comprising 50 – 70% of total leukocytes.
- They provide the **major defense against acute pyogenic infections**.
- Neutrophils exhibit active ameboid movements. In infections, they immediately migrate to the site of microbial invasion in response to chemical factors. They ingest organisms and kill them.
- Thus, in neutropenia, body is vulnerable to bacterial infections.
- **Structure:**
- The average size of neutrophils varies between **10–14 μm.**
- The cytoplasm of neutrophils contains **fine pink colored granules**.
- The nucleus is usually **multilobed** and the lobes are connected by **thin strand**. Nucleus may contain **Barr body.**
- **Hypersegmented nucleus** of neutrophils is typically seen in megaloblastic anemia that occurs due to folate and vitamin B12 deficiency
- **Granules of Neutrophils:**
- Neutrophils have **four types of granules**:
  - Primary or azurophilic granules
  - Secondary or specific granules
  - Tertiary granules
  - Secretory granules.

Primary granules are formed during granulopoiesis, whereas other granules are formed at later stages.

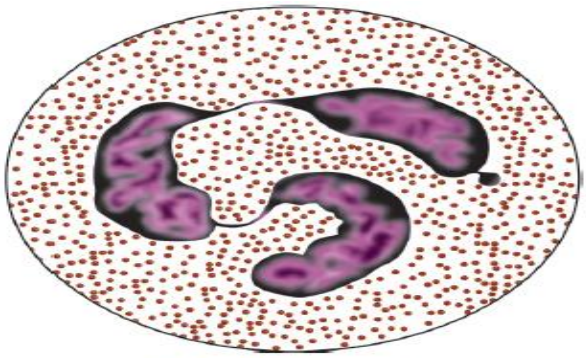
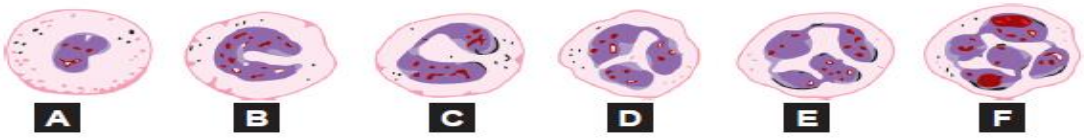


Fig. 18.1: Structure of neutrophil. Note the presence of fine granules in the cytoplasm and a thin strand separating nuclear lobes. Also note small drumstick appendage attached to the nuclear lobe.



Figs. 18.2A to F: Neutrophils having varying degrees of lobes (Arneth count). (A and B) N1 having single lobe (band form); (C) N2 having 2 lobes; (D) N3 having 3 lobes; (E) N4 having 4 lobes; (F) N5 having 5 lobes.

Primary Granules:

- ***Peroxidase positive granules*.**
- In addition to **myeloperoxidase**, they contain **lysosomal enzymes** and elastase, proteinase and α-1 antitrypsin.
- They also contain **antimicrobial proteins** like cathepsin-G, defensins and bactericidal-permeability increasing proteins.
- The ***primary granules may be decreased*** in number and absent in various diseased conditions like myeloid leukemia.
- The granules may also become abnormal as they form **Auer bodies** in acute myeloid leukemia.
- Abnormalities of granules are also seen in **Chediac-Higashi syndrome.** This is an autosomal recessive disease having abnormality of neutrophil azurophilic granules. This is characterized by oculo-cutaneous albinism and increased susceptibility to infection.

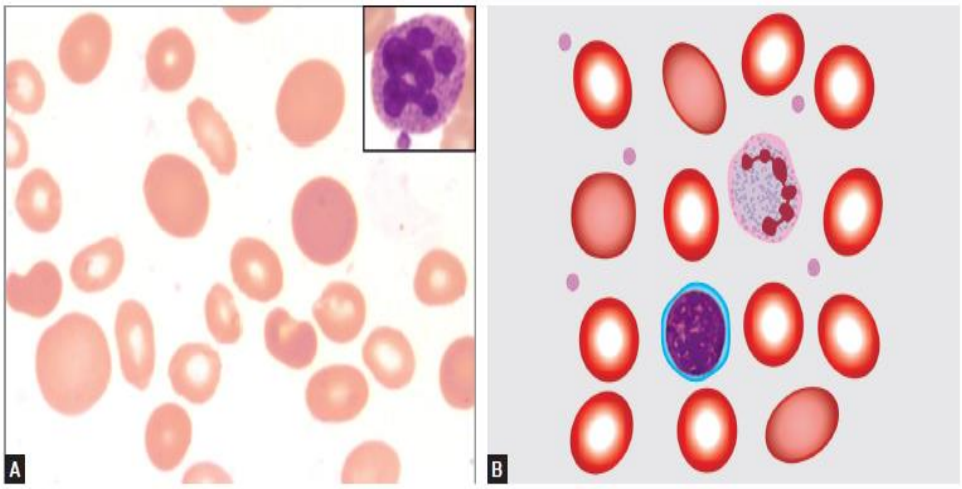
Clinical Box 18.1

Chédiac–Higashi syndrome: This is an autosomal recessive disease having abnormality of neutrophil azurophilic granules. This is characterized by oculocutaneous albinism and increased susceptibility to infection. The abnormal azurophil granules form large inclusions in the cells. The granules fuse to form megagranules. There is absence of elastase, cathepsin-G, and defensins. Therefore, the antibacterial activity (phagocytic activity) decreases that leads to severe infections.

Secondary Granules:

Peroxidase negative granules.

- The secondary granules contain **lactoferrin, gelatinase, lysozyme**, vitamin B12 binding protein and other proteins.
- Lysozyme is microbicidal and lactoferrin is antibacterial.
- About 16% granules contain only lactoferrin, 24% contain only gelatinase and 60% contain both.
- In inflammatory responses, gelatinase containing granules are more readily released than the other granules.
- The granules may disappear, and nuclear lobes may become big giving spectacular appearance in **Pelger-Huet anomaly.**



Figs. 18.3A and B: Hypersegmented neutrophil in megaloblastic anemia (in the inset), as shown in original peripheral blood smear (A) and drawn picture of the smear (B).

- Morphologically, abnormalities of specific granules are **Alder-Reilly anomaly** and **May-Hegglin anomaly**.

Tertiary Granules

- Tertiary granules contain **gelatinase, alkaline phosphatase** and cytochrome-b.
- The ***low leucocyte alkaline phosphatase score is associated with chronic myeloid leukemia***.

