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Myeloid Cell Disorders

M2 Hematology/Oncology Sequence
John Levine, MD

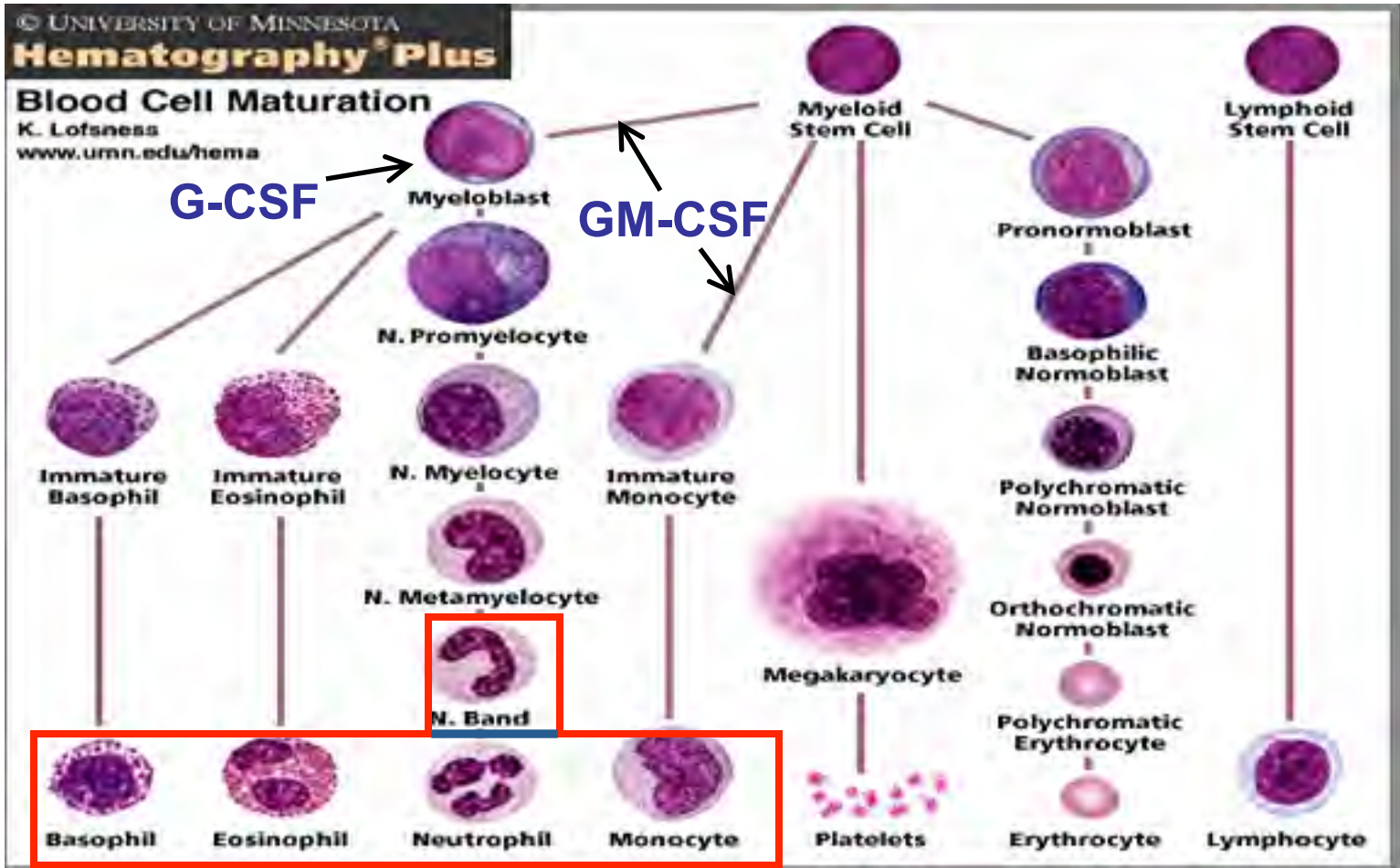
Winter 2009



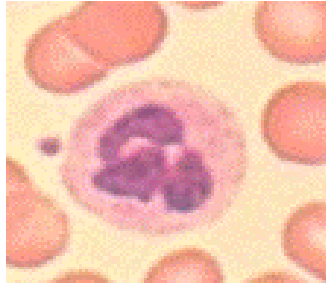
Myeloid Cell Disorders: Goals

- **Define members of the myeloid series**
- **Understand:**
 - white blood cell maturation
 - the white blood cell count and differential
 - ‘philiias’ and ‘penias’ of the myeloid series members and associated clinical settings
 - recruitment of WBC from the circulation.
- **Associate white blood cell defects with function**

