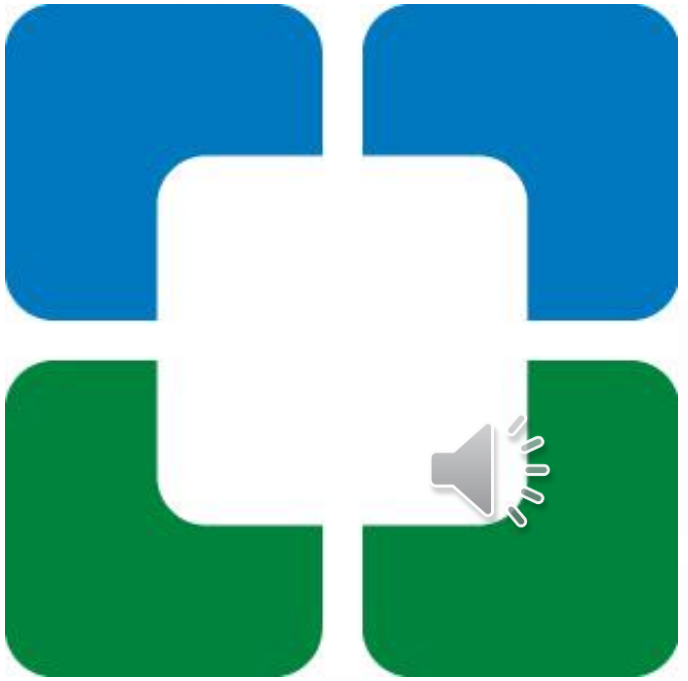
Nonmalignant Leukocyte Disorders

Pinal Patel, MLS (ASCP)CM



Goals

- Knows qualitative and quantitative changes in leukocyte disorders
- Identify morphologic abnormalities of leukocytes in peripheral blood smear and expected results associated with these conditions.
- Knows characteristics qualitative/functional disorders of leukocytes
- Identify reactive changes seen in granulocytes.
- Knows the enzyme deficiency and accumulated products in the lysosomal storage diseases

Morphologic Abnormalities of Leukocytes with and without Functional Defects

- Pelger-Huet anomaly
- Alder-Reilly anomaly
- May-Hegglin anomaly
- Chediak-Higashi syndrome

Pelger-Huet Anomaly

- Benign inherited defect and cells function normally
- Autosomal dominant
- Mutation in lamin β- receptor gene
- Neutrophil nucleus does not segment beyond the bilobular
- Coarsely clumped chromatin
- “Pseudo pelger- huet” can acquired with myeloproliferative and myelodysplastic states