Secretory Granules

- These are **secretory vesicles** and different from azurophilic and specific granules.
- They contain CD3, phospholipase and tyrosine kinase.
- Toxic granulations occur in severe infections.

Toxic granulations of neutrophils:

- In severe infections, **toxic granulations** and **Döhle bodies** are seen in neutrophils in addition to nuclear pyknosis.

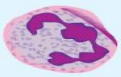
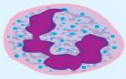
	Mode of inheritance	Characteristic morphology	Appearance of leukocyte	Functional abnormalities
Pelger-Hüet anomaly	Autosomal dominant	Lack of neutrophil nuclear segmentation beyond 2 lobes		Nil
Alder-Reilly anomaly	Autosomal recessive	Large lilac inclusions in cytoplasm of all leukocytes		Nil
May-Hegglin anomaly	Autosomal dominant	Large basophilic inclusions in all leukocytes. Giant platelets and thrombocytopenia		Abnormal bleeding due to thrombocytopenia
Chediak-Higashi anomaly	Autosomal recessive	Large gray blue granules in cytoplasm of monocytes and granulocytes. Defective lysosomal granules		Poor chemotaxis. increased susceptibility to pyogenic infections. Bleeding tendency
Chronic granulomatous disease of childhood (CGD)	X-linked Autosomal recessive	Normal appearance but defective function		Deficient NADPH oxidase, with absent H_2O_2 production. Phagocytosis and killing of organisms is impaired

Fig. 18.4: Qualitative dysfunctions of neutrophils.

Life History:

Neutrophils like other leucocytes have four stages in their life: *marrow pool, circulation pool, margination pool and tissue pool.*

Marrow Pool

- This is the developmental stage of neutrophil. As soon as neutrophils are developed from metamyelocytes, they are released into circulation.
- However, large number of juvenile neutrophils are present in bone marrow, which constitutes marrow pool of the cell. This ***serves as the reservoir for peripheral neutrophils***

Circulation Pool

- In peripheral blood, about 50% of neutrophils are present in circulation pool that actually circulate in the blood. Rest, 50% remains in the margination pool.

Margination Pool

- About **50% of the neutrophils** in the blood remain adhered or ***marginated to endothelial lining*** of the blood vessels. This is called **margination** of leucocytes.
- Neutrophils present in the margination pool serve as the immediate source for circulation pool.
- In fact, any factor that causes ***disruption of margination*** increases neutrophil count and causes **acute leucocytosis**.

Tissue Pool

- After their usual life in circulation for about 6 – 8 hours, neutrophils enter tissues where they live for about 4 - 6 days.
- **Conditions that alter neutrophil count:**

NEUTROPHILIA

- ***A. Acute Neutrophilia***
- 1. Physical stimuli: Exercise, cold, pain, labor, surgery
- 2. Emotional stimuli: Panic, severe stress, depression
- 3. Infections: Acute bacterial, mycotic and rickettsial infections
- 4. Inflammation or tissue necrosis: Burn, infarction, trauma, electric shock, gout
- 5. Drugs: Epinephrine, glucocorticoids, vaccines

B. Chronic Neutrophilia

- 1. Inflammation: Pancreatitis, myositis, colitis, rheumatoid arthritis
- 2. Endocrine disorder: ACTH excess, thyroid storm
- 3. Tumors: Gastric, renal, bronchial and hepatic tumors
- 4. Blood diseases: Chronic hemolysis, myeloproliferative diseases

NEUTROPENIA

- ***A. Decreased neutrophil production***
- 1. Congenital, e. g. Kostmann syndrome
- 2. Infections: Typhoid and paratyphoid fevers
- 3. Drugs: Chloramphenicol, phenylbutazone, phenytoin
- 4. Aplastic anemia

B. Increased neutrophil destruction

1. Parasitic infections: Malaria, kala azar

2. Viral infections: Measles, influenza

3. Hypersplenism

4. Autoimmune diseases: SLE, Felty syndrome

Functions:

- Neutrophil is **actively phagocytic**. They contain many antimicrobial and bactericidal chemicals in their granules.
- During inflammation due to acute bacterial infections, neutrophils soon migrate to the site of infection and kill the organisms. Hence, neutrophils are considered as the **first line of defense against acute bacterial infections**.
- Neutrophils provide major nonspecific defense against invasion of pyogenic organisms. Consequently, **neutropenia predisposes body to pyogenic infection**.

Neutrophil Phagocytosis

- **Phagocytosis** is the process of ingestion and killing of microbes or a foreign substance by a phagocyte. **Actively phagocytic cells** are neutrophils, monocytes and macrophages.
- **Steps of phagocytosis**

  - Chemotaxis
  - Diapedesis
  - Adherence
  - Ingestion
  - Killing

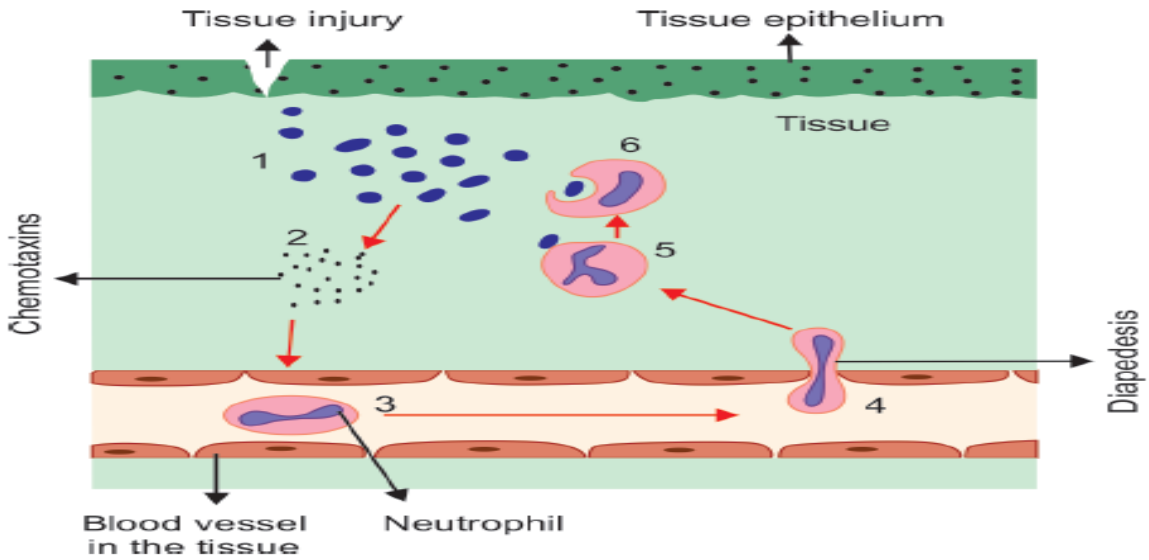


Fig. 18.5: General steps of phagocytosis by neutrophil. (1) Invasion of organism into the tissue; (2) Release of chemotaxins from organism and injured tissue; (3) Chemotaxis; (4) Diapedesis; (5) Opsonization and adherence; (6) Ingestion and killing.

