LEUCOCYTES
BENIGN DISORDERS

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LEUCOCYTES BENIGN DISORDERS

- **Quantitative**
  - Change in number

- **Terminology**
  - Cytosis / philia
    - Increase in number
  - Cytopenia
    - Decrease in number

- **Qualitative**
  - Morphologic changes
  - Functional changes
LEUCOCYTES BENIGN DISORDERS

Quantitative changes

Relative vs Absolute values

- Total white blood cell count
- Differential count
- Absolute count

- Differential gives the relative percentage of each WBC
- Absolute value gives the actual number of each WBC/mm$^3$ of blood

  - Calculation: absolute count = Total WBC x percent
Regulation of cell production
- Regulatory mechanisms must operate in close controlled way

Haemopoietic growth factors

The control of cell death

Inhibitors of cell proliferation

Stromal cell factors (cell-cell and cell-matrix interaction)
Quantitative changes (LEUCOCYTOSIS)

- Leucocytes
  - Phagocytes
    - Granulocytes
      - Neutrophils
      - Eosinophils
      - Basophils
    - Mononuclear phagocytic cells
      - Monocytes
      - Macrophage and dendritic cells
  - Lymphocytes
    - B-cells
    - T-cells
Definition

Raised TWBC due to elevation of any of a single lineage.

- Note: elevation of the minor cell populations can occur without a rise in the total white cell count.

Normal reference range (adult 21 years)

- 4.5 -- 11.0 x 10⁹/L
**LEUCOCYTES BENIGN DISORDERS**

Quantitative changes (LEUCOPENIA)

- **Definition**
  
  TWBC lower than the reference range for the age is defined as leucopenia.

  - Leucopenia may affect one or more lineages and it is possible to be severely neutropenic or lymphopenic without a reduction in total white cell count.
Granulocytosis
Increase in the count of all or one of the granulocytic component
- Neutrophils
- Basophils
- Eosinophils

Agranulocytosis
Decrease in the count of all or one granulocytic component
### WBC Histogram:

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<td>LY</td>
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</tr>
<tr>
<td>MO</td>
<td>7.8</td>
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<tr>
<td>EO</td>
<td>2.5</td>
<td>0.2</td>
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<tr>
<td>BA</td>
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Neutrophils

- Count 2.5 - 7.5 x 10⁹/l
- Granular cytoplasm
- Transient stay in blood
- Major phagocytic role
- Bacterial killing
- 3-5 lobes of nucleus
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Quantitative changes (NEUTROPHILIA)

Definition

- Increase in the number of neutrophils and/or its precursors
- In adults count >7.5 x 10^9/L but the counts are age dependent
- Increase may result from alteration in the normal steady state of:
  - Production
    - Increased progenitor cell proliferation
    - Increased frequency of cell division of committed neutrophil precursors
  - Transit
    - Impaired transit to tissue
  - Migration
  - Destruction
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Quantitative changes (NEUTROPHILIA) contd.

- **Causes of Neutrophilia**
  - **Infection**
    - Bacterial
  - **Inflammatory conditions**
    - Autoimmune disorders
    - Gout
  - **Neoplasia**
  - **Metabolic conditions**
    - Uraemia
    - Acidosis
    - Haemorrhage
  - **Corticosteroids**
  - **Marrow infiltration/fibrosis**
  - **Myeloproliferative disorders**
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Quantitative changes (NEUTROPHILIA) contd.

- **Acute Neutrophilia**
  - Mobilized rapidly by stress, suggested by adrenaline stress test; due to reduced neutrophil adhesion
    - Bacterial infection
    - Stress
    - Exercise
  - Slower rise when cells are released from the bone marrow storage pool
    - Steroid
    - Infections (reactive changes; left shift, toxic granulation, high NAP score and Dohle bodies.

- Steroids also reduces the passage to the tissues
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Quantitative changes (NEUTROPHILIA) contd.

- **Chronic neutrophilia**
  - Long term corticosteroid therapy
  - Chronic inflammatory reactions
  - Infections or chronic blood loss
  - Infections
    - Less common organisms e.g. poliomyelitis

- **Leukemoid reactions**
  - Applied to chronic neutrophilia with marked leucocytosis (>20 x 10⁹/L)
  - The usual feature is the shift to the left of myeloid cells
  - Causes include
    - Infections
    - Marrow infiltration
    - Systemic disease (Acute liver failure)
Neutropenia is an absolute reduction in the number of circulating neutrophils

- Mild (1- 1.5 x 10^9/L)
- Moderate (0.5 – 1 x 10^9/L)
- Severe (<0.5 x 10^9/L)

- Symptoms are rare with the neutrophil count above 1 x 10^9/L
- Bacterial infections are the commonest
- Fungal, viral and parasitic infection are relatively uncommon
**Causes of Neutropenia**

- Racial
- Congenital
- Cyclical neutropenia
- Marrow aplasia
- Marrow infiltration
- Megaloblastic anemia
- Acute infections
  - Typhoid, Miliary TB, viral hepatitis
- Drugs
- Irradiation exposure
- Immune disorders
  - HIV
  - SLE
  - Felty’s syndrome
  - Neonatal isoimmune and autoimmune neutropenia
- Hypersplenism
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Quantitative changes (NEUTROPENIA) contd.

