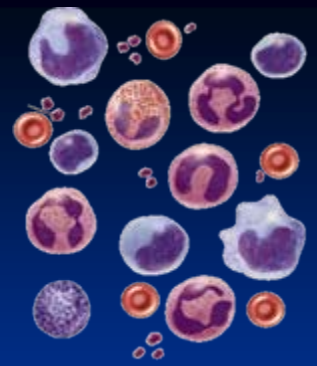
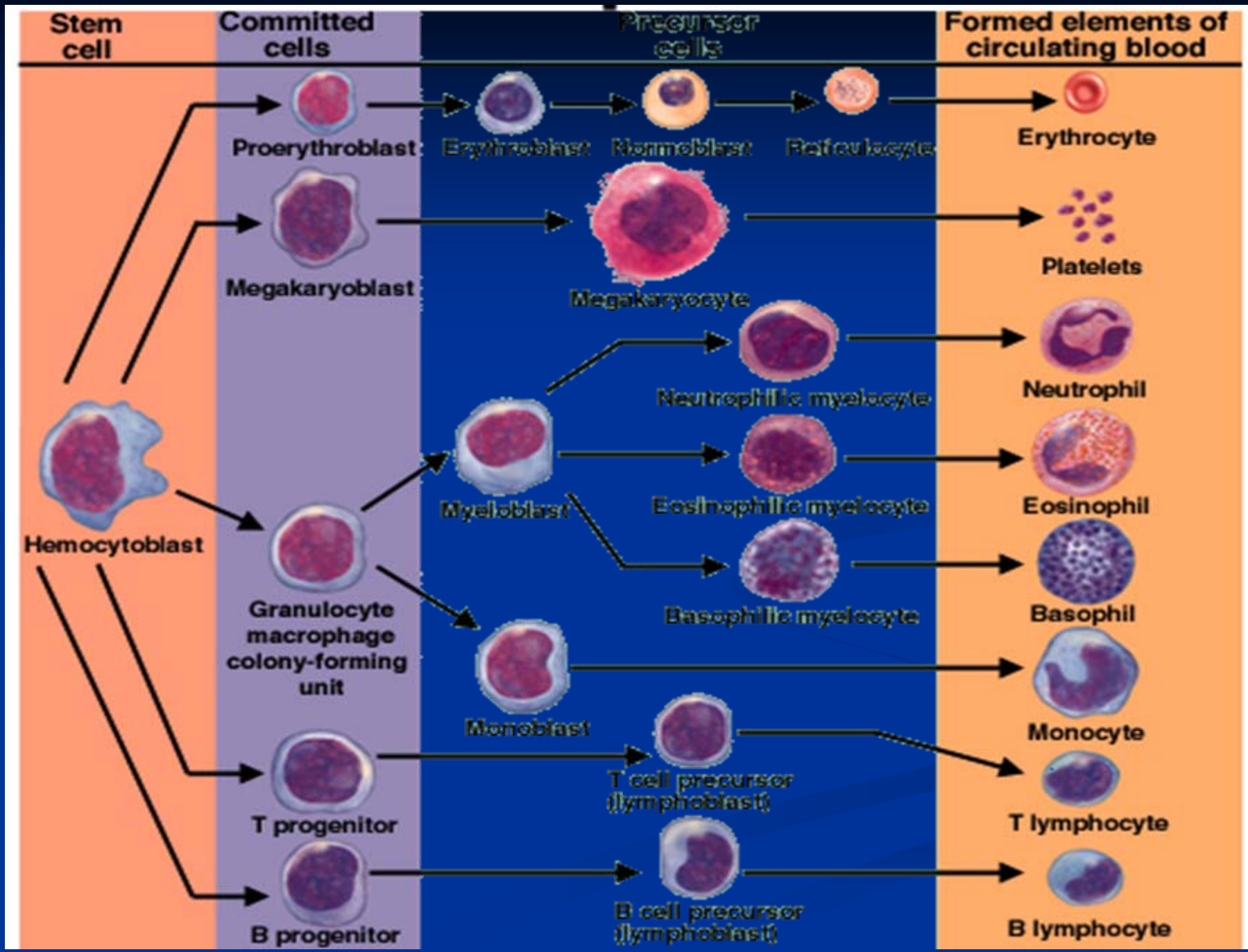
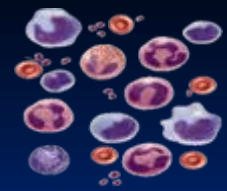


LEUCOCYTES BENIGN DISORDERS

Dr Adel M Abuzenadah


Stem cell
Committed cells
Precursor cells
Formed elements of circulating blood
Proerythroblast
Erythroblast
Normoblast
Reticulocyte
Erythrocyte
Megakaryoblast
Megakaryocyte
Platelets
Neutrophilic myelocyte
Neutrophil
Hemocytoblast
Myeloblast
Eosinophilic myelocyte
Eosinophil
Basophilic myelocyte
Basophil
Granulocyte macrophage colony-forming unit
Monoblast
Monocyte
T progenitor
T cell precursor (lymphoblast)
T lymphocyte
B progenitor
B cell precursor (lymphoblast)
B lymphocyte

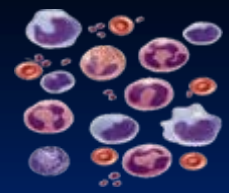
LEUCOCYTES BENIGN DISORDERS



- Quantitative
  - Change in number
  - Terminology
    - Cytosis / philia
      - Increase in number
    - Cytopenia
      - Decrease in number
- Qualitative
  - Morphologic changes
  - Functional changes

LEUCOCYTES BENIGN DISORDERS

Quantitative changes



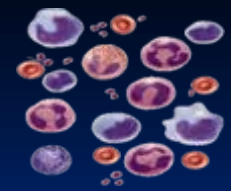
Relative vs Absolute values

- 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

LEUCOCYTES BENIGN DISORDERS

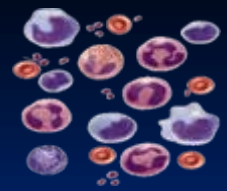
Quantitative changes

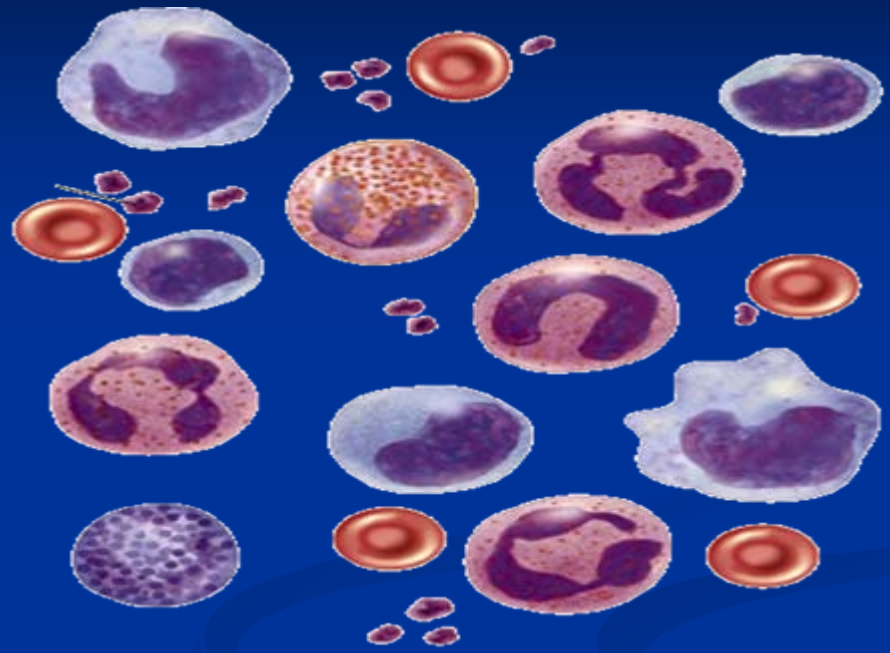


- Regulation of cell production
  - Regulatory mechanisms must operate in close controlled way
- Haemopoietic growth factors
- The control of cell death
- Inhibitors of cell proliferation
- Stromal cell factors (cell-cell and cell-matrix interaction)

LEUCOCYTES BENIGN DISORDERS

Quantitative changes (LEUCOCYTOSIS)

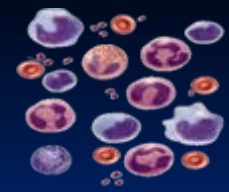




- Leucocytes
  - Phagocytes
    - Granulocytes
      - Neutrophils
      - Eosinophils
      - Basophils
    - Mononuclear phagocytic cells
      - Monocytes
      - Macrophage and denderetic cells
  - Lymphocytes
    - B-cells
    - T-cells

LEUCOCYTES BENIGN DISORDERS

Quantitative changes (LEUCOCYTOSIS)



- Definition

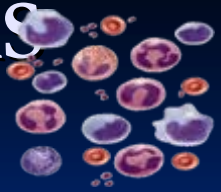
  Raised TWBC due to elevation of any of a single lineage.