1. **Chemotaxis:**

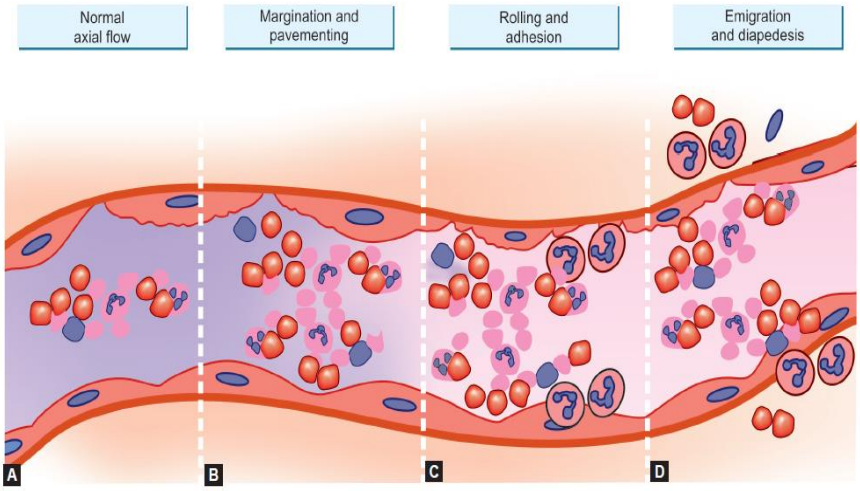
- Chemotaxis is the ***process of migration of neutrophils to the site of infection***. The bacterial invasion triggers acute inflammatory response.
- The **chemical substances are released** from the site of inflammation or infection by the infecting organisms or inflammatory cells.
- These chemical factors **attract neutrophils** to the site of infection. Consequently, they are called **chemotaxins** (*taxin* means movement; chemical that produces movement is a chemotaxin) or ***chemoattractants*** or ***chemotactic factors***.

Chemotaxis: (Contd.)

- **Chemotaxins are usually the microbial products or chemicals secreted from leucocytes or chemicals released from damaged tissue.**
- **Complement proteins, especially C5a and C3 also act as chemotaxins.**
- **During chemotaxis, neutrophils change their shape and become highly ameboid.**
- **Also, leukopoiesis is stimulated in bone marrow in response to plasma factors and more neutrophils are produced.**

Diapedesis

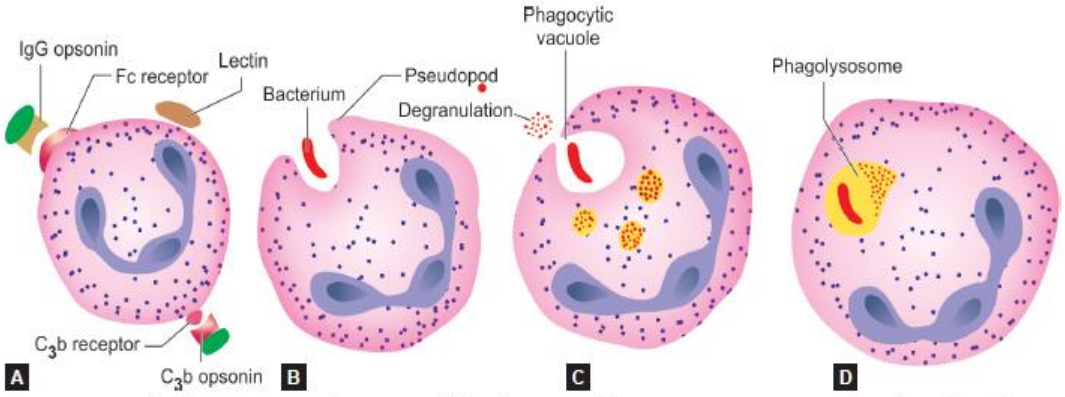
- **The process, by which neutrophils pass through the capillary endothelial cells to reach the invader in the tissue, is called diapedesis.**
- **By diapedesis, neutrophils enter the tissue from their circulation pool to kill organisms at the site of inflammation in the tissue.**
- **The activated neutrophils first marginate (margination and pavementing) and adhere tightly to endothelial lining (rolling and adhesion) with the help of L-selectins.**
- **Then, by their active ameboid movement they squeeze through the space between endothelial cells (emigration and diapedesis).**



Figs. 18.6A to D: Details of diapedesis of neutrophils. It occurs in three phases: margination and pavementing, rolling and adhesion, and emigration and diapedesis.

Opsonization and Adherence

- **The process by which the bacteria are made tasty to the phagocyte is called opsonization. In this process, antigen is coated by opsonins. The chemicals that facilitate the process of opsonization are called opsonins.**
- **IgG antibody and complement proteins (C5a, C3b) are known high-quality opsonins.**
- **Bacteria coated by opsonins bind to the receptor on the neutrophil membrane.**
- **The attachment of membrane of phagocyte to the membrane of microbe is called *adherence*.**
- **Opsonization facilitates the process of adherence**



Figs. 18.7A to D: Details of opsonization, endocytosis and killing by neutrophils. (A) Opsonization; (B) Pseudopod engulfing the opsonized particle; (C) Phagocytic vacuole formation; (D) Phagolysosome formation.

Ingestion (Endocytosis)

- **Adherence facilitates the motor activity of neutrophils.**
- **The membrane of phagocyte extends projections from both the sides to encroach on to the microbe. These extensions are called pseudopodia.**
- **Pseudopodia finally surround the microbe and form phagocytic vesicle.**
- **The phagocytic vesicle fuses with the lysosome to form *phagolysosome*.**

5. Killing

The bactericidal (killing of bacteria) mechanisms can broadly be divided into two types: Non-oxidative and Oxidative.