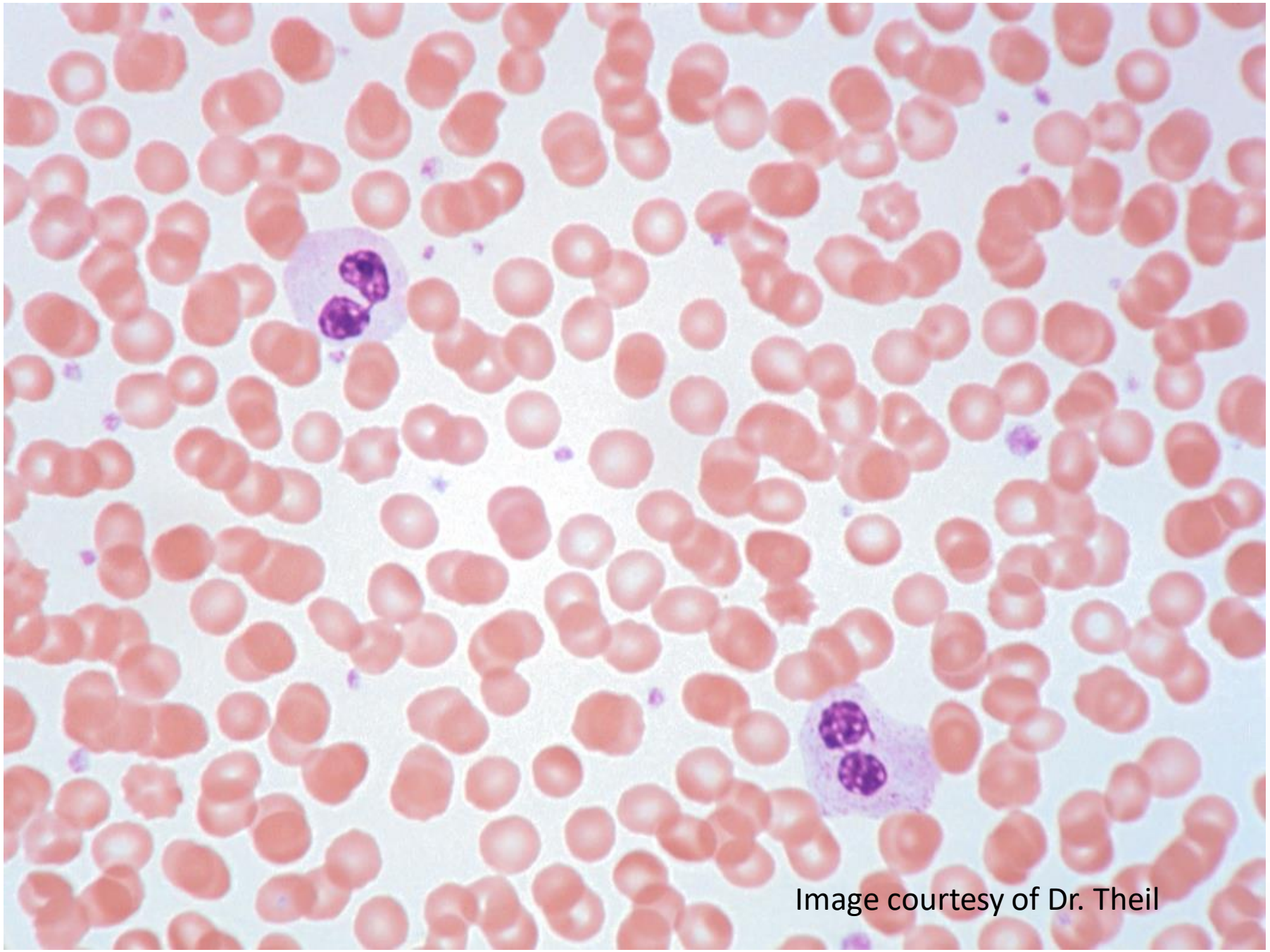
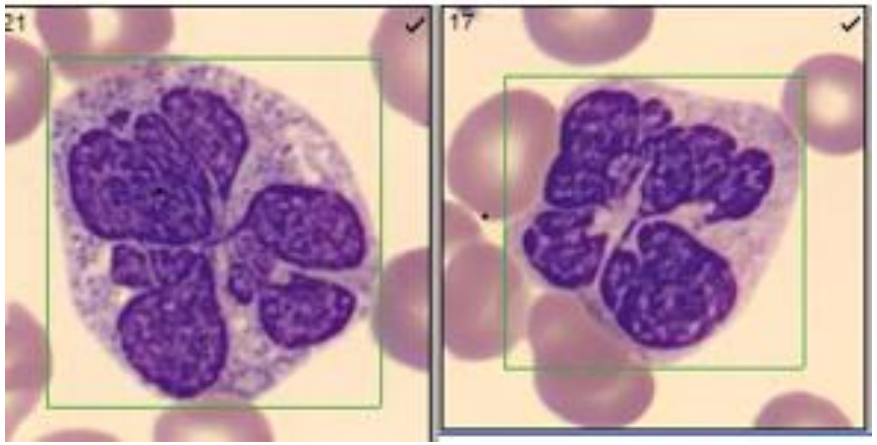