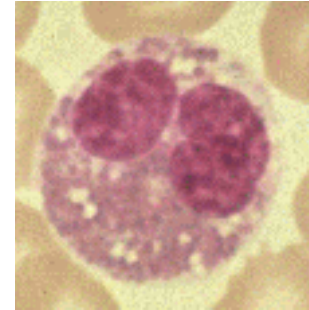
Maturation of Myeloid Cells



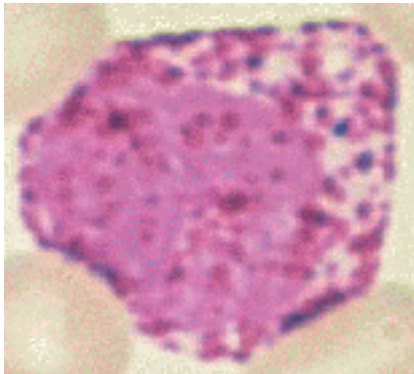
Mature Myeloid Cells



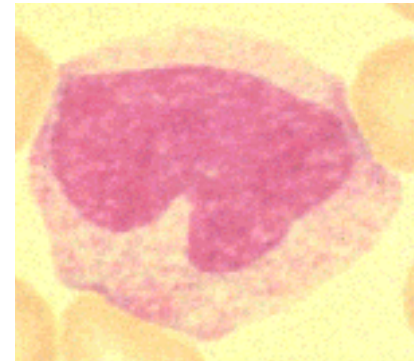
Neutrophil



Eosinophil



Basophil



Monocyte

Assessment of Circulating WBC

- The total white blood cell count (**WBC**) and differential are measured in an automated counter
- WBC reflects the circulating pool of myeloid and lymphoid cells
- WBC in each microliter ($\mu\text{l};\text{mm}^3$) is reported
- **Relative proportion** of each type of WBC is indicated by a percentage
- **Absolute number** is the percentage of each type of WBC multiplied by the total WBC

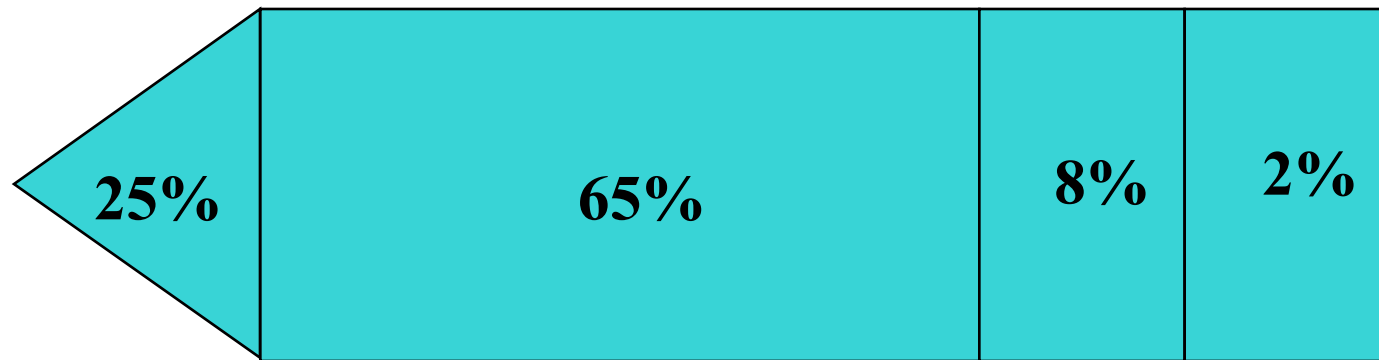
White Blood Cell Counts: Normal Ranges

	WBC	PMN	Band	Lymph	Mono	Eos	Baso
Birth (0-1m)	6-30K	42-80%	2%	26-36%	3-8%	0-5%	0-2%
Child (1m – 12m)	6-18K	18-44%	3%	46-76%	3-8%	0-5%	0-2%
Child (1y – 16y)	5-14K	37-75%	3%	25-57%	3-8%	0-5%	0-2%
Adult	4-10K	36-75%	2%	20-50%	3-8%	0-5%	0-2%