Nonoxidative Mechanisms

- **Neutrophil granules contain a wide variety of *antibacterial chemicals* such as degradative enzymes, proteases, defensins and cationic proteins.**
- **Lysozyme that hydrolyzes the cell wall of bacteria and lactoferrin that sequesters iron (iron is required for bacterial growth) are nonoxidative components of bacterial killing.**

- **Defensins (α and β defensins) released from azurophil granules have unusual cyclic structure and kill bacteria by disrupting their outer membrane and breaking single-strand DNA structure.**

Oxidative Mechanisms

- **Activated neutrophils produce a number of *oxygen metabolites* that are antimicrobial.**
- **The metabolites are superoxide anion (O2–), H2O2, free hydroxyl radicals (OH·), hypochlorous acid (HOCl) and singlet oxygen (´O2). *O2– is the most effective oxidant metabolite*.**
- **Two superoxide anions (O2–) react with two H+ to form H2O2 by the action of *superoxide dismutase* (SOD). Both O2– and H2O2 are active oxidants and are effective bactericidal agents.**
- **Myeloperoxidase, the enzyme of primary granules facilitate conversion of Cl– to HOCl, which is also a potent oxidant.**

Application Box 18.2

Amyotrophic lateral sclerosis (ALS) occurs due to defective dismutase: ALS is a motor system disease in which progressive degeneration of spinal motor neurons results in atrophy of skeletal muscles (amyotrophy). O_2^- reacts with H^+ to form H_2O_2 with the help of cytoplasmic dismutase and H_2O_2 is converted to H_2O and O_2 by the enzymes catalase. Defective dismutase results in accumulation of O_2^- in the motor neurons that damages the neurons. In ALS, genetic mutation of dismutase results in oxidative damage to the motor neurons in the spinal cord, which is progressively fatal.

Clinical Box 18.3

Chronic granulomatous disease (CGD) occurs due to defective NADPH-oxidase: In CGD, a genetic disorder, neutrophils fail to generate O_2^- and related metabolites. Neutrophils and monocytes ingest catalase positive microorganisms but cannot kill them due to lack of adequate active oxidants that result from decreased NADPH-oxidase activity. This leads to formation of chronic granulomas, the abnormal inflammatory tissue reactions.

EOSINOPHILS

- **Eosinophils are known for their protective function against allergy including asthma, and helminthic parasite infections.**
- **Cytokines produced by eosinophil such as leukotrienes and PAF, aid to their defense functions.**
- **Eosinophils have short life-span in circulation, whereas they live longer in tissue. They are primarily tissue dwelling cells. There are 100 eosinophils in tissue to 1 eosinophil in peripheral blood.**
- **Eosinophils are present in the epithelia of respiratory, gastrointestinal and genitourinary tract.**

- **Their production and function are mainly influenced by IL-5. IL-5 also stimulates production and function of basophils that are closely related to eosinophils.**

<u>Structure</u>

- **Eosinophils are granular leucocytes having the size same as that of neutrophils.**
- **The eosinophil granules are coarse and brick red in color in blood smear stained by Leishman stain.**
- **The nucleus is usually bilobed and the lobes are separated by a thick strand. This gives eosinophil nucleus an appearance of a pair of *spectacles.***
- **The granules are plenty, and sometimes encroach upon the nucleus.**

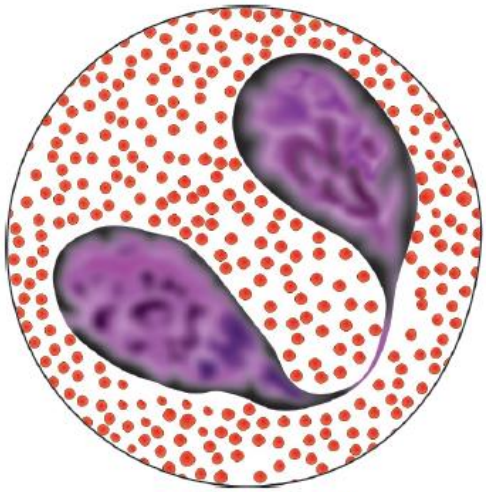


Fig. 18.8: Structure of eosinophil. Note the presence of brick red coarse granules in the cytoplasm and spectacular nuclear lobes.

Eosinophil-derived chemicals:

A. Granule derived chemicals

1. **Major basic protein**
2. **Eosinophil cationic protein**
3. **Eosinophil peroxidase**
4. **Eosinophil-derived neurotoxin**
5. **Lysophospholipase**
6. **Phospholipase D**
7. **Arylsulphatase**
8. **Acid phosphatase**
9. **Catalase**
10. **Histaminase**
11. **Hexoseaminidase**

B. Cytokines (may or may not be stored in granules)

1. GM-CSF
2. TGF-α and TGF-β
3. Macrophage inhibition factor (MIF)
4. IL1-6, IL8 and IL12
5. Tumor necrosis factor (TNF- α)

C. Lipid-derived chemicals

1. Leukotriene C
2. Platelet activating factor
3. PGE1 and PGE2
4. Thromboxane B2

Other Chemicals:

1. **Lysophospholipase** constitutes 10% of eosinophil proteins.

2. The enzymes secreted from eosinophils like **phospholipase D, arylsulphatase-B, acid phosphatase, catalase and histaminase** are other granular proteins that take part in ***eosinophil-mediated inflammatory reactions*** and ***killing of parasites***.

<u>Functions</u>

- Like neutrophils, eosinophils migrate into the tissues.
- There are selective chemoattractants for eosinophils such as **eosinophil chemotactic factor of anaphylaxis** (ECF-A).
- ECF-A in humans is a tetrapeptide that facilitates tissue accumulation of eosinophils.
- Eosinophils exhibit endothelial cell adhesion and chemotaxis to migrate into the tissues.

Eosinophils participate in two important defense mechanisms of the body:

1. Against helminthic infections

2. Against allergy.

Alterations in Eosinophil Count

The normal eosinophil count is 2–4% in differential count (by examining blood smear), or 40–440 per µl of blood in absolute count (by hemocytometry).