  - *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 10^9/L

LEUCOCYTES BENIGN DISORDERS

Quantitative changes (LEUCOPENIA)



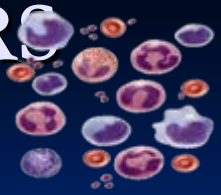
- Definition

  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.

LEUCOCYTES BENIGN DISORDERS

Quantitative changes (contd.)

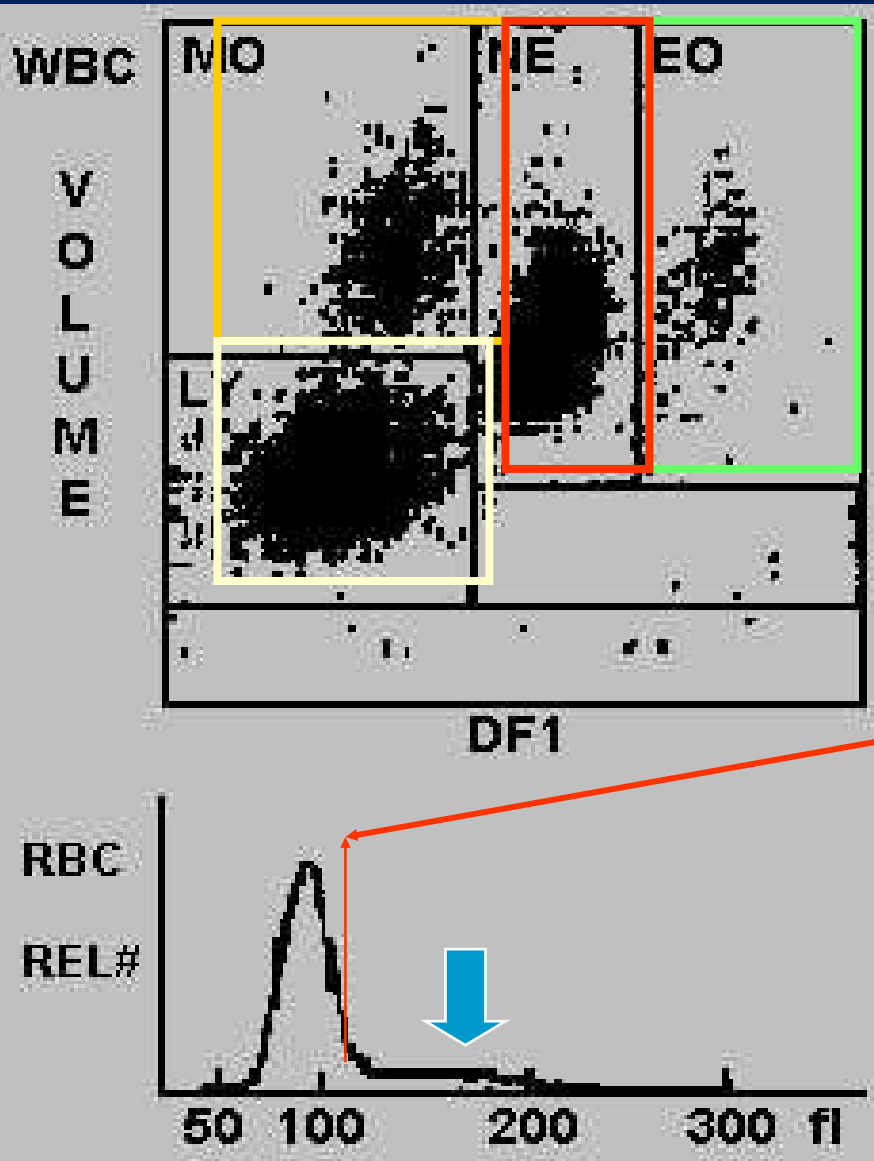


- Granulocytosis

  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

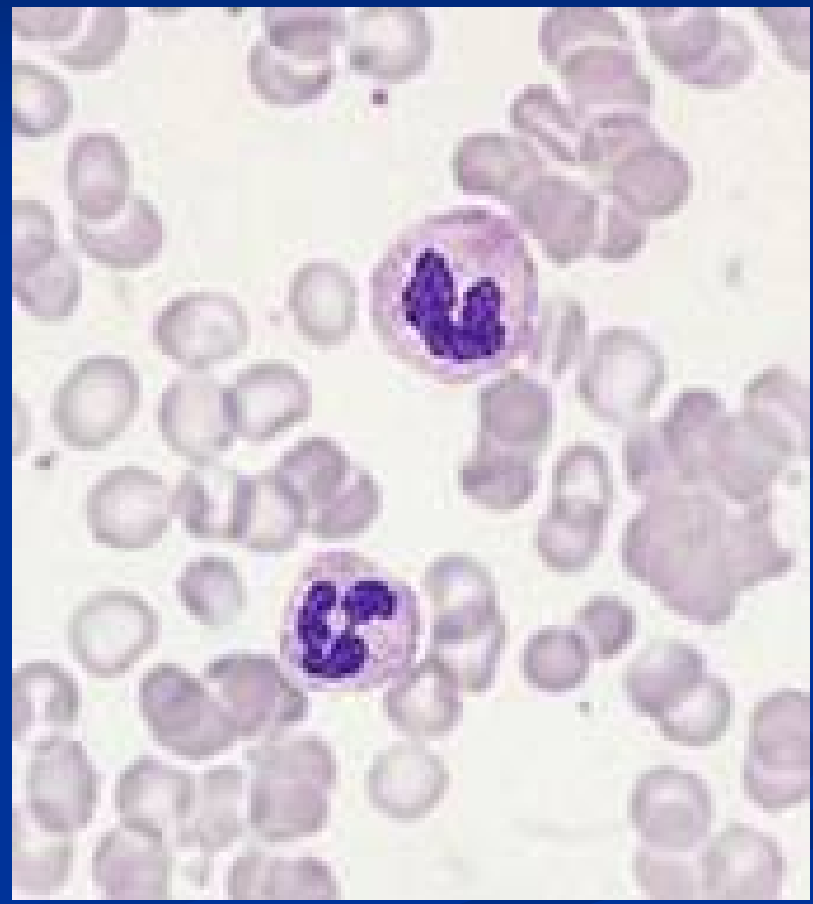
WBC Histogram:



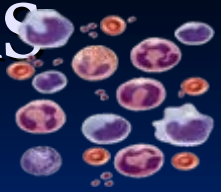
WBC	6.8	
	%	#
NE	52.6	3.6
LY	36.7	2.5
MO	7.8	0.5
EO	2.5	0.2
BA	0.4	0.0
RBC	5.29	
HGB	16.2	
HCT	47.0	
MCV	88.8	
MCH	30.7	
MCHC	34.5	
RDW	12.5	
PLT	179	
MPV	8.4	

Neutrophils

- Count 2.5 - 7.5 x 10^9/l
- Granular cytoplasm
- Transient stay in blood
- Major phagocytic role
- Bacterial killing
- 3-5 lobes of nucleus



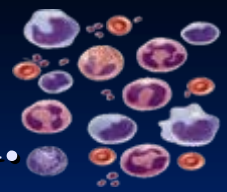
LEUCOCYTES BENIGN DISORDERS
Quantitative changes (NEUTROPHILIA)



- 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 results 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

LEUCOCYTES BENIGN DISORDERS

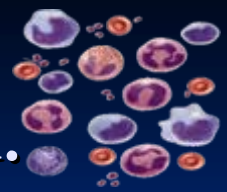
Quantitative changes (NEUTROPHILIA) contd.



- Causes of Neutrophilia
  - Infection
    - Bacterial
  - Inflammatory conditions
    - Autoimmune disorders
    - Gout
  - Neoplasia
  - Metabolic conditions
    - Uraemia
    - Acidosis
    - Haemorhage
  - Corticosteroids
  - Marrow infiltration/fibrosis
  - Myeloproliferative disorders

LEUCOCYTES BENIGN DISORDERS

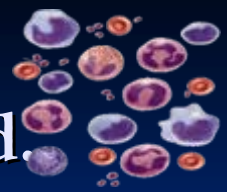
Quantitative changes (NEUTROPHILIA) contd.