White Blood Cell Counts: Disease States

	WBC	PMN	Band	Lymph	Mono	Eos	Baso
Bacterial Infection	16K↑	79%↑	8%↑	8%	3%	1%	1%
Steroid Therapy	12K↑	79%↑	4%	14%	3%	0%	0%
Splenectomy	13K↑	50%	2%	40%	5%	2%	1%
Viral Infection	3.5K↓	50%	2%	40%	5%	2%	1%
Chemo	<3K↓	65%	0%	20%	12%↑	2%	1%

Neutrophil Maturation



Proliferation
6-7 days

Maturation
6-7 days

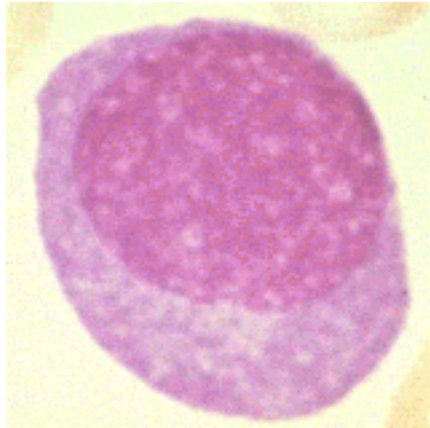
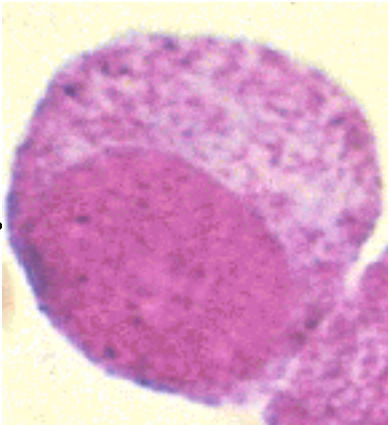
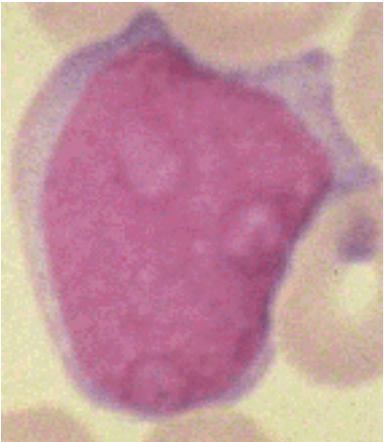
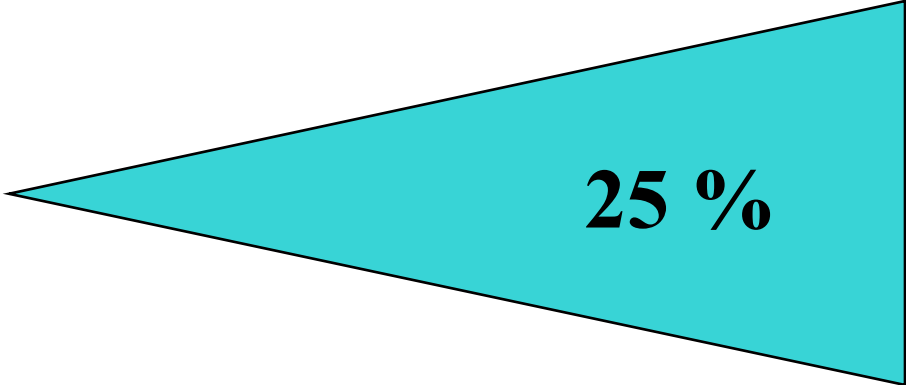
Intravascular
12 h