Eosinophilia:

1. Helminthic infections
2. Allergic diseases
3. Drug reactions (drug allergy)
4. Eosinophilic leukemia
5. Tropical pulmonary eosinophilia
6. Addison's disease
7. Eosinophilia-myalgia syndrome

Eosinopenia

1. Glucocorticoid therapy
2. Cushing's syndrome
3. Aplastic anemia
4. Drug-induced agranulocytosis

BASOPHILS & MAST CELLS

- Basophils are least frequent granulocytes.
- They account for less than 0.5% of leucocytes in blood.
- Though they recruit into tissues in response to immunological and inflammatory reactions, unlike eosinophils they ordinarily do not reside in the tissue.

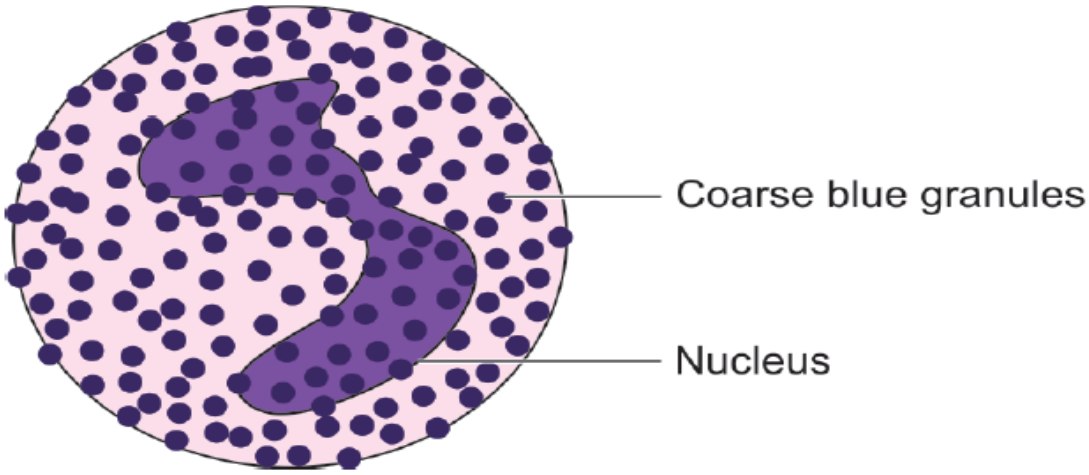


Fig. 18.9: Structure of basophil.

Table 18.4: Differences between basophils and mast cells.

	Basophils	Mast cells
Origin	Bone marrow	Bone marrow
Cells in blood	Present	Absent
Normal residence in connective tissue	No	Yes
Life span	Few days	Few months
Growth factor	IL-3	SCF
Major secretion	Histamine, IL-4,	Histamine, heparin
Receptors for	IgE, IgG	IgE

(Ig: immunoglobulin; IL: interleukin)

Structure:

1. They have the same diameter as of neutrophils (10 – 14 µm).

2. The nucleus is usually less segmented and often appear 'S' shaped.

3. **Nuclear chromatin** shows ***marked condensation***.

4. The **granules are large in size** and oval or round in shape, and more in number. As cell is heavily studded with granules, nucleus is often not visible. Granules are surrounded by membranes and contain dense particles called **Chracot-Lyeden crystals**.

5. Cytoplasm contains glycogen deposits, mitochondria, free-ribososmes and few lipid bodies.

Basophil granules secrete histamine, chondroitin sulphate, tryptase, carboxypeptidase A, cathepsin G, leukotrienes, eosinophil chemotactic factor of anaphylaxis (ECF-A), neural protease and MBP.

Mast Cells

- Mast cells that remain in the tissues are round or elongated cells with nonsegmented nucleus.
- Granules are numerous, but smaller in size.
- There are many cytoplasmic filaments, numerous lipid bodies and no glycogen deposits.
- **Mast cell granules** secrete histamine, heparin, chondroitin sulphate, carboxypeptidase, cathepsin, ECF-A and neural protease.
- **Types of mast cells:** There are two types of mast cells: **mucosal mast cells** (mast cell present in the mucosa) and **connective tissue mast cell**.

Functions

- Basophils and mast cells are mainly involved in **allergic reactions**.
- During allergy, these cells release the content of their granules.
- Mediators such as histamine released by degranulation produce antimicrobial and anti-host effects.
- The usual stimulus for basophil and mast cell degranulation is an allergen, which should ideally cross-link IgE molecule bound to the surface of basophils or mast cells via its high affinity Fc receptor for IgE.

Table 18.5: Alteration in basophil count.

A. Basophilia
1. Allergic and inflammatory conditions: ◆ Ulcerative colitis ◆ Erythroderma ◆ Urticaria ◆ Drug and food hypersensitivity
2. Infections: - Chickenpox - Smallpox - Influenza - Tuberculosis
3. Endocrinal disorders: - Myxedema (hypothyroidism) - Diabetes mellitus
4. Iron deficiency
5. Basophilic leukemia
6. Polycythemia
B. Basopenia
1. Cortisol therapy
2. Cushing's syndrome
3. Hyperthyroidism
4. Ovulation
5. Hypersensitivity reactions

MONOCYTES & MACROPHAGES

- Monocyte is the largest leucocyte in the peripheral blood. After spending life in blood, monocytes enter the tissues, where they are transformed into **tissue macrophages**.
- Monocytes and macrophages are **mononuclear phagocytes**.
- In the tissues, they play an important role in nonspecific defense against microbial invasion.
- The tissue macrophage system was previously called as ***reticuloendothelial system*** (now the term is obsolete). Presently, this is known as **mononuclear phagocyte system (MPS)**.
- Monocyte is the **second line of defense against** microbial infections.

Morphology:

Monocytes are the largest blood cells. The identifying features are:

1. The diameter of monocytes varies between 12–25 µm.

2. **Nucleus** occupies half of the cell and remains eccentrically. **Cytoplasmic-nuclear ratio** is 50:50.

3. Often the nucleus is reniform (kidney shaped), but may be horse-shoe shaped, round or irregular.

4. There are characteristic fine nuclear chromatin net connecting small chromatin clumps. This gives the nucleus a **non-homogenous** or **stringy appearance**.

5. **Cytoplasm** is abundant and **ground glass in appearance**.

Monocytes have a number of **receptors on its surface** such as Fc receptors for IgG, IgA and IgE, receptors for complements, cytokines, and hormones like insulin, glucocorticoid and angiotensin.