- 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

LEUCOCYTES BENIGN DISORDERS

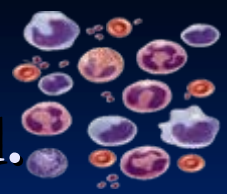
Quantitative changes (NEUTROPHILIA) contd.



- 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 10^9/L)
  - The usual feature is the shift to the left of myeloid cells
  - Causes include
    - Infections
    - Marrow infiltration
    - Systemic disease (Acute liver failure)

LEUCOCYTES BENIGN DISORDERS

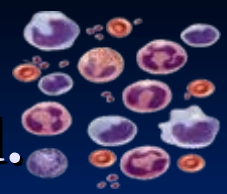
Quantitative changes (NEUTROPENIA) contd.



- 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

LEUCOCYTES BENIGN DISORDERS

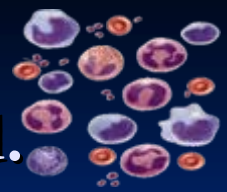
Quantitative changes (NEUTROPENIA) contd.



- 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
  - Hyperslplenism

LEUCOCYTES BENIGN DISORDERS

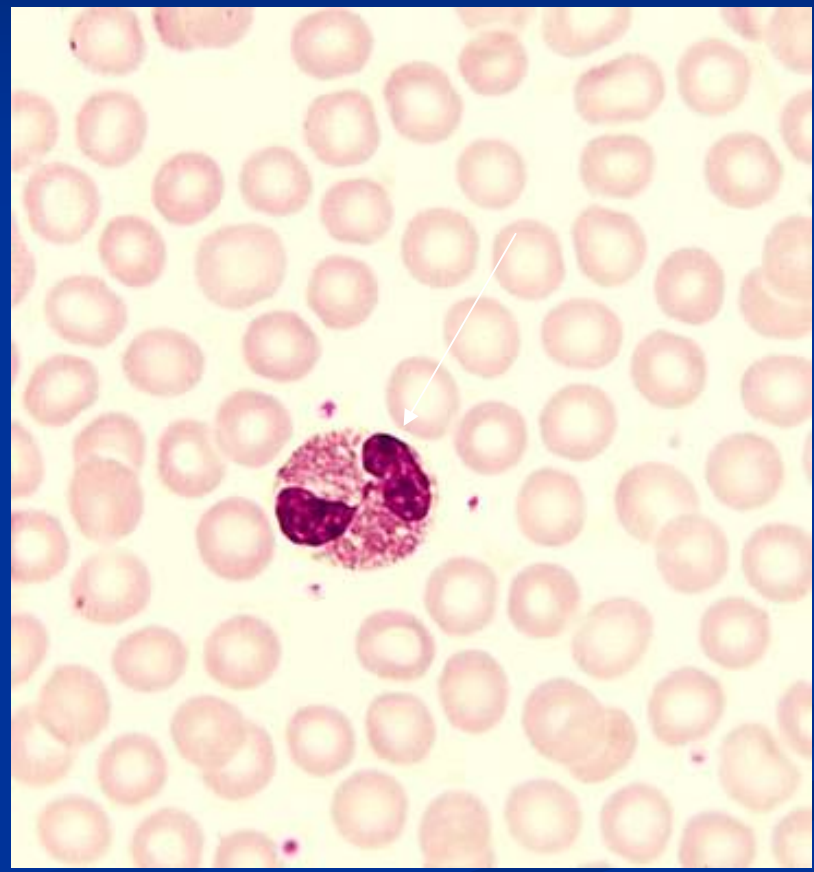
Quantitative changes (NEUTROPENIA) contd.



- 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 ($<0.2 \times 10^9/L$) 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

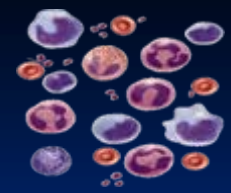
Eosinophils

- Count 0.2 – 0.8 x 10^9/l
- Bilobed nucleus
- Phagocytic activity is low
- Modulation of hypersensitivity and allergic reactions



LEUCOCYTES BENIGN DISORDERS

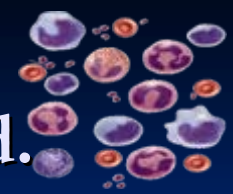
Quantitative changes (EOSINOPHILIA)



- Increase in the eosinophil count must prompt for further investigation (>0.6 x 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

LEUCOCYTES BENIGN DISORDERS

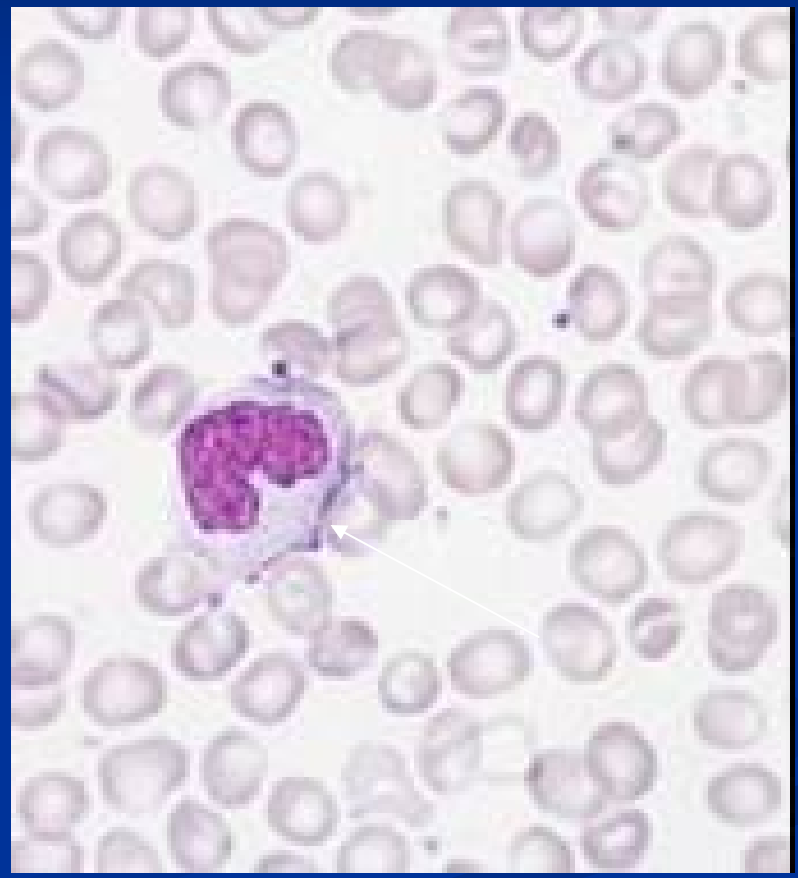
Quantitative changes (EOSINOPHILIA) Contd.



- Hypereosinophilic syndrome
  - Criteria of diagnosis
    - Peripheral blood eosinophil >1.5 x 10^9/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

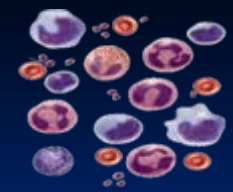
Monocytes

- Count is 0.2-0.8 x 10^9/l
- Functions
  - Antigen presentation
  - Cytokine production
  - Phagocytosis



LEUCOCYTES BENIGN DISORDERS

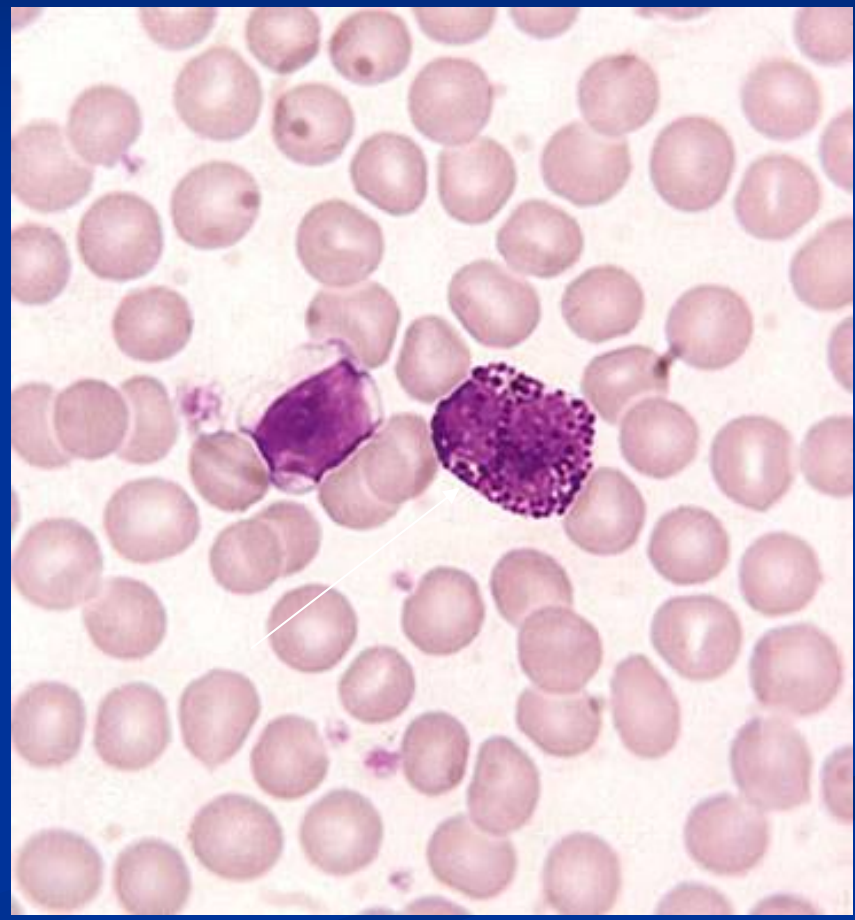
Quantitative changes (MONOCYTOSIS)