Image courtesy of Dr. Theil

Neutrophilic hypersegmentation

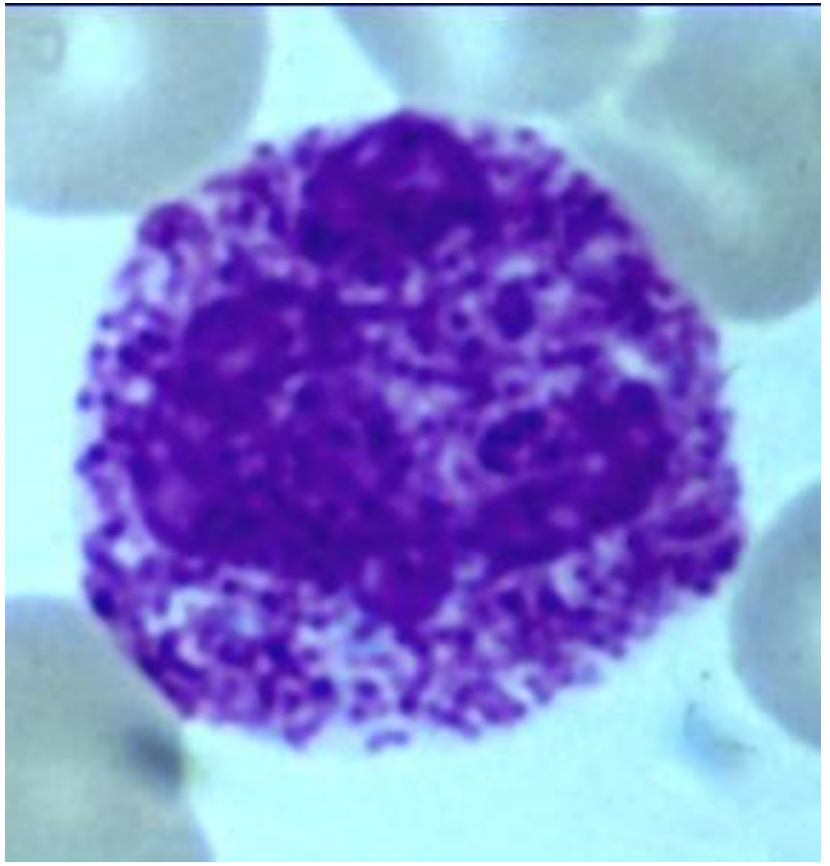


Neutrophils with more than five lobes

Associated with megaloblastic anemia and usually larger than normal

Seen in myelodysplastic syndrome representing dysplastic form

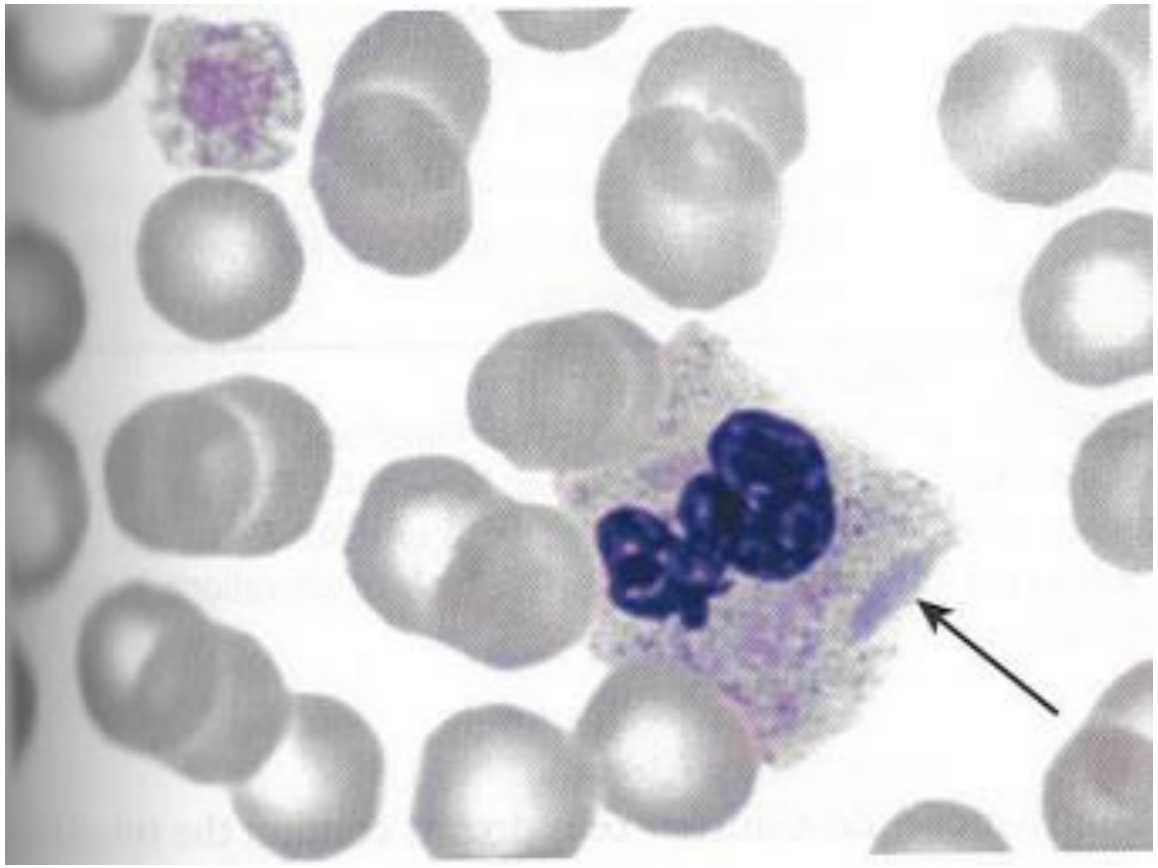
Alder–Reilly Anomaly



- A rare but an interesting morphologic finding characterized by large, intensely metachromatic inclusions or granules
  - also referred to as “Reilly bodies,”
  - cytoplasm of neutrophils, lymphocytes, and monocytes usually also accompanied by defects in eosinophilic and basophilic granules.
- Hurlers and hunters syndromes in which there is an incomplete break down of mucopolysaccharides.
- Decreased mucopolysaccharide degradation results in deposits of lipids into the cytoplasm of most cells.

May-Hegglin Anomaly

- A rare Autosomal dominant disorder
- A mutation in the MYH9 gene
- Leukocytes contain Dohle bodies like inclusions in their cytoplasm
- Thrombocytopenia and giant platelets



Chediak Higashi Anomaly

- A rare autosomal recessive disorder in which abnormal lysosomes are formed by the fusion of primary granules
  - grays green inclusions in leukocytes
- This cells are ineffective in killing micro-organisms and affected individuals often die early in life from pyogenic infections.