Tissues
12h

Bone Marrow

Neutrophil Maturation - Proliferative Phase

Proliferation



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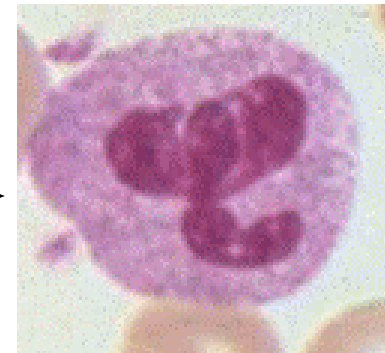
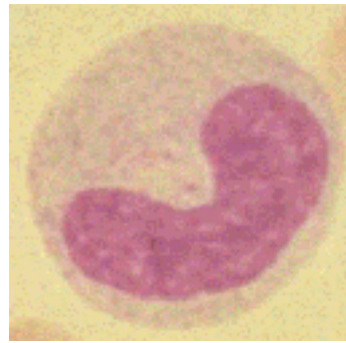
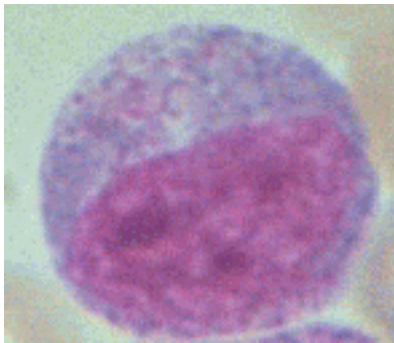
Myeloblast

Promyelocyte

Myelocyte

65 % of myeloid cells

Maturation 6-7 days



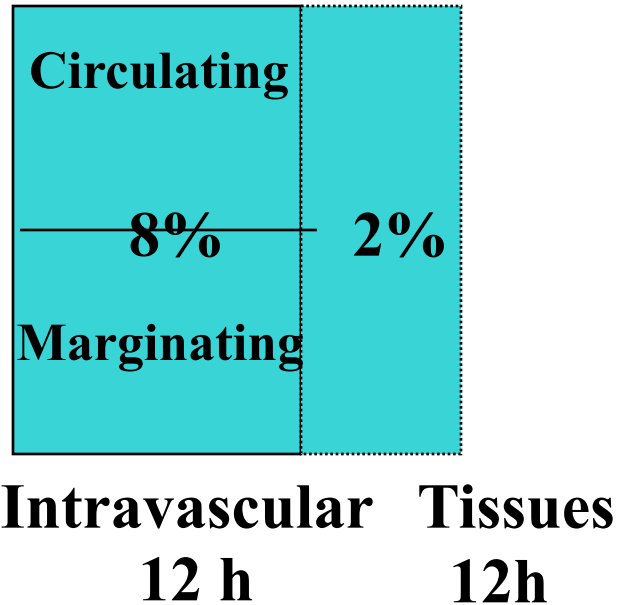
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Metamyelocyte