- Absolute monocyte count is age dependent
- Count rarely exceeds >1.0 x 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

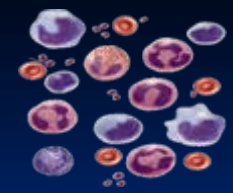
Basophils

- 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)



LEUCOCYTES BENIGN DISORDERS

Quantitative changes (BASOPHILIA)



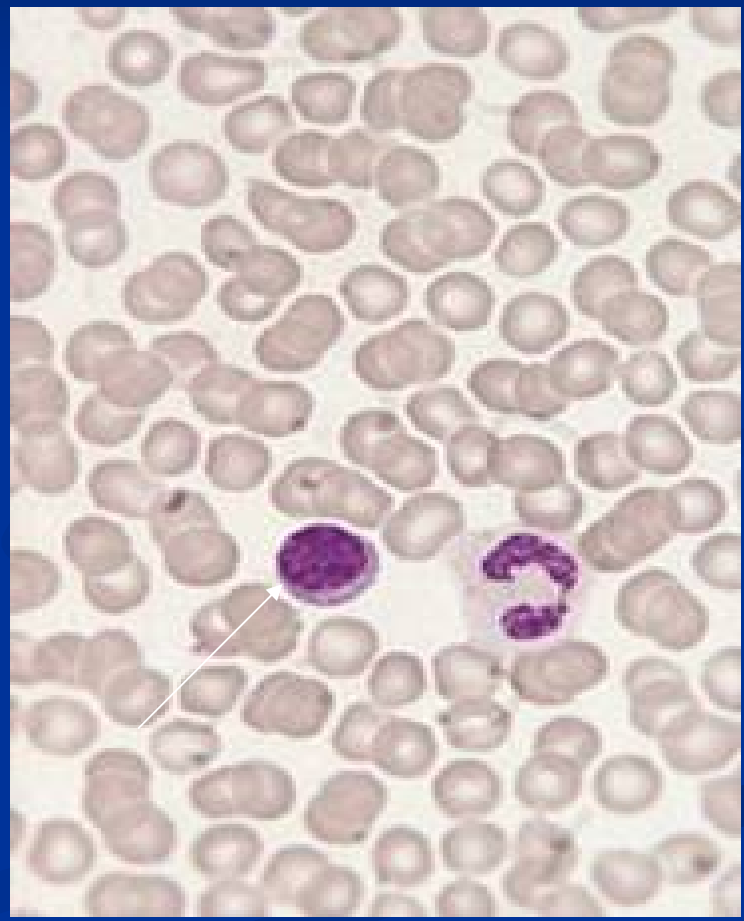
- Basophils are least common of the granulocytes
- Reference range for adult is $0 – 0.2 \times 10^9/L$
- Most commonly associated with hypersensitivity reactions to drugs or food
- Inflammatory conditions e.g RA, ulcerative colitis are also sometime associated with basophilia
- Myeloproliferative disorders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

Lymphocytes

- Count varies with age

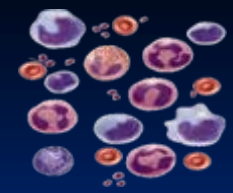
$1.5 – 3.5 \times 10^9/l$

- The subset cells are
  - B-cells
    - Antibody mediated immunity
  - T-cells
    - Cell mediated immunity
  - NK cells



LEUCOCYTES BENIGN DISORDERS

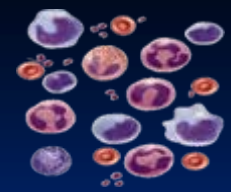
Quantitative changes (LYMPHOCYTOSIS)



- 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

LEUCOCYTES BENIGN DISORDERS

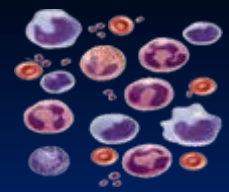
Quantitative changes (LYMPHOCYTOSIS)



- 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

LEUCOCYTES BENIGN DISORDERS

Quantitative changes (LYMPHOCYTOSIS)

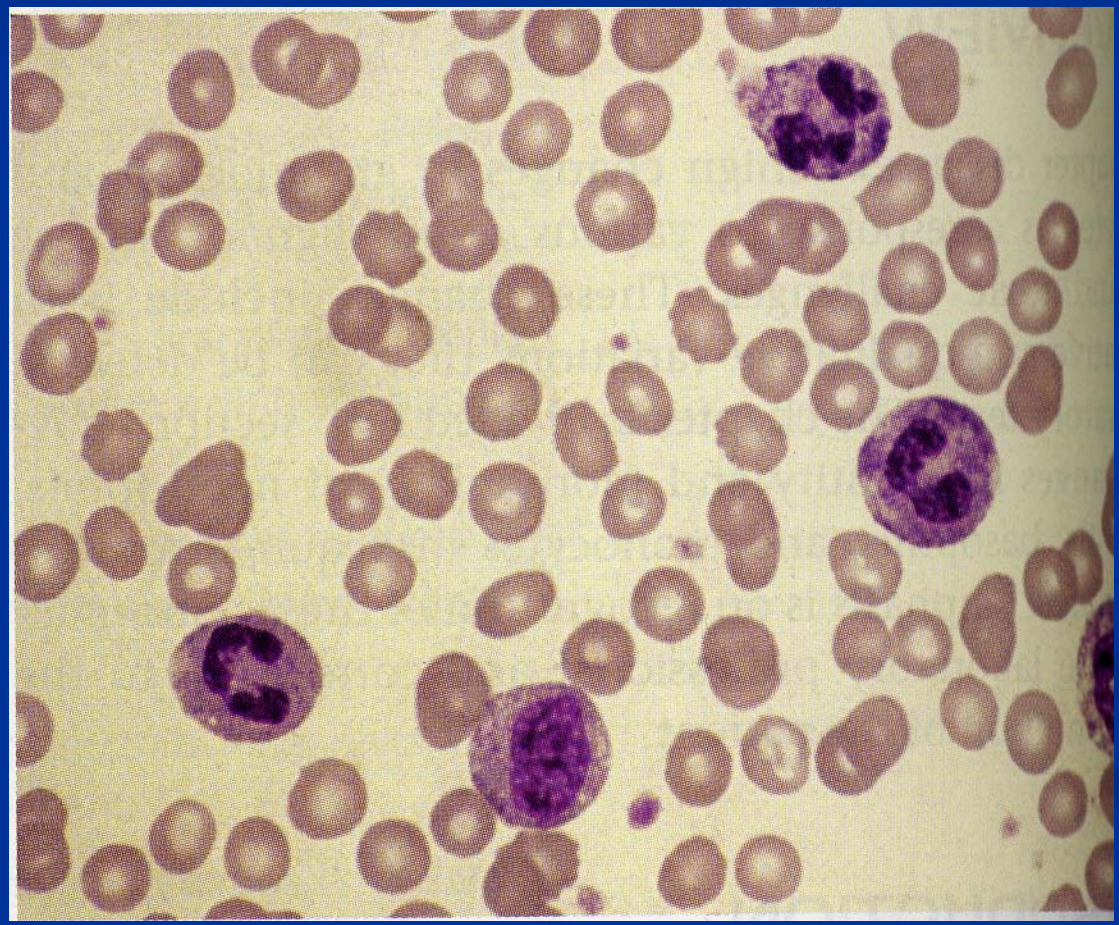


- Infectious Mononucleosis
  - Epstein-Barr virus
  - Saliva from infected person is the main contagion
  - Virus infect epithelial cells and B cells
  - Autocrine growth stimulation
  - Infection in children under the age of 10 does not cause illness and result in life long immunity
  - Clinical features
    - Fever, malaise, fatigue, sore throat, diagnostic red spots at the junction of soft and hard palate, splenomegaly
    - Blood picture shows leucocytosis (10 – 20 x 10^9/L) due to absolute increase in the number of lymphocytes
    - Diagnosis is by serological tests
    - There is no specific treatment