Chediak Higashi Anomaly

- Partial oculocutaneous albinism
- Recurrent severe infections

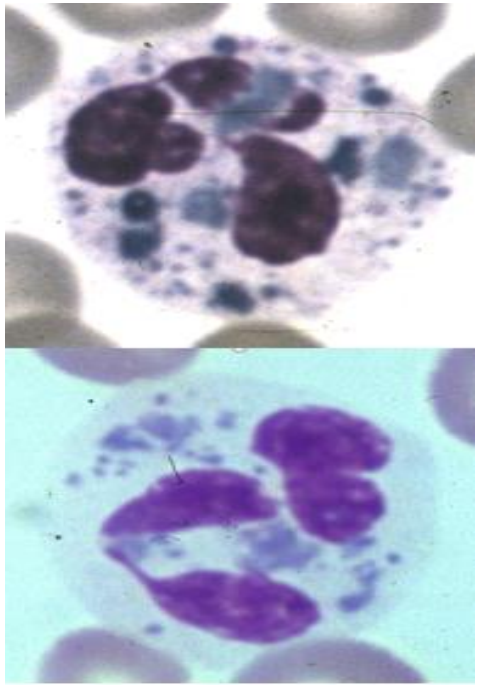


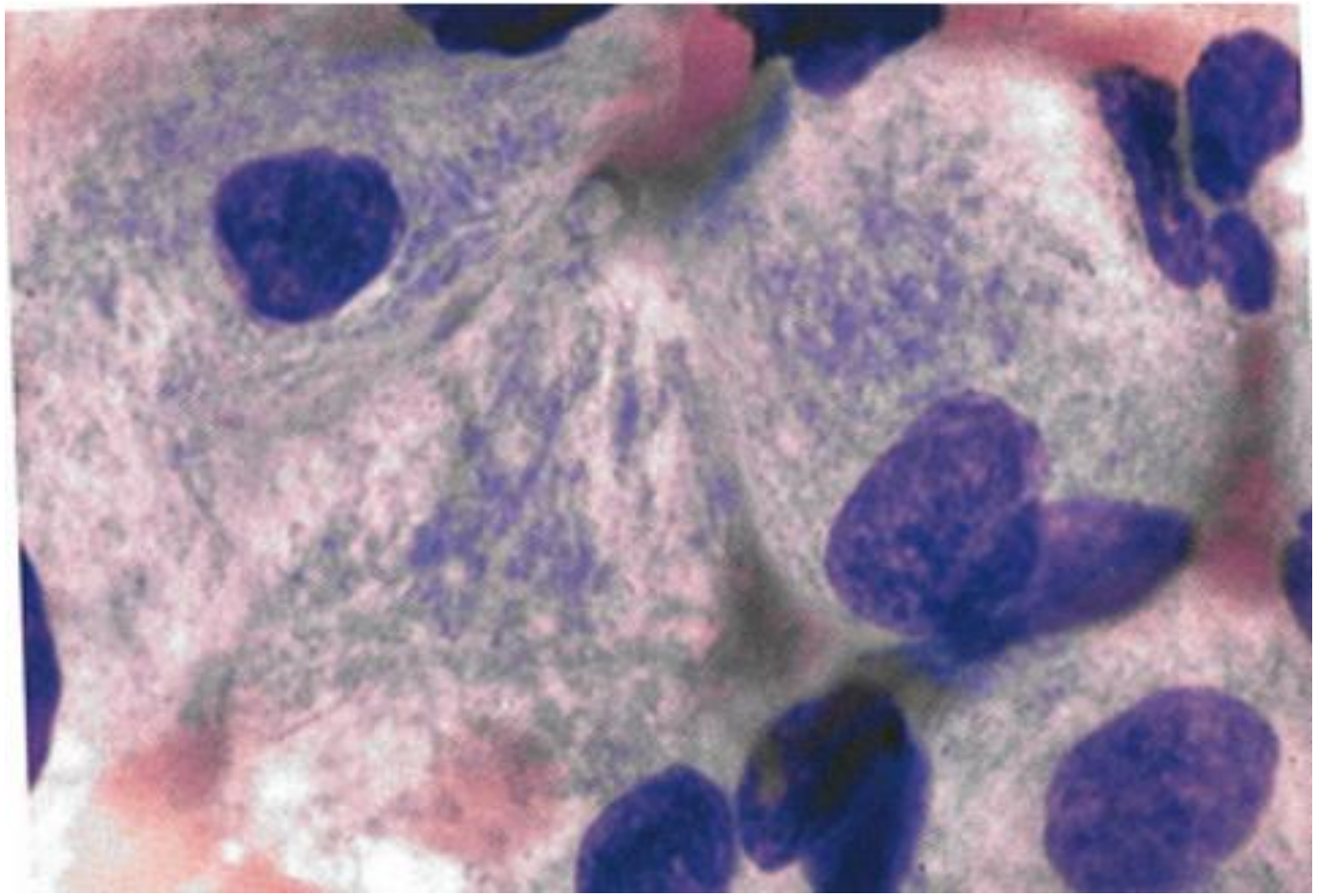
Image courtesy of Dr. Theil

Lipid Storage Diseases

Gaucher Disease

- The most common lysosomal lipid storage diseases
- An autosomal recessive disorder caused by deficiency in β-glucocerebrosidase deficiency
- Macrophages(wrinkled, striated)with lipid in bone marrow, lymph node, liver, spleen
- Type I , II, and III
  - Fifteen-fold increase for developing hematological malignancies

Macrophages in Gaucher Disease



Rodak's Hematology Clinical Principles and Applications . 6th ed.