- **Management of Neutropenia**
  - Remove the cause if possible
  - Treat any infection aggressively
  - Role of
    - Growth factors
    - Splenectomy

- **Cyclical neutropenia**
  - Regular recurring episodes of severe neutropenia (<0.2 x 10^9/L) usually lasting for 3-6 days
  - Can be familial & inherited with maturation arrest
  - Three suggested mechanisms for cyclical neutropenia
    - Stem cell defect & altered response to growth factors
    - Defect in humoral or cellular stem cell control
    - Periodic accumulation of an inhibitor
Eosinophils

- Count 0.2 – 0.8 x 10⁹/l
- Bilobed nucleus
- Phagocytic activity is low
- Modulation of hypersensitivity and allergic reactions
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Quantitative changes (EOSINOPHILIA)

- Increase in the eosinophil count must prompt for further investigation ($>0.6 \times 10^9/L$)
- The causes of eosinophilia can be considered under following headings
  - Allergy
    - Atopic, drug sensitivity and pulmonary eosinophilia
  - Infection
    - Parasites, recovery from infections
  - Malignancy
    - Hodgkin’s disease, NHL and myeloproliferative disorders
  - Drugs
  - Skin disorders
  - Gastrointestinal disorders
  - Hypereosinophilic syndrome
Hypereosinophilic syndrome

Criteria of diagnosis

- Peripheral blood eosinophil >1.5 x 10⁹/L
- Persistence of counts more than 6 months
- End organ damage
- Absence of any obvious cause for eosinophilia

Organ most commonly involved

- Heart
- Lung
- Skin
- Neurological
Monocytes

- Count is 0.2-0.8 x 10⁹/l
- Functions
  - Antigen presentation
  - Cytokine production
  - Phagocytosis
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Quantitative changes (MONOCYTOSIS)

- Absolute monocyte count is age dependent
- Count rarely exceeds $>1.0 \times 10^9/L$
- Have no marrow reserves
- Useful harbinger of engraftment
- Causes of monocytosis can be grouped as
  - Infections
    - Chronic infection (TB, typhoid fever, infective endocarditis)
    - Recovery from acute infection
  - Malignant disease
    - MDS, AML, HD, NHL
  - Connective tissue disorders
    - Ulcerative colitis, Sarcoidosis, Crohn’s disease
  - Post splenectomy
Basophils

- Count 0.1 – 0.2 x 10^9/l
- Bilobed nucleus
- Nucleus is hided behind the granules
- Inflammatory response
- Basophilia is seen in Myeloproliferative disorders (CML)
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Quantitative changes (BASOPHILIA)

- Basophils are least common of the granulocytes
- Reference range for adult is 0 – 0.2 x 10^9/L
- Most commonly associated with hypersensitivity reactions to drugs or food
- Inflammatory conditions e.g. RA, ulcerative colitis are also sometime associated with basophilia
- Myeloproliferative disorders
- Chronic myeloid leukemia
Lymphocytes

- Count varies with age
  - 1.5 – 3.5 x10^9/l
- The subset cells are
  - B-cells
    - Antibody mediated immunity
  - T-cells
    - Cell mediated immunity
  - NK cells
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Quantitative changes (LYMPHOCYTOSIS)

- The blood contain only few percent of total body lymphocytes
- The most consistent variation is seen with age
- Alteration of lymphocyte counts can result from:
  - The redistribution of lymphocytes
    - Results in variation in count in serial measurements
  - Absolute increase of lymphocyte number
  - Loss of lymphocytes
  - Combination of these
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Quantitative changes (LYMPHOCYTOSIS)

- Non-malignant causes of lymphocytosis
  - Infections
    - Viral infections
      - Infectious mononucleosis
      - CMV
      - Rubella, hepatitis, adenoviruses, chicken pox, dengue
    - Bacterial infections
      - Pertussis
      - Healing TB, typhoid fever
    - Protozoal infections
      - Toxoplasmosis
  - Allergic drug reactions
  - Hyperthyroidism
  - Splenectomy
  - Serum sickness
Infectious Mononucleosis

- Epstein-Barr virus
- Saliva from infected person is the main contagion
- Virus infect epithelial cells and B cells
- Autocrine growth stimulation
- Infection in children under the age of 10 does not cause illness and result in life long immunity