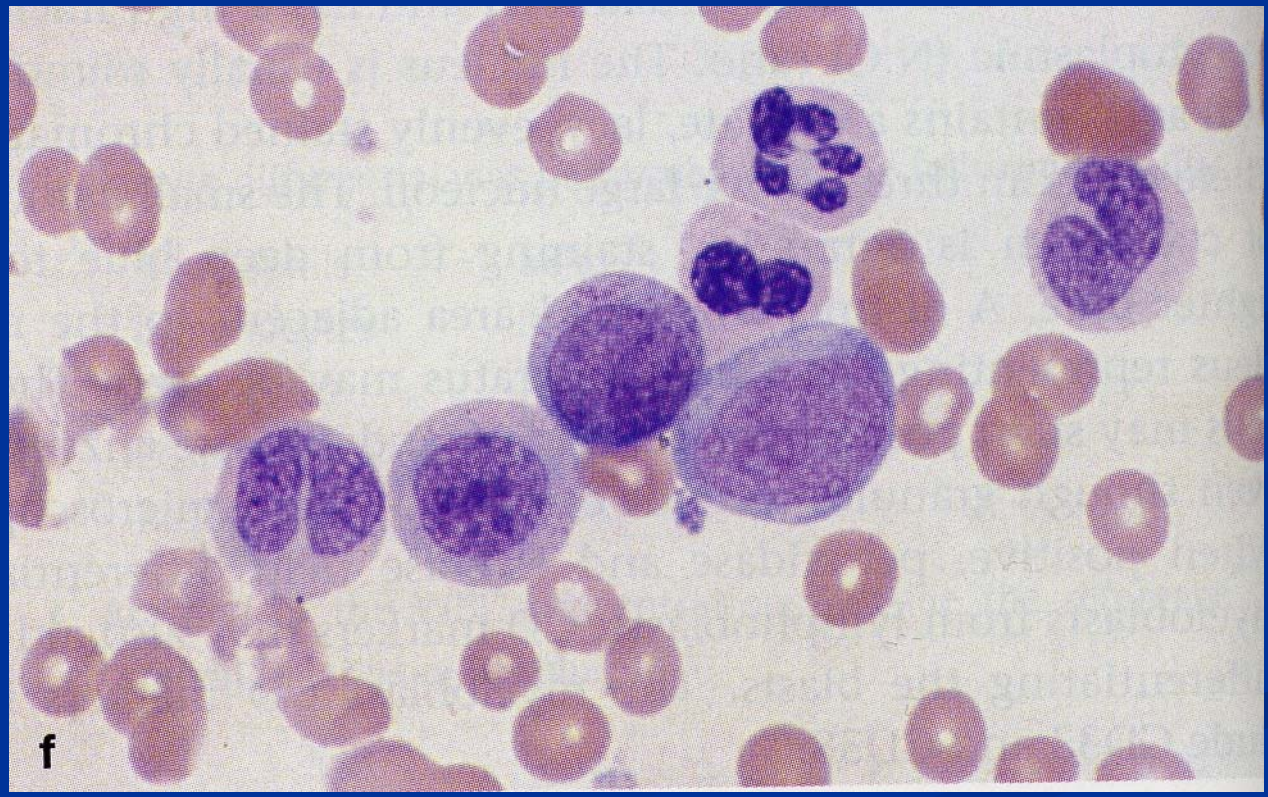
Nonmalignant Leukocyte Disorders

- Leukemoid reaction – this is an extreme neutrophilia with a WBC count > 30 x 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