Band

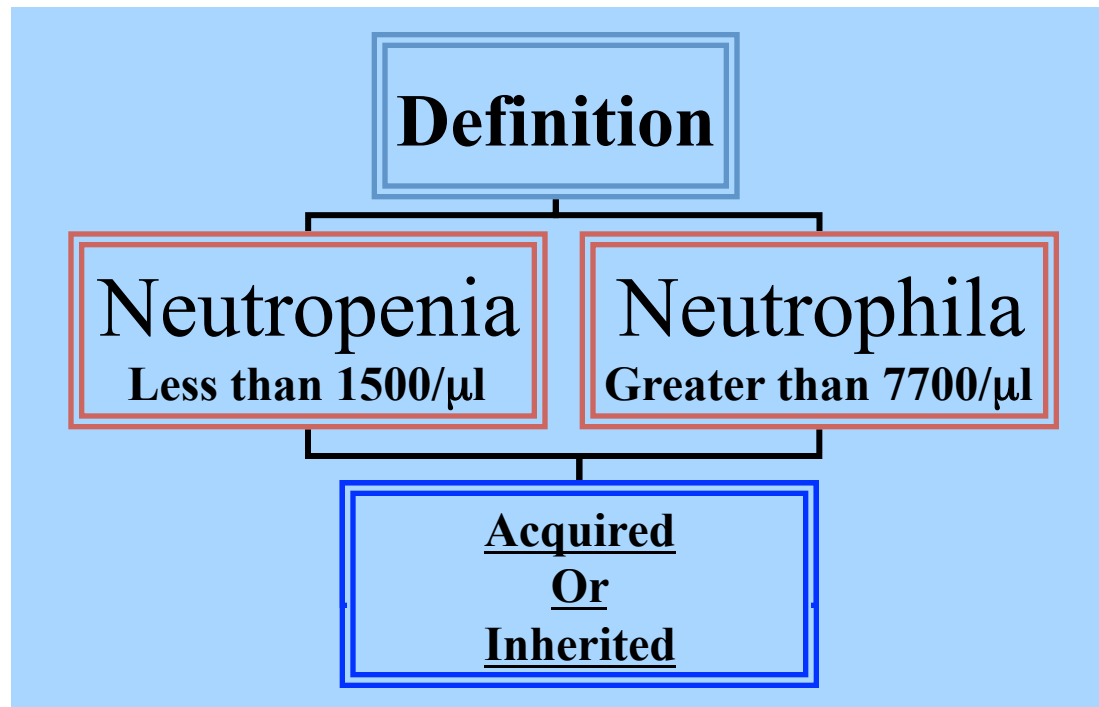
Neutrophil

Fate of the mature neutrophil



Approximately 10% of the developing neutrophils are in the circulation, marginated or in the tissue.

Disorders of Neutrophil Numbers



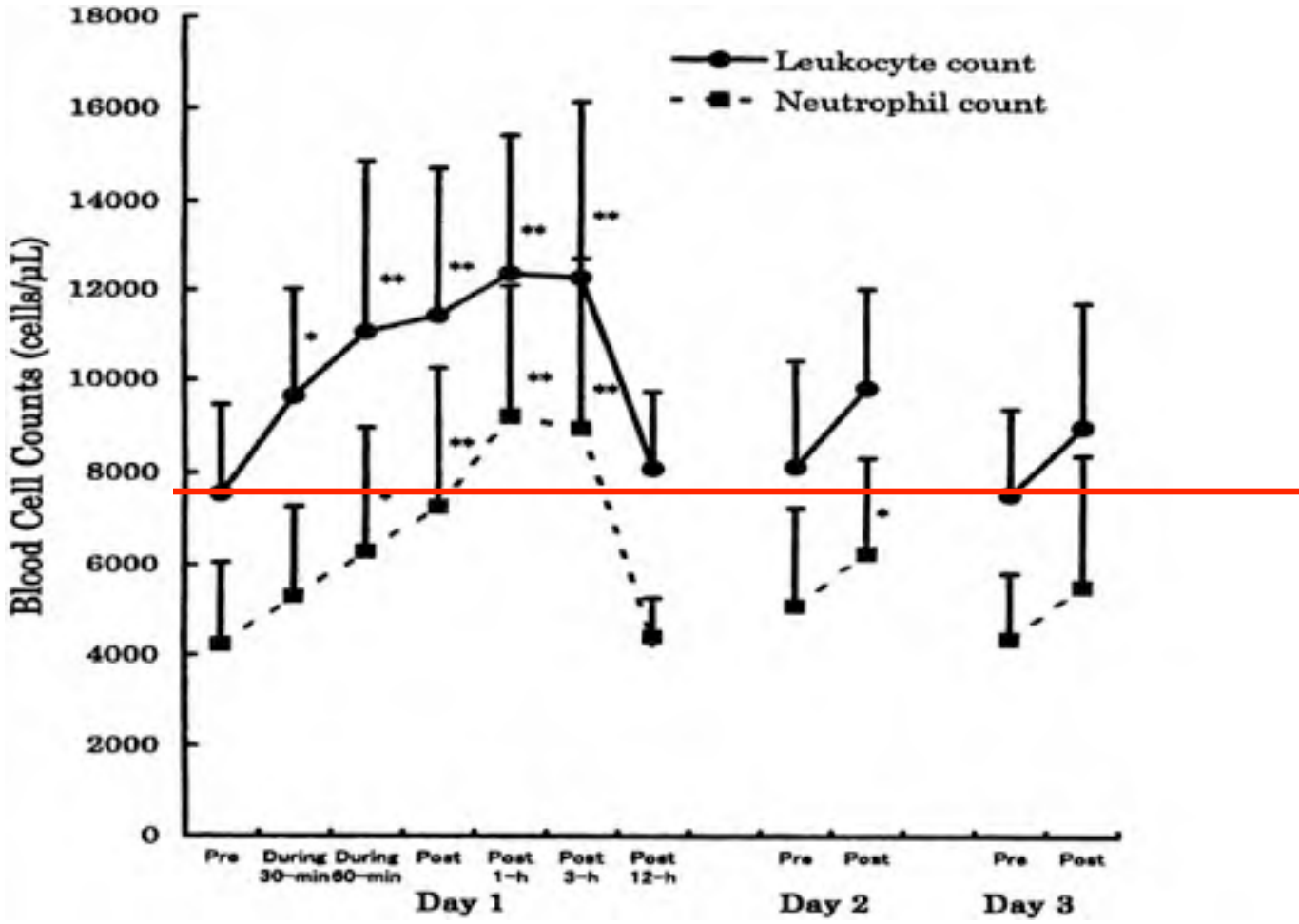
Definition of Neutrophilia - too many

- **Normal ANC is 1500-7700/ μ l**
- **Neutrophilia: abnormally high ANC**
- **Shift to the left: \uparrow 'd release of precursors from the bone marrow**
 - **not necessarily associated with neutrophilia**