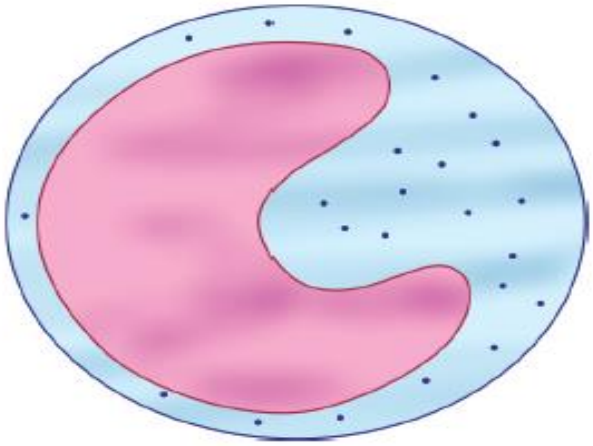


Fig. 18.10: Structure of monocyte.

Functions

1. **Phagocytosis and microbial killing:** Monocyte is an active phagocyte.

- It exhibits ***motility and chemotaxis***.
- The presence of various ***surface receptors*** enhances their phagocytic activity by facilitating the recognition of various host-derived factors including immunoglobulins, complements, and integrins.
- The receptors also *identify various sugar units* on microbial membranes.
- The organisms once phagocytosed, are destroyed by **oxidants** produced by NADPH oxidase, nitric oxide synthase, and intracellular hydrolytic enzymes.
- Monocyte also ***kills intracellular pathogens*** like viruses, and parasites.
- Monocyte is the **second line of defense** against infections.

2. **Antigen presentation:**

Monocyte is an important ***antigen presenting cell*** (APC).

- Partially digested product of the antigen (Ag) combines with the MHC II molecules produced by APC, and MHC+Ag complex expresses on the surface of APC.
- Lymphocytes, especially T cells are activated when they come in contact with MHC+Ag present on the APC surface.

This is the first step in the activation of cellular immunity

3. **Release of cytokines:** Monocyte secretes various chemokines that carry out different physiological functions.

- Monocyte produces ***IL-1 and IL-6*** that are essential for coactivation of immunological responses.
- Monocyte secretes ***TNF-α and interferons*** that facilitate killing of viruses and other microbial organisms.
- Monocyte also secretes various ***growth factors*** like GM-CSF, M-CSF and erythroid colony potentiating factor that promote leucopoiesis and erythropoiesis, and transforming growth factors (TGF), PDGF and fibroblast growth factors (FGF).
- Monocytes by secreting ***complement factors*** augment the local tissue defense responses.
- Monocyte releases various ***enzymes*** like collagenase, elastase, plasminogen activator etc. that participate in wound healing and tissue remodeling.

Life Span

- Monocytes in circulation have a wide range of half-life between 10–72 hours.
- Then, they enter the tissues where they live few weeks to months.
- The average life in tissues is three months.
- In tissue, they are transformed into **tissue macrophages**.
- If there is tissue infection or inflammation, within few hours monocytes migrate to the site of injury.
- However, initially the monocyte numbers are less than neutrophils.
- **If inflammation persists for more than 12 hours**, monocytes predominate over neutrophils.

Table 18.6: Causes of alteration in monocyte count.
A. Monocytopenia
1. Aplastic anemia
2. Hairy cell leukemia
3. Septicemia
B. Monocytosis
1. Acute monocytic leukemia
2. Chronic myelomonocytic leukemia
3. Hodgkin's disease
4. Polycythemia vera
5. Hemolytic anemia
6. Postsplenectomy state
7. Cytomegalovirus infection
8. Collagen diseases
9. Malaria
10. Kala-azar
11. Glucocorticoid therapy
12. Chronic idiopathic monocytosis

Table 18.7: Distribution of cells of mononuclear phagocyte system.
A. In blood:
– Monocytes
B. In bone marrow:
– Monoblasts
– Promonocytes
C. In tissues:
– Kupffer cell in liver
– Osteoclasts in bone marrow
– Alveolar macrophages in lungs
– Histiocytes in connective tissue
– Microglia in brain
– Red pulp macrophages in spleen
– Macrophages in lymph nodes and thymus
– Mesangial cells in kidney
– Dendritic cells/histiocytes in skin
– Type A cells in synovium
D. In body cavities:
– Pleural macrophages
– Peritoneal macrophages
E. In inflammatory tissues:
– Epithelioid cells
– Multinucleate giant cells

Macrophages:

- Macrophages are capable of cell division and resident or non-inflammatory macrophages in the tissue are self-sustaining.
- The exact mechanism of **differentiation of monocyte to macrophages** is not known. However, on becoming macrophage there is increase in cell size, number of cytoplasmic granules and vacuoles, and increase in heterogeneity of the cell shape.
- The average diameter of macrophages varies from **25 to 50 µm**.
- The nucleus is fusiform or reniform and is eccentrically placed with one or two nucleoli in it.
- Cytoplasm contains multiple **large azurophil granules**.
- They contain all the surface receptors that are present in monocytes.
- In chronic tissue inflammations, macrophages are converted into **multinucleated giant cells** that are highly phagocytic and microbicidal.

Dendritic Cells:

- Few monocytes are transformed into highly specialized mononuclear cells called dendritic cells.
- They play important role in **antigen processing and presentation** to the T cells.
- They are specialized in antigen capture, rather than in phagocytosis. Thus, they are specific ***antigen presenting cells***.
- However, unlike macrophages, dendritic cells **lack receptors** for immunoglobulins, complements and colony-stimulating factors, and specific granules in cytoplasm. Therefore, they are weakly phagocytic.
- They are present in blood and bone marrow, where they account for about 0.1 to 1 % of total mononuclear cells.
- They are also present as Langerhans cells in skin, interdigitating cells in thymic medulla, and interstitial cells in the lung and heart.