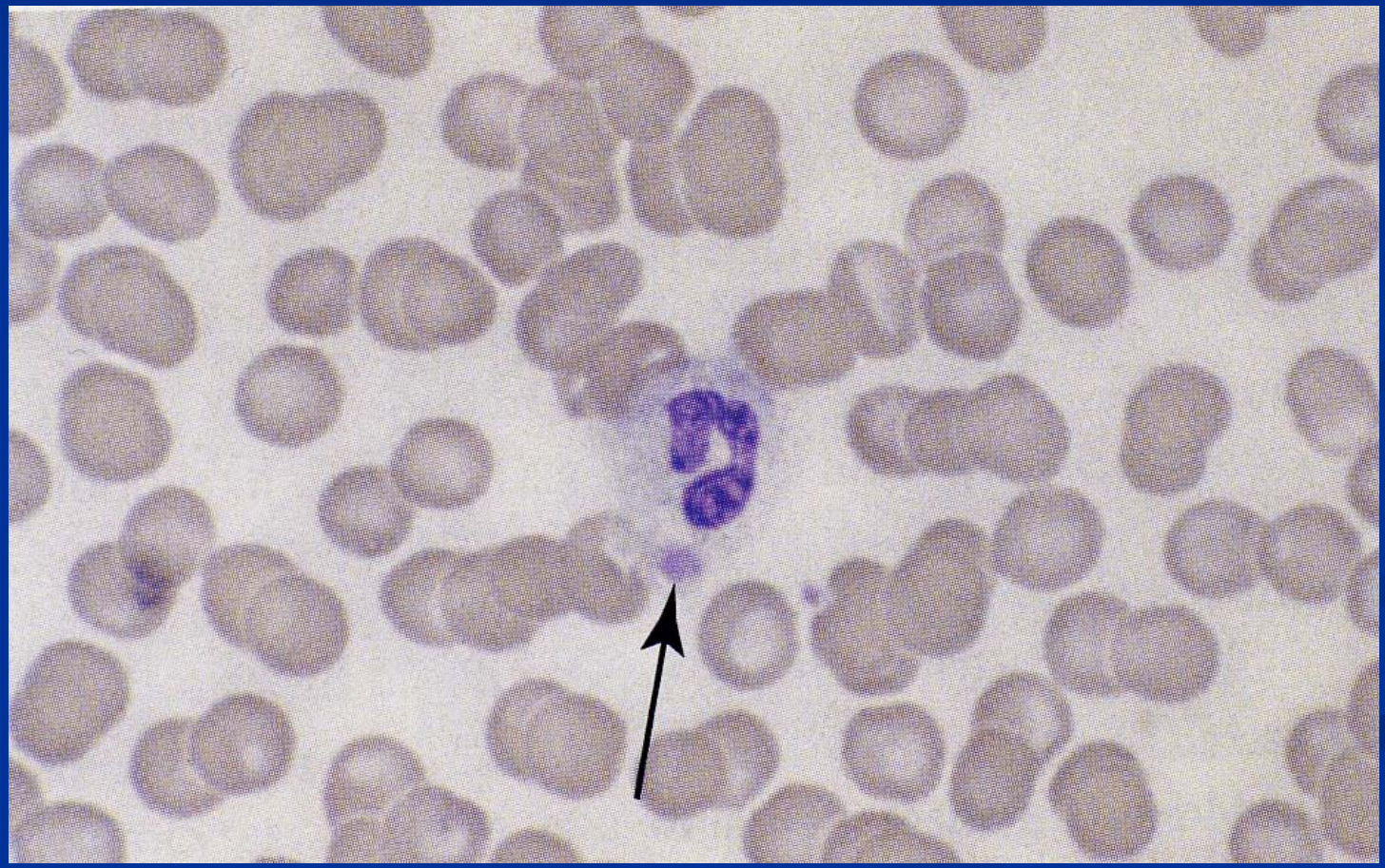
Leukemoid reaction



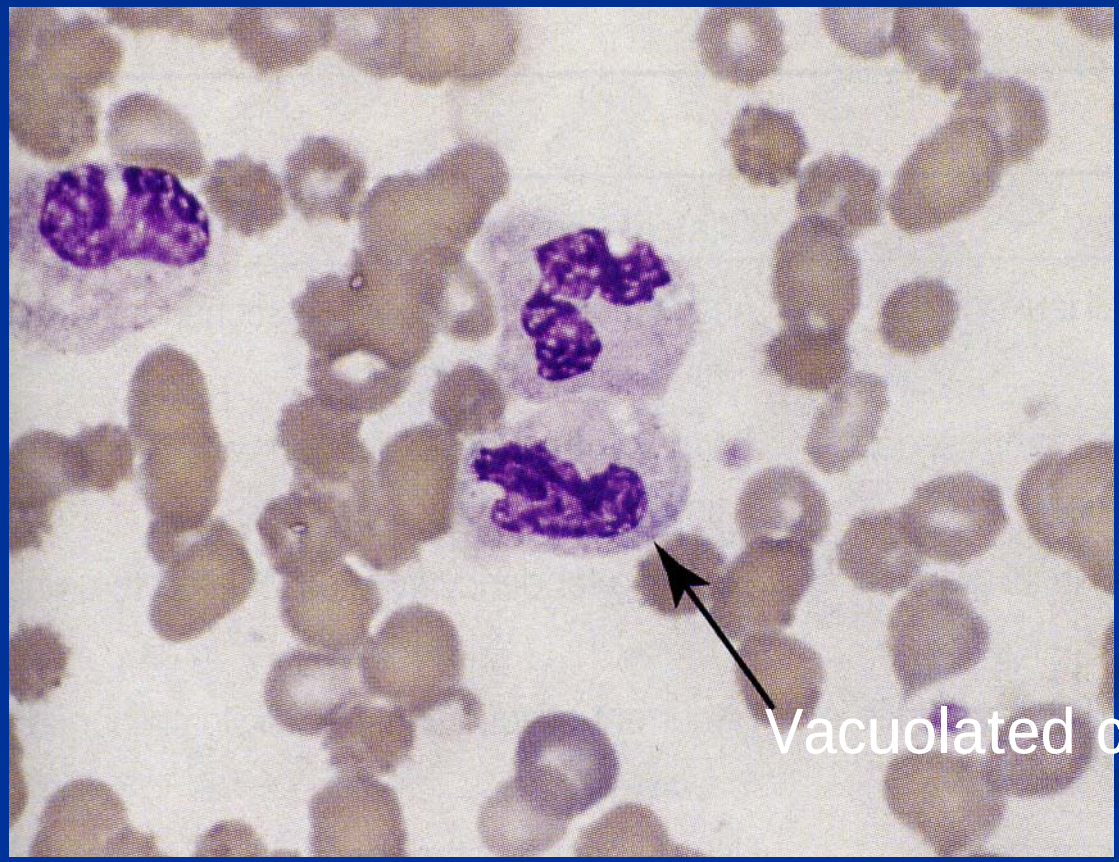
Nonmalignant Leukocyte Disorders

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

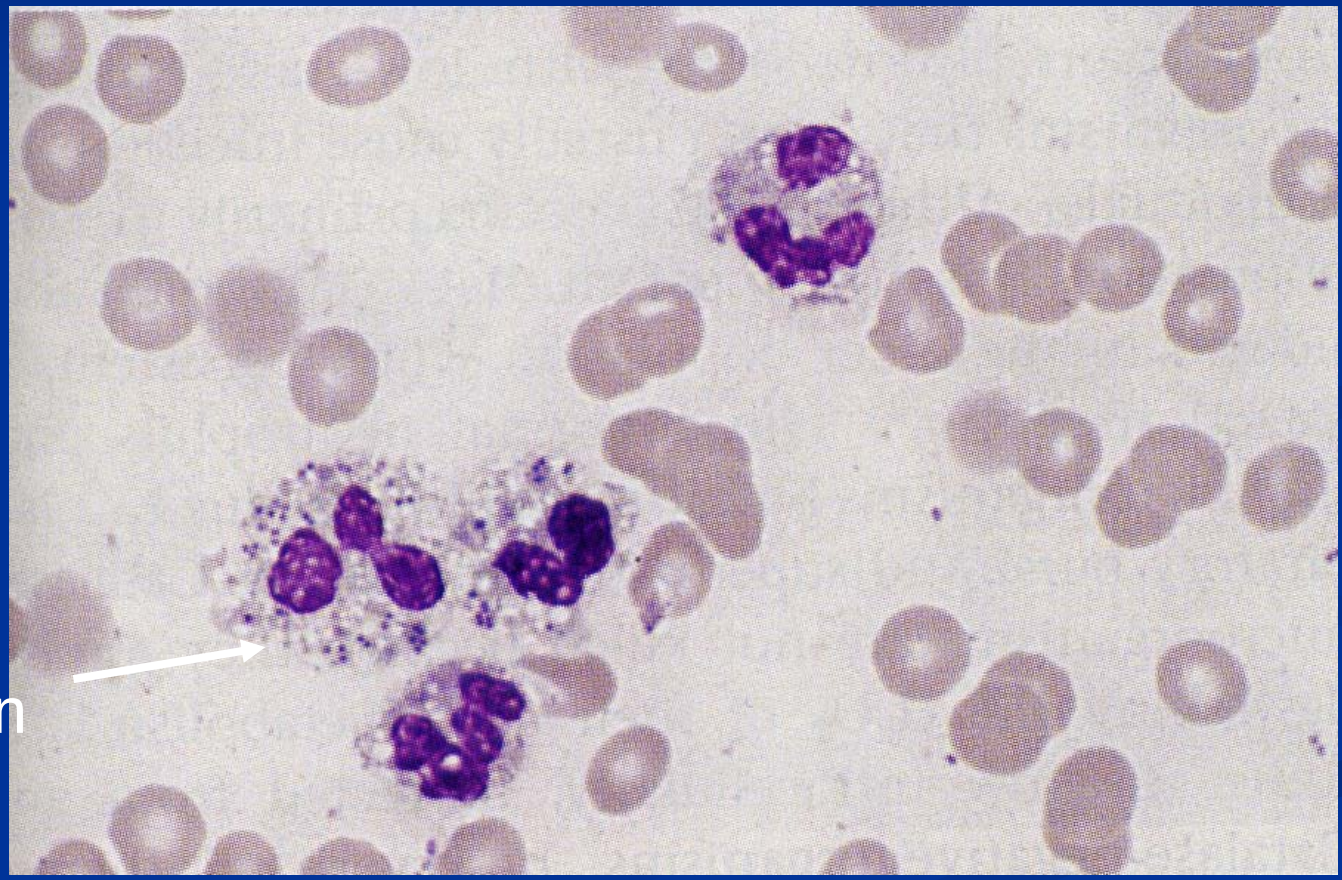
Dohle bodies



Morphologic neutrophil changes



Morphologic neutrophil changes

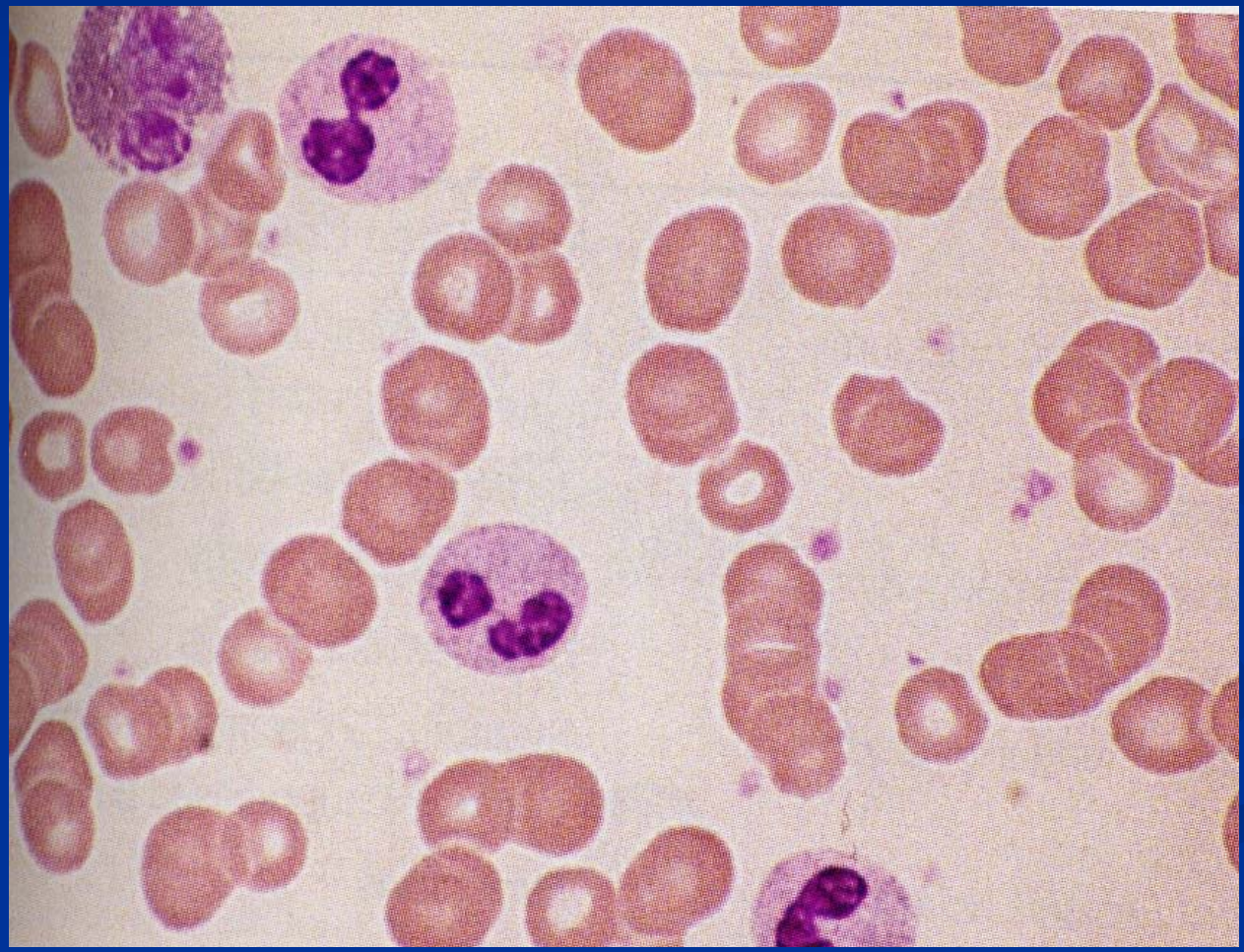


Toxic granulation