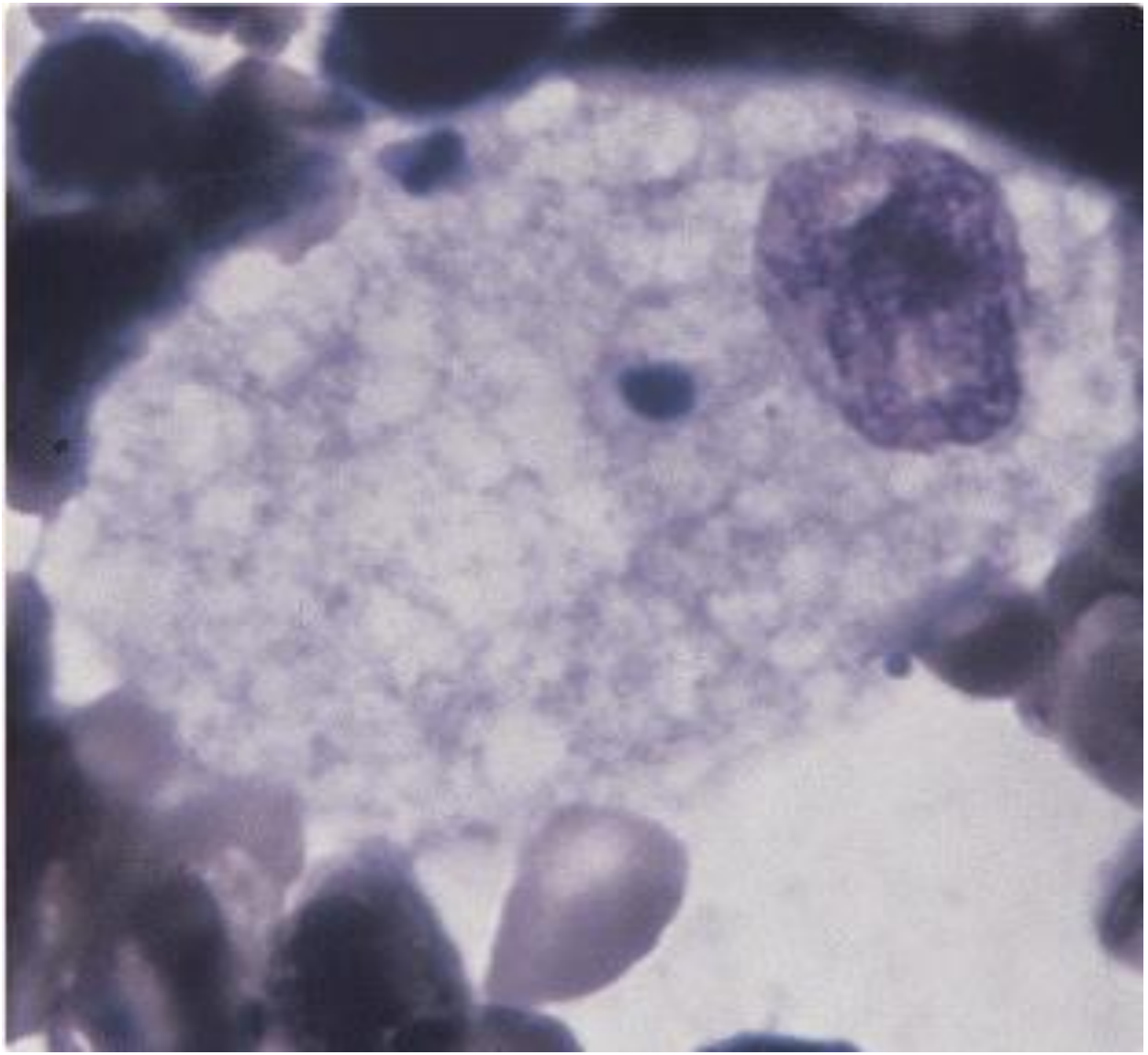
Niemann-Pick Disease

Sphingomyelinase deficiency

Abundant sphingomyelin-laden cytoplasm with foamy, vacuolated, or mulberry appearance

Small, uniform cytoplasmic vacuoles

Niemann-Pick Cell



(From Rodak, B. F., & Carr, J. H. [2017]. *Clinical Hematology Atlas*. [5th ed.]. St. Louis: Saunders.)