LYMPHOCYTES

Structure

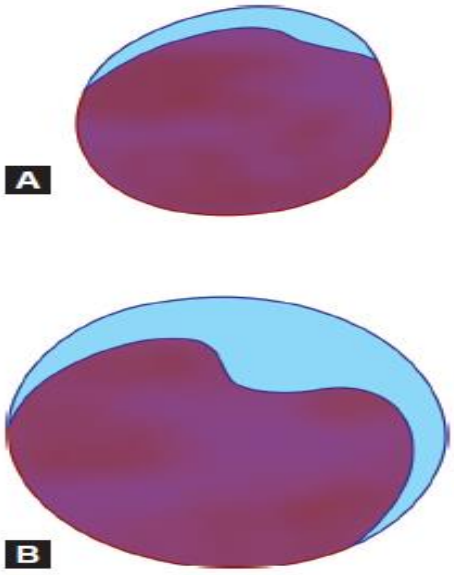
Small Lymphocytes:

Small lymphocytes are same in size to that of red cells. They constitute 35% (20–50%) of total lymphocytes. The **identifying features** are:

1. The cells are 6–9 µm in diameter.

2. They have ovoid or kidney shaped nucleus with densely packed nuclear chromatin. **Nucleus** is usually **eccentrically placed** and occupies about **90% of the cell area.**

3. There is a ***thin rim of bluish cytoplasm*** that does not contain granules.



Figs. 18.11A and B: Structure of small lymphocyte (A) and large lymphocyte (B).

Normal Count & Functions

- Normal lymphocyte count is 20–40% of total leucocytes. The absolute count is 500 – 8000 per cu mm of blood. Increase in count is called **lymphocytosis** and decrease in count is called **lymphocytopenia.**
- Functionally, lymphocytes are divided into three categories: B cells, T cells and NK cells.
- **B cells** on stimulation are transformed into **plasma cells** that secrete antibodies. B cells mediate humoral or antibody-mediated immunity.
- **T cells** mediate cellular or cell-mediated immunity.
- **NK cells** mediate natural and nonspecific immunity.
- **Causes of lymphocytosis and lymphocytopenia**
- **A. Lymphocytosis**
- 1. Primary lymphocytosis
- - Acute lymphocytic leukemia
- - Chronic lymphocytic leukemia
- - Adult T-cell leukemia
- - NK-cell leukemia
- - Monoclonal B-cell lymphocytosis
- 2. Reactive lymphocytosis
- - Infectious mononucleosis
- - Bordetella pertusis
- - Tuberculosis
- - Postsplenectomy
- - Cigarette smoking
- - Septic shock
- - Drugs

B. Lymphocytopenia

- 1. Acquired lymphocytopenia
- - Aplastic anemia
- - AIDS
- - Hepatitis
- - Glucocorticoid therapy
- - Typhoid fever
- - Systemic lupus erythematosus
- 2. Inherited lymphocytopenia
- - Severe combined immunodeficiency states
- - Wiskott-Aldrich syndrome
- - Immunodeficiency with thymoma
- - Cellular immunodeficiency with immunoglobulins

Table 18.9: Summary of the formed elements in blood.

Name	Count	Features	Functions
A. Red blood cells (erythrocytes)	5.4 million/mm³ in males; 4.8 million/mm³ in females	7–8 µm diameter, biconcave discs, without a nucleus, life span about 120 days	Transport oxygen and carbon dioxide
B. White blood cells (leukocytes)	4,000–11,000/mm³	Live for a few hours to few days	Kill pathogens (body defense)
Neutrophils	50–70% of all WBCs	10–14 µm diameter; nucleus is multilobed, connected by thin strands of chromatin; cytoplasm has fine, pink granules	Phagocytosis of organisms (first line of defense)
Eosinophils	1–4% of all WBCs	10–14 µm diameter; nucleus is bilobed; coarse brick-red granules in cytoplasm	Combat the effects of histamine in allergic reactions and kill parasitic worms
Basophils	0–1% of all WBCs	10–14 µm diameter; nucleus is bilobed or irregular in shape; Large cytoplasmic granules are deep blue-purple	Release heparin, histamine, and serotonin in allergic reactions that promote overall inflammatory response
Lymphocytes	20–40% of all WBCs	Small lymphocytes are 6–9 µm in diameter; large lymphocytes are 10–14 µm in diameter; nucleus is round or slightly indented; cytoplasm forms a clear rim around the nucleus	Mediate immune responses
Monocytes	2–8% of all WBCs	12–25 µm diameter; nucleus is oval or kidney-shaped or horseshoe-shaped; cytoplasm turbid in appearance	Phagocytosis (after transforming into tissue macrophages)
C. Platelets (thrombocytes)	150,000–400,000/mm³	2–4 µm diameter, cell fragments, no nucleus	Form platelet plug in hemostasis (temporary hemostatic plug)

LEUKEMIA

<u>Definition & Concept</u>

- Leukemia is defined as a malignant neoplasia of hemopoietic cells in which there is **abnormal proliferation of leucocytes and their precursors** resulting in appearance of ***abnormal and immature cells*** in the peripheral blood associated with ***very high leucocytosis***, and infiltration of tissues by leukemic cells.
- There is increased ***infiltration of bone marrow*** by the proliferating leukemic cells.

- The total leucocyte count is usually very high, except in subleukemic or aleukemic form of leukemia.
- Usually, the proliferation involves leucocytic series.
- Occasionally, erythroid precursors or megakaryocytes may also be involved in the disease process.

Types

Leukemia is classified into two main categories:

- Myeloid (myelocytic) and
- Lymphocytic leukemia.

These two varieties are sub-classified into

- Acute and
- Chronic types.

Acute Leukemias

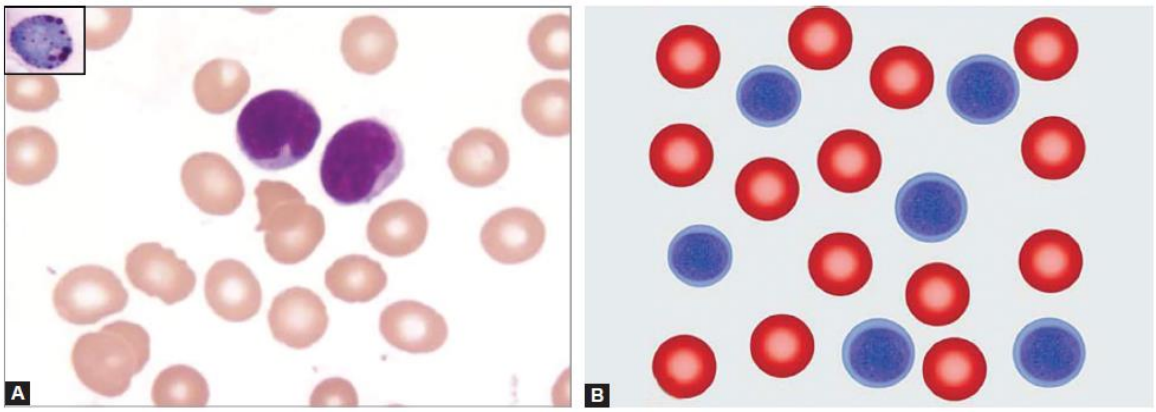
Acute Lymphoblastic Leukemia

- Acute lymphoblastic leukemia (ALL) is primarily a disease of children and young adults.
- This constitutes 80% of **childhood acute leukemias**. It rarely occurs in adults.