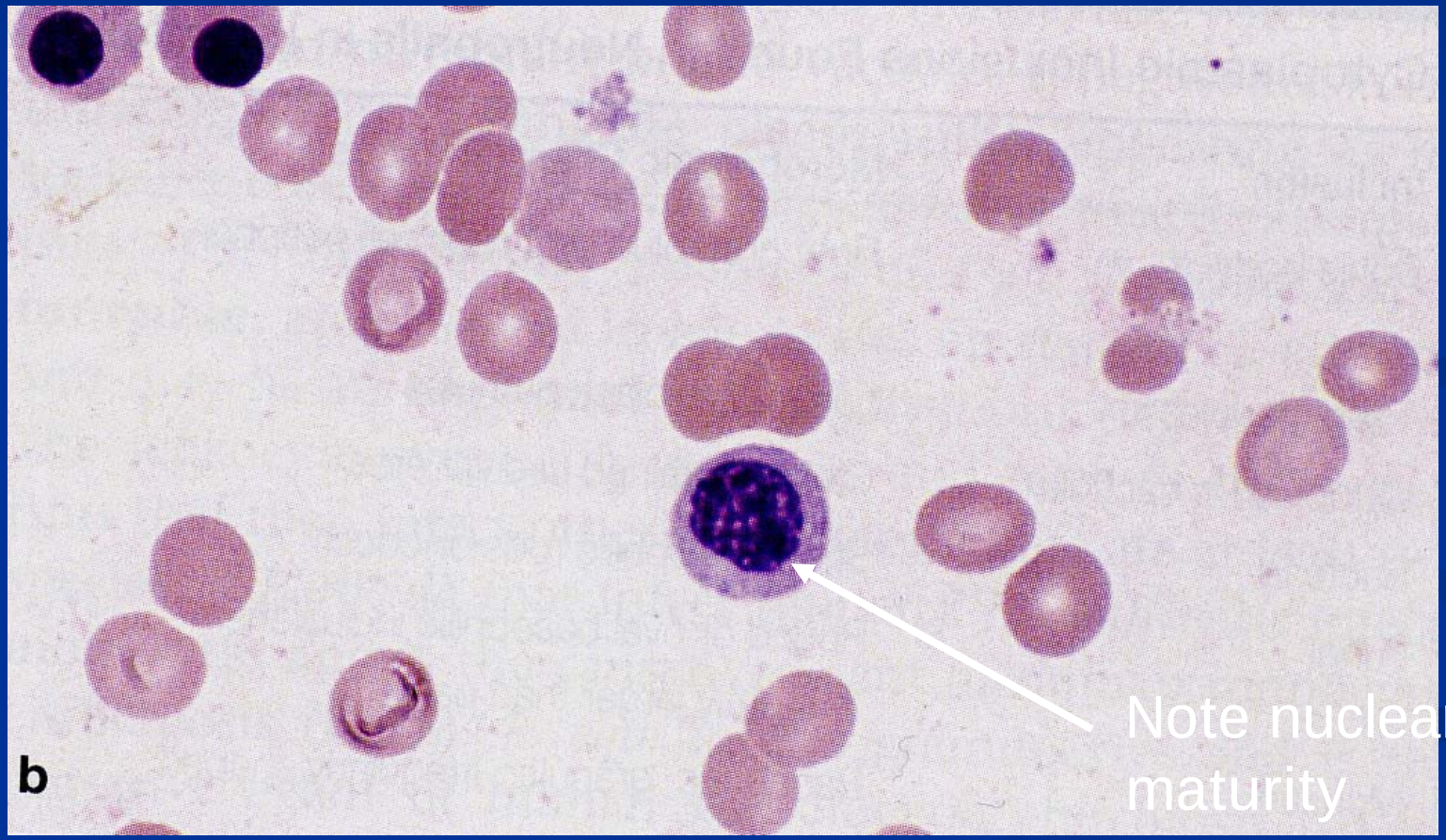
Nonmalignant Leukocyte Disorders

- 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



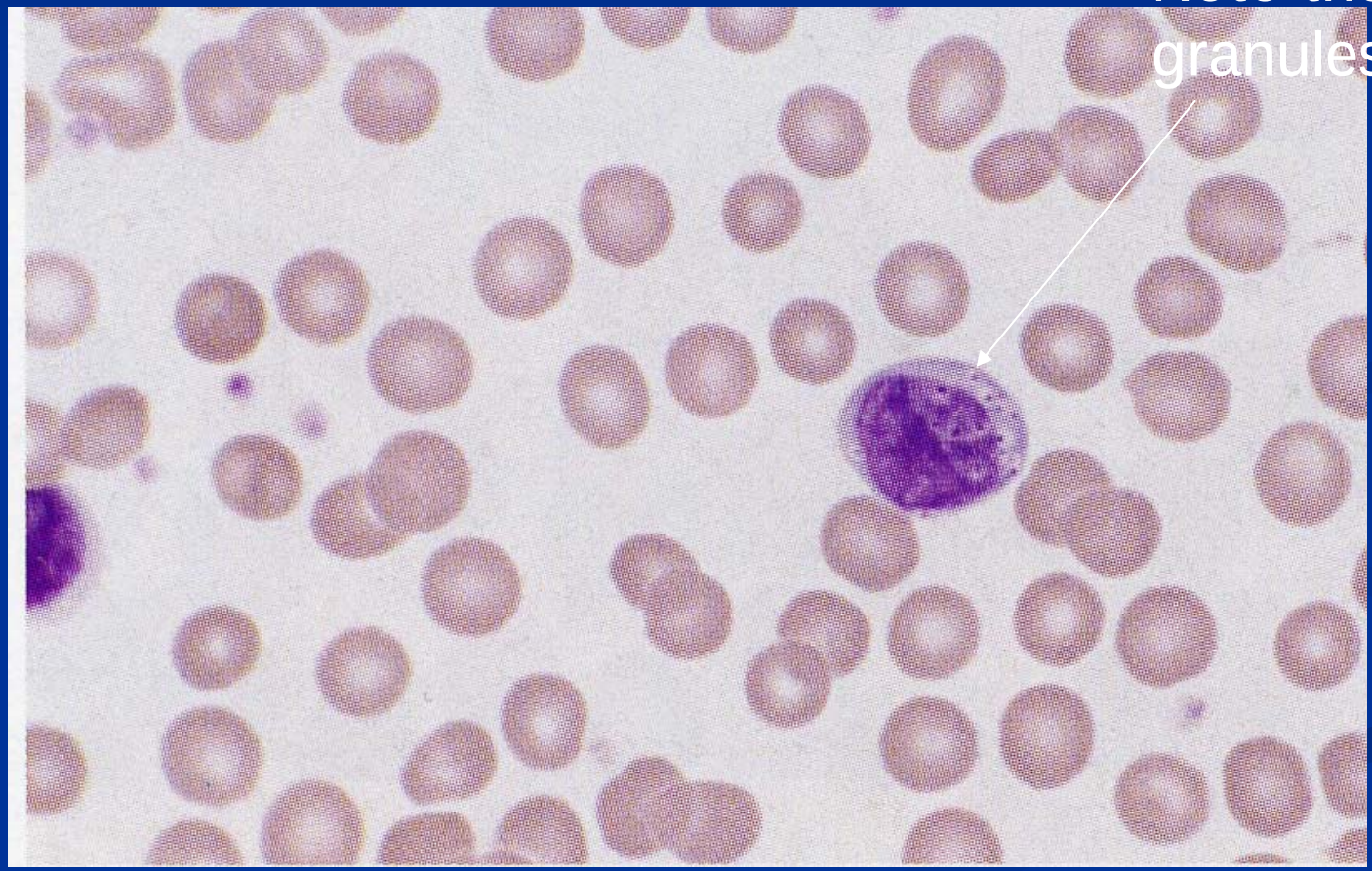
Pseudo Pelger-Huet Anomaly



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

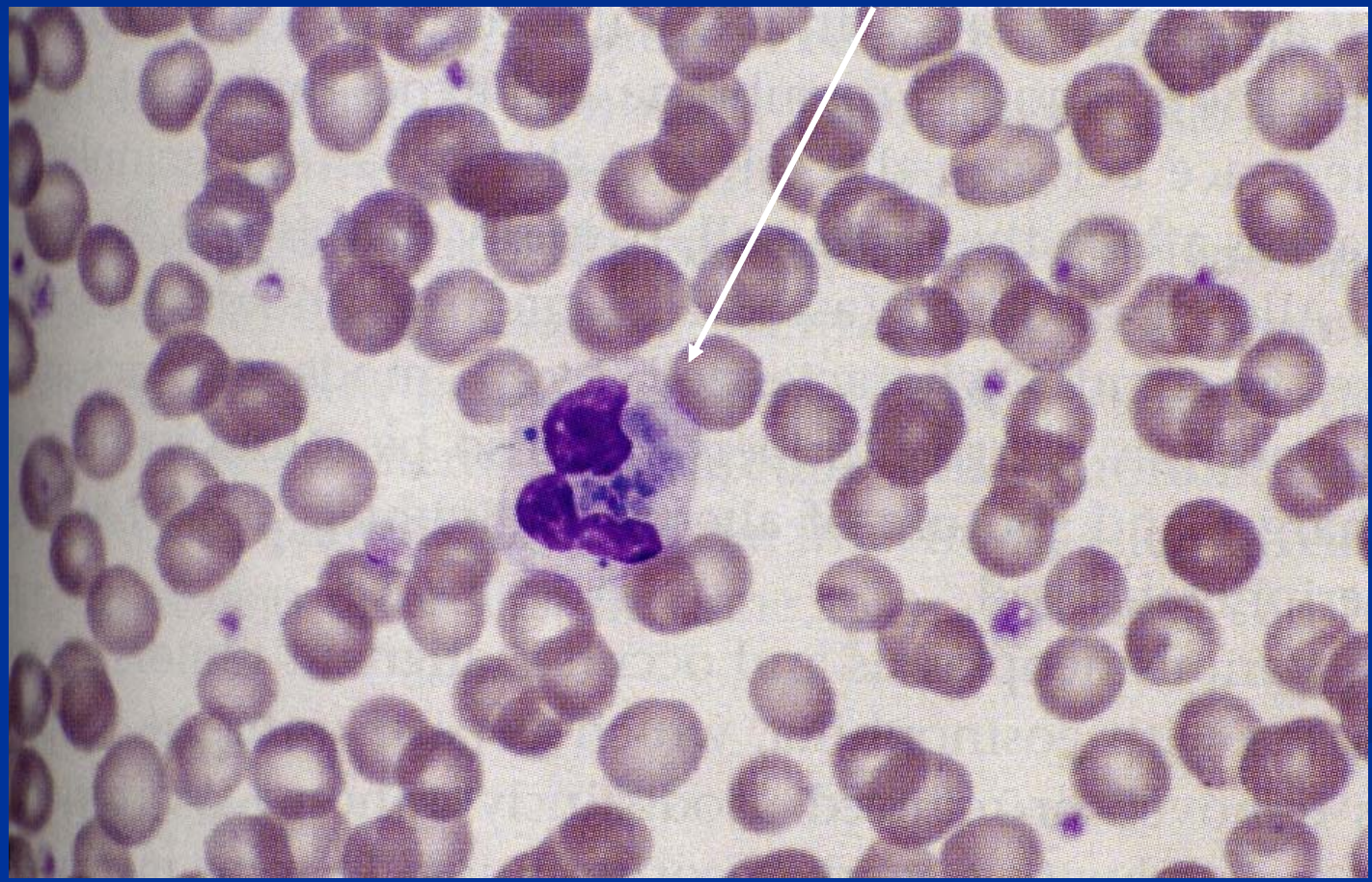


Nonmalignant Leukocyte Disorders