Inherited Functional Abnormalities of Leukocytes

Chronic granulomatous disease (CGD)

- X-linked and autosomal recessive
- Defect in genes responsible for proteins that makes NADPH oxidase
- Decreased ability of neutrophils to undergo a respiratory burst
- Recurrent infections
- Affected individuals have chronic infection with organisms that do not normally cause infections in normal people.

Leukocyte Adhesion Deficiency

- Rare, autosomal recessive disorder
- Inability of neutrophils and monocytes to adhere to endothelial cells
- Defect in gene responsible for cell adhesion molecules integrin and selectins
- Leukocyte have functional defect in:
  - Chemo taxis, phagocytosis, respiratory burst activation and degranulation.
- Frequent bacterial and fungal infections in affected individuals
- Mortality in childhood is high

Severe Combined Immune Deficiency(SCID)

- X-linked SCID is the most common, primarily affects male infants.
- Fatal condition and usually symptoms occur in infancy
- T cells and NK are absent and B cells are dysfunctional
- Autosomal recessive SCID is caused by adenosine deaminase (ADA) deficiency
- life-threatening bacterial, viral and fungal infections

Wiskott-Aldrich Syndrome

- Rare X-linked disorder with a characteristic triad of Immunodeficiency, thrombocytopenia and eczema
- Decreased production of WASp protein(produced by WAS gene) which is important for cytoskeletal remodeling and nuclear transcription in HSCs.
- T cells are deceased
- Dysfunctional B cells, NK cells , and T cells , neutrophils and monocytes
- Bacterial, viral and fungal infections

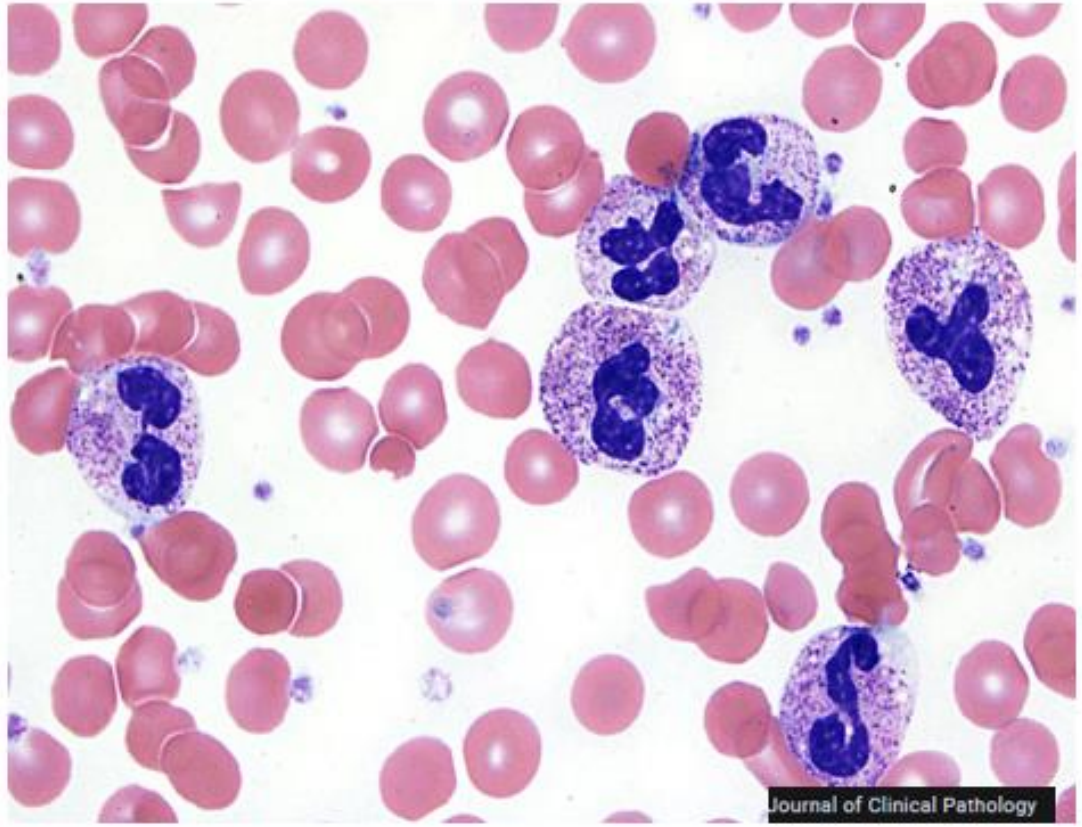
Quantitative Abnormalities of Neutrophils

- Normal absolute neutrophil count (ANC) 2 x 7.7 X 10^9/L
- Neutrophilia – an increase in neutrophils
  - Shift in neutrophils from the marginal to circulating pool
  - Often accompanied by a left shift
  - A response to physiologic or pathologic process
  - Causes:
    - Bacterial and viral infections
    - Burns/Trauma/Injury
    - Pregnancy
    - Strenuous exercise
    - Chronic myeloproliferative disorders/leukemia
    - Acute and chronic blood loss