Neutrophilia

- **Acute shift from marginating to circulating pool**
 - ↑ measured WBC, not total WBC
- **Chronic Stimulation**
 - Excess cytokine stimulates proliferative pool
- **Causes:**
 - Steroid treatment
 - Exercise
 - Epinephrine
 - Hypoxia
 - Seizures
 - Other stress
- **Causes:**
 - Infection
 - Down's Syndrome
 - Pregnancy/Eclampsia
 - Chemotherapy recovery
 - Myeloproliferative disorders
 - Marrow metastases

Example: exercise induced neutrophilia



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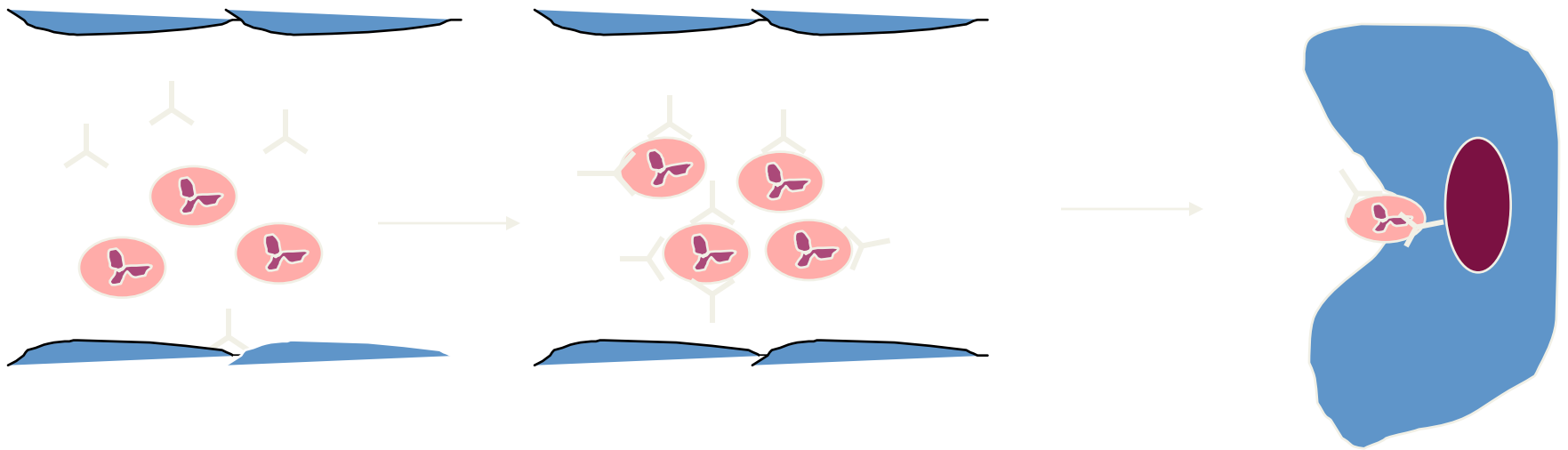
Neutropenia: too few

- Neutropenia
 - Definition: ANC < 1500/ μ l
 - ANC 500-1000 increased risk of infection from exposure
 - ANC < 500: increased risk of infection from host organisms
- African-Americans: lower normal neutrophil counts (1000-1200)

Acquired Causes of Neutropenia

Decreased Production	Increased Destruction	Shift to Marginating Pool
Bone marrow	Peripheral circulation	Move from the circulating pool to attach along the vessel wall
Medication: Chemotherapy Antibiotics, etc	Autoimmune diseases (Rheumatoid arthritis, SLE, etc)	Severe infection Endotoxin release Hemodialysis Cardiopulmonary bypass