- 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

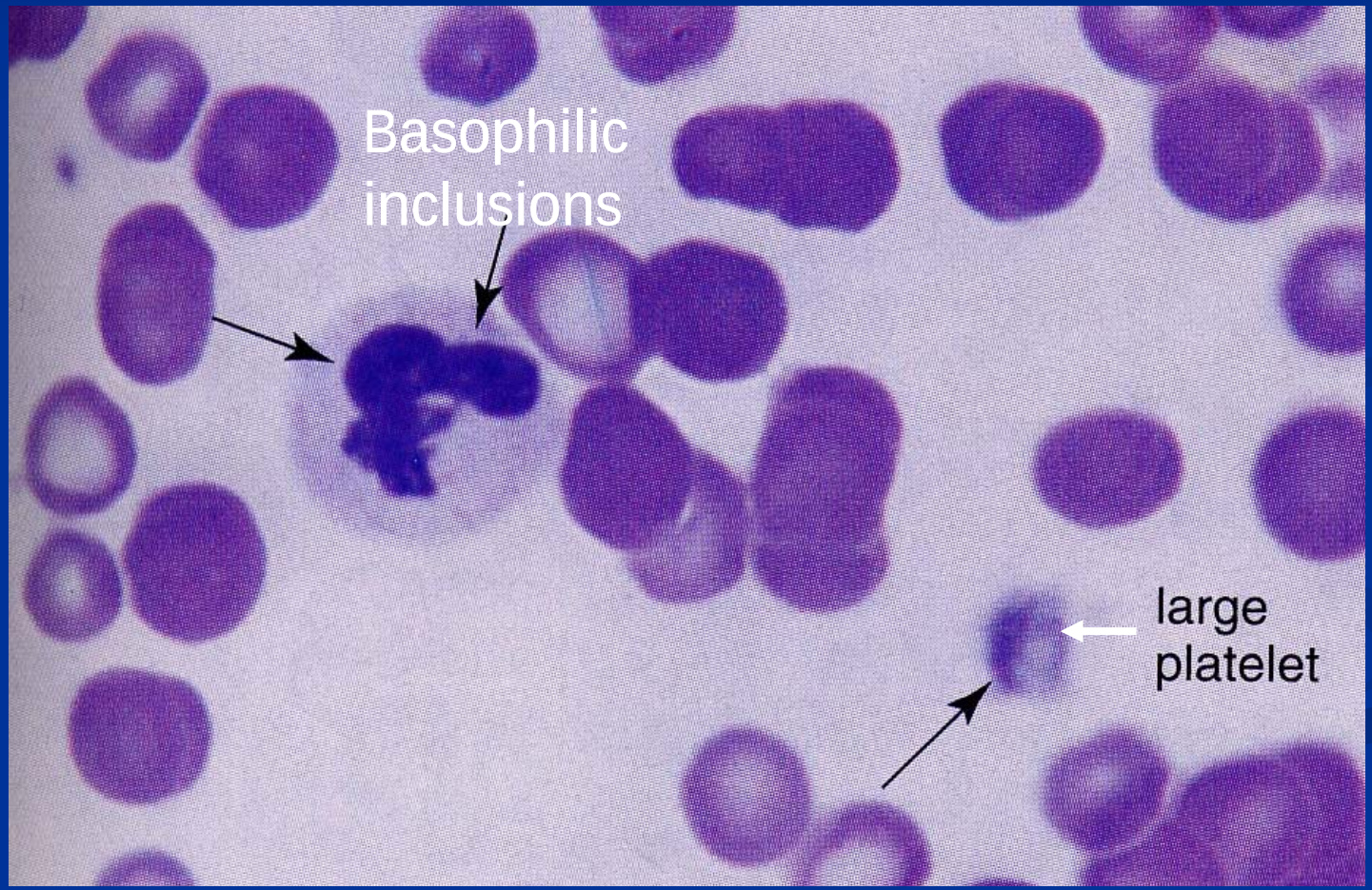
Note abnormal lysosomes



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 platlets 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



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.

Nonmalignant Leukocyte Disorders

- 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)