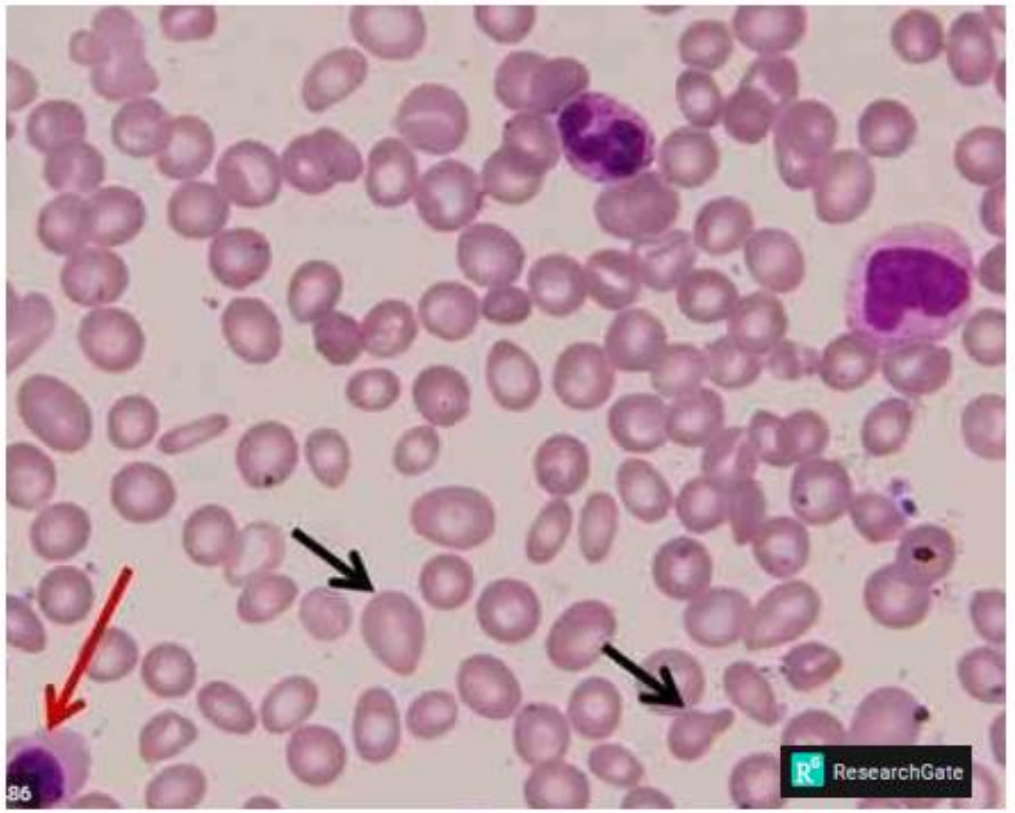
Neutrophilia

- Leukemoid Reaction
  - Neutrophilia with WBC count > 50 X 10^9/L, left shift
  - Infection, inflammation or inflammatory response to malignancy
  - Presence of toxic granulation and Dohle bodies
  - Elevated LAP score
  - Philadelphia chromosome not present
- Leukoerythroblastic reaction
  - Presence of NRBCs, teardrop cells, and a shift to the left in granulocyte maturation in peripheral blood smear
  - Associated with myelophthisic processes, hemolytic anemia or myelofibrosis