Increased Destruction

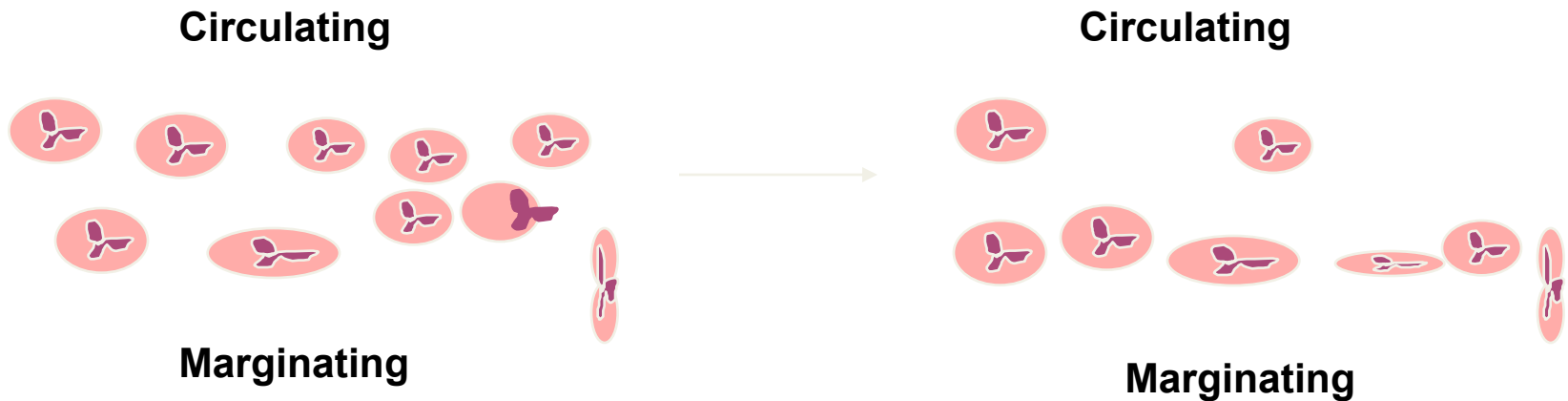



**Anti-neutrophil
antibody**

**Neutrophil-Antibody
Complex**

**Uptake and
destruction of
neutrophil by the
RE system**

Shift to Marginating Pool



Severe infection / Endotoxin release
Hemodialysis
Cardiopulmonary bypass

Evaluation of Neutropenia

- If visit prompted by a fever and ANC is low, treat promptly for infection
- Suspect medication: major cause of neutropenia
- If no culprits, bone marrow exam for:
 - Malignancy
 - Infiltration by non-marrow cells
 - Arrest of cell growth
 - Myeloproliferative disorder

Cyclic Neutropenia

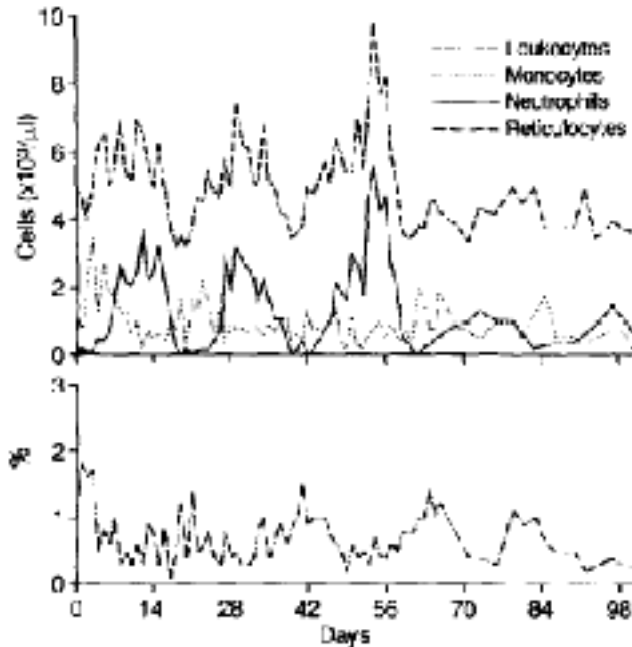


Figure Blood cell counts of Patient No. 15 show regular 21 day cyclic variation. Note that monocytes and reticulocytes tend to rise when the neutrophils fall.