The most common mode of presentation is with symptoms of anemia or hemorrhage, infective lesions of the mouth and pharynx, fever, prostration, headache and malaise.

Acute Lymphoblastic Leukemia

- Generalized ***lymphadenopathy, splenomegaly*** **and** ***hepatomegaly*** are common and occur due to infiltration of organs by leukemic cells.
- The typical blood picture is of ***anemia and thrombocytopenia***, with a moderate or marked ***increase in white cells***, the majority of which are blast cells '**lymphoblasts**'

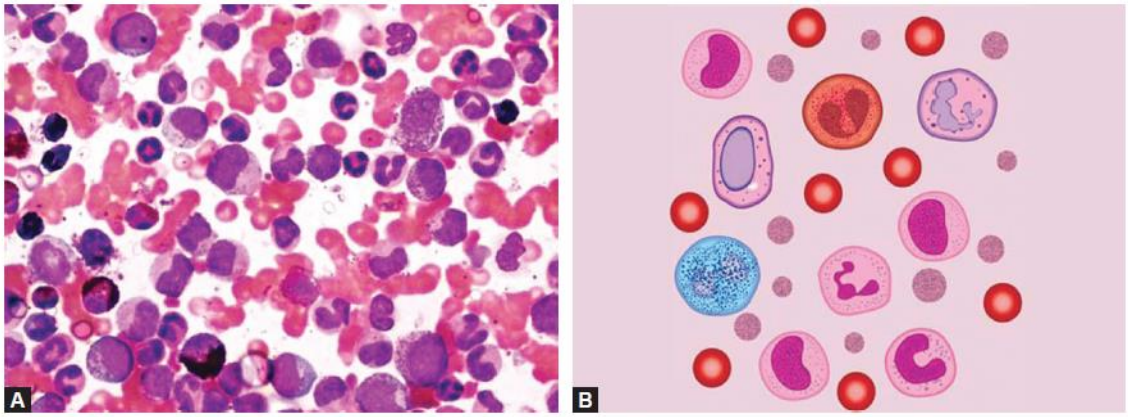


Figs. 18.12A and B: Peripheral blood film picture of acute lymphoblastic leukemia. Note the presence of many lymphoblasts.

Chronic Leukemias

Chronic Myeloid Leukemia

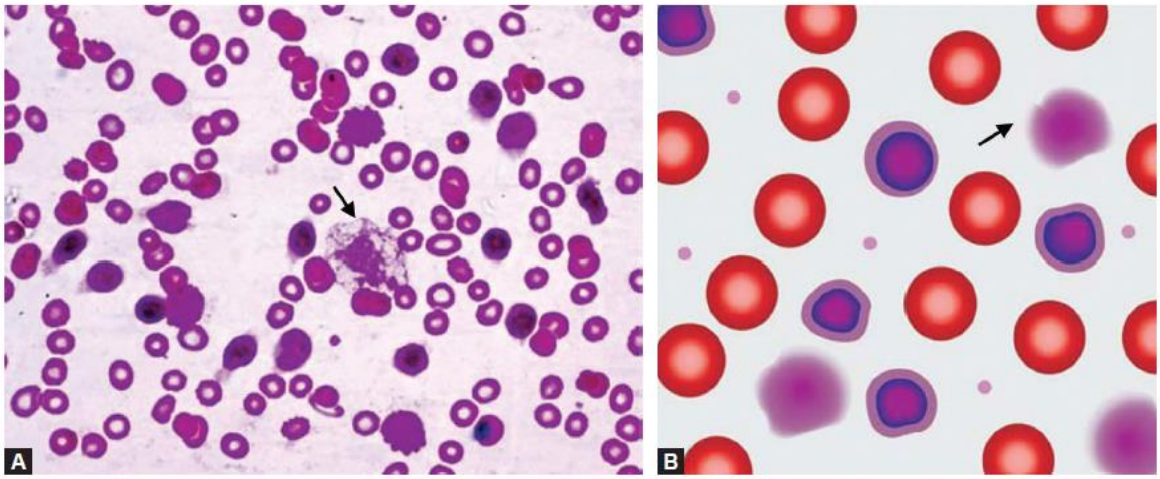
- Chronic myeloid leukemia (CML) accounts for about 20% of all cases of leukemia. It is primarily a disease of **adults between the ages of 30 to 60 years** with the peak incidence in the 4th and 5th decades of life.
- Onset is usually slow with nonspecific features like anemia, weight loss, weakness, and easy fatigability.
- **Splenomegaly** *is the outstanding physical sign*. Hepatomegaly may be present, but lymph node enlargement is rare.



Figs. 18.14A and B: Peripheral blood film picture of chronic myeloid leukemia. Note the presence of many myelocytes and metamyelocytes.

Chronic Myeloid Leukemia

- **Markedly elevated total leucocyte count** usually more than one lakh cells per cubic mm of blood is seen commonly.
- **Neutrophils, myelocytes and metamyelocytes** constitute most of the circulating cells.
- Blasts cells are present rarely except in the blastic crisis.



Figs. 18.15A and B: Peripheral blood film picture of chronic lymphocytic leukemia. Note the presence of many small lymphocytes.

Chronic Lymphocytic Leukemia

- Chronic lymphocytic leukemia (CLL) is the **most indolent** of all leukemias. It occurs typically in **persons over 50 years**.
- Males are affected twice as frequently as females.
- Patients present with nonspecific symptoms.
- **Lymphadenopathy** *is the outstanding physical sign.*
- Hepatosplenomegaly may be present.
- Mild to severe increase in leucocyte count is seen.
- More than **90% of leucocytes are mature lymphocytes**

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