Leukomoid Reaction



Leukoerythroblastic Reaction

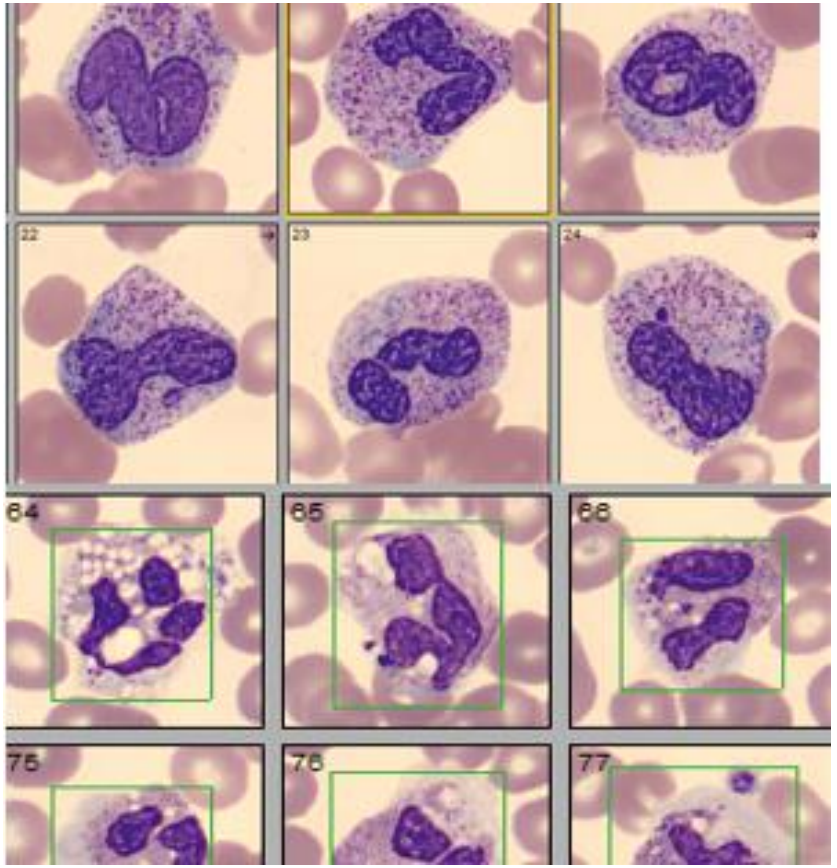


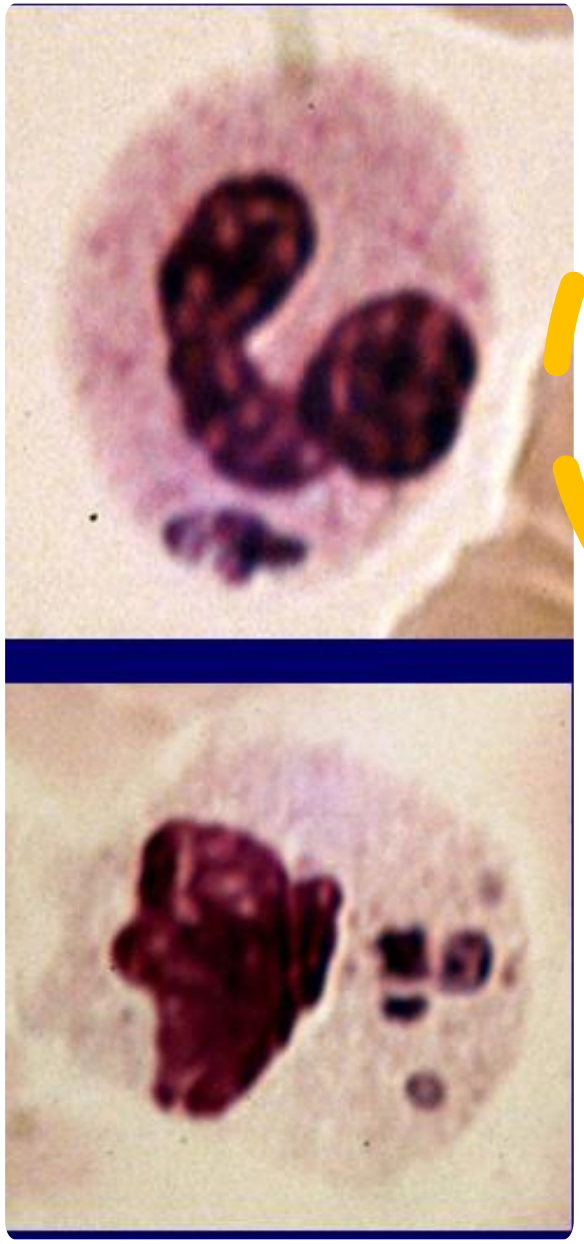
Neutropenia

- Neutropenia may result from
  - Decreased marrow production
    - Chemotherapy or myelopthesis
    - Lead to overwhelming infections
  - Ineffective marrow production
    - Hyperplastic bone marrow
    - Megaloblastic anemia and myelodysplastic syndromes where cells are destroyed before released from the marrow
  - Increased cell loss
    - Immune neutropenia

Morphological changes of neutrophils

- Reactive , transient changes accompanying Infectious states.
- Toxic granulation
  - Inflammation, infection, GCSF therapy
- Dohle bodies
  - bluish cytoplasmic inclusions consisting of remnants of ribosomal RNA
- Cytoplasmic vacuoles
  - associated with septicemia





Ehrlichiosis and Anaplasmosis

- Small, obligate, intracellular bacteria transmitted to humans by ticks
- Form intracellular aggregates called morulae in neutrophils and monocytes
- Leukocytopenia, thrombocytopenia ,elevated liver enzymes and anemia
- Diagnosis by PCR testing

Reactive morphological changes in lymphocytes

- Lymphocytes are stimulated when interacting with antigens in peripheral lymphoid organs.
- Heterogeneous population of various shapes and sizes of reactive lymphocytes.
- Increase basophilic cytoplasm that may vary in intensity within and between cells.
- The cytoplasm may be indented by surrounding RBCs.

Infectious mononucleosis

- Infection with Epstein Barr virus
- Virus preferentially infects B lymphocytes
- Proliferation and activation of NK cells, T cells in response to B cell infection.
- Laboratory features:
  - CBC- leukocytosis , absolute lymphocytosis
  - PBS- reactive lymphocytes
  - Positive heterophile antibody
  - Positive EBV specific antigen and antibody