Clinical features

- Fever, malaise, fatigue, sore throat, diagnostic red spots at the junction of soft and hard palate, splenomegaly
- Blood picture shows leucocytosis (10 – 20 x 10⁹/L) due to absolute increase in the number of lymphocytes
- Diagnosis is by serological tests
- There is no specific treatment
Nonmalignant Leukocyte Disorders

- **Leukemoid reaction** – this is an extreme neutrophilia with a WBC count $> 30 \times 10^9/L$
  - Many bands, metamyelocytes, and myelocytes are seen
  - Occasional promyelocytes and myeloblasts may be seen.
  - This condition resembles a chronic myelocytic leukemia (CML), but can be differentiated from CML based on the fact that in leukemoid reactions:
    - There is no Philadelphia chromosome
    - The condition is transient
    - There is an increased leukocyte alkaline phosphatase score (more on this later)
    - Leukemoid reactions may be seen in tuberculosis, chronic infections, malignant tumors, etc.
Leukemoid reaction
Leukemoid reaction
Nonmalignant Leukocyte Disorders

- Morphologic and functional abnormalities of neutrophils
  - Acquired, morphologic – these are reactive, transient changes accompanying infectious states. They include
    - Toxic granulation
    - Dohle bodies
    - Cytoplasmic vacuoles
Dohle bodies
Morphologic neutrophil changes

Vacuolated cell
Morphologic neutrophil changes

Toxic granulation
Nonmalignant Leukocyte Disorders

- Inherited functional and/or morphological abnormalities
  - Pelger-Huet Anomaly – this is a benign, inherited, autosomal dominant abnormality in which the neutrophil nucleus does not segment beyond the bilobular stage (“Prince-nez cells”).
    - The cells may sometimes resemble bands, but the chromatin is more condensed (mature).
    - The cells function normally.
  - Acquired or pseudo Pelger-Huet Anomaly is seen in myeloproliferative and myelodysplastic states
Pelger-Huet Anomaly
Pseudo Pelger-Huet Anomaly

Note nuclear maturity
Nonmalignant Leukocyte Disorders

- Alder-Reilly Anomaly – in this disorder all leukocytes contain large, purplish granules (due to partially degraded protein-carbohydrates) in the cytoplasm, but the cells function normally.
  - This is seen in Hurler’s and Hunter’s syndromes in which there is an incomplete breakdown of mucopolysaccharides.
Hurler’s Syndrome

Note the granules
Nonmalignant Leukocyte Disorders

- Chediak-Higashi Anomaly –
  - This is a rare autosomal recessive disorder in which abnormal lysosomes are formed by the fusion of primary granules. These are seen as grayish-green inclusions.
  - The cells are ineffective in killing microorganisms and affected individuals often die early in life from pyogenic infections.
Chediak-Higashi Anomaly

Note abnormal lysosomes
Nonmalignant Leukocyte Disorders

- May-Hegglin Anomaly
  - This is a rare, autosomal dominant disorder in which the leukocytes contain large basophilic inclusions containing RNA that look similar to Dohle bodies.
  - It can be differentiated from an infection because toxic granulation is not seen.
  - The patients also have giant platelets that have a shortened survival time. Because of this, patients may have bleeding problems, but they usually have no other clinical symptoms.
May-Hegglin Anomaly

Basophilic inclusions

large platelet
Nonmalignant Leukocyte Disorders

- **Chronic granulomatous disease**
  - This is a lethal, sex-linked disorder affecting the function of the neutrophil.
  - The neutrophil can function in phagocytosis, but it cannot kill microorganisms because the cells have a defect in the respiratory burst oxidase system.
  - Affected individuals have chronic infections with organisms that do not normally cause infections in normal individuals.

- **Myeloperoxidase deficiency**
  - This is a benign, autosomal recessive disorder characterized by a lack of myeloperoxidase in the neutrophils.
Nonmalignant Leukocyte Disorders

- Affected individuals may have occasional problems with *Candida* infections, but usually they have no problems with infections because they have other mechanisms to kill microorganisms.

- **Leukocyte adhesion deficiency**
  - This is a rare, autosomal recessive disorder characterized by the absence of leukocyte cell surface adhesion proteins.
  - Because of the lack of the adhesion molecules, the leukocytes have functional defects in:
    - Chemotaxis
    - Phagocytosis
    - Respiratory burst activation
    - Degranulation
  - Affected individuals have frequent bacterial and fungal infections and mortality in childhood is high.
Inherited abnormalities of neutrophils are also seen in monocytes because they originate from a common stem cell:

- **Chronic granulomatous disease** (defective respiratory burst)
- **Chediak Higashi** (abnormal lysosomes caused by fusion of primary granules)
- **Alder Reilly Anomaly** (large purple-blue granules)