PD-INCL Source Undetermined

- 21 day cycle
- autosomal dominant
- fever, mouth ulcers
- Treatment G-CSF
- usually improves after puberty

Congenital Neutropenia

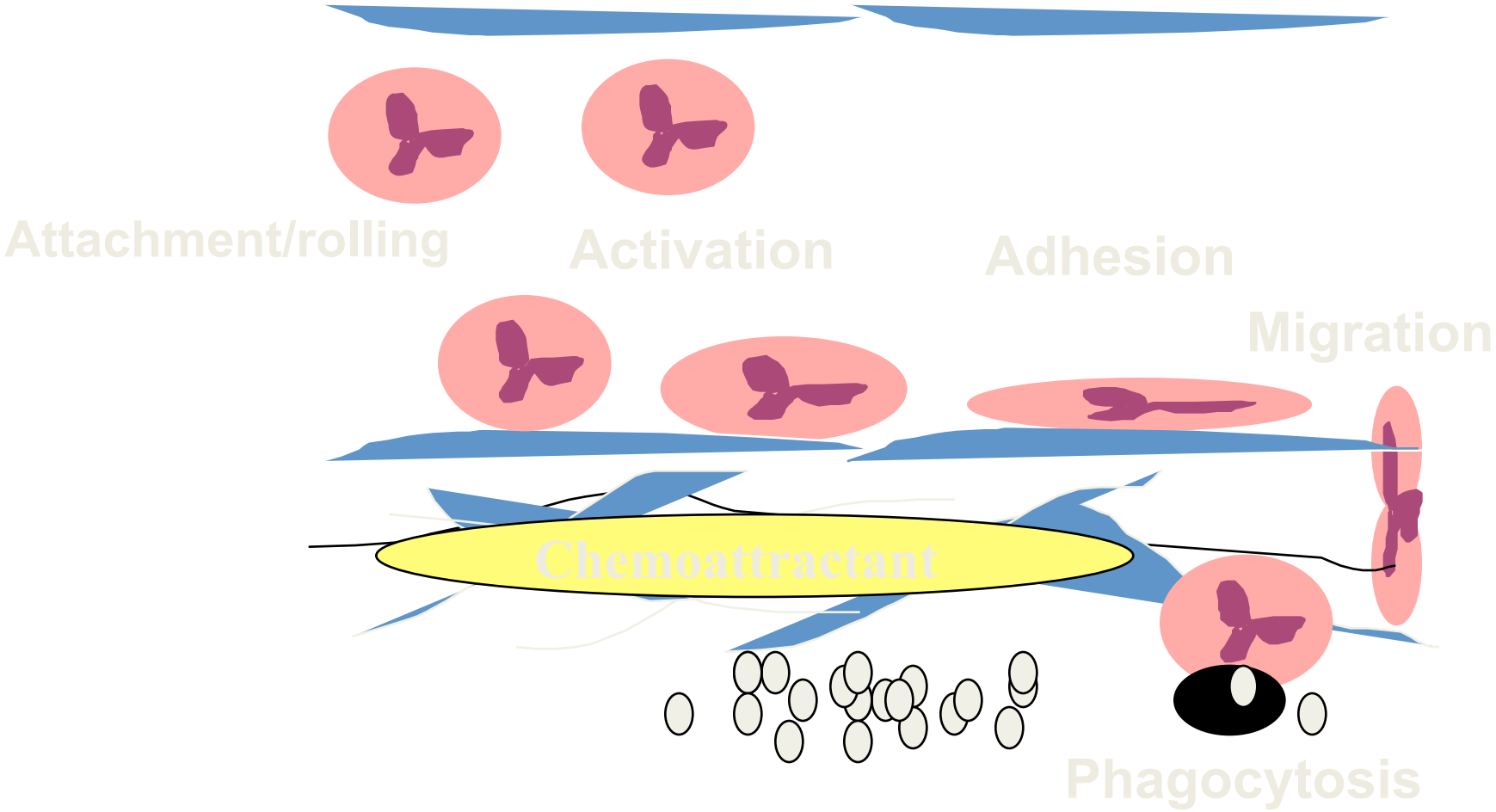
- Maturation arrest
- frequent infections, often serious
- mouth sores
 - may lose teeth or develop severe gum infections
- Increased risk of leukemia
- Tx: G-CSF, BMT



Role of Neutrophil

- Responds to **chemotactic factors** released from damaged tissue
- **Rolls and attaches** to the endothelial cell wall
 - protein and carbohydrate interactions (selectins and their ligands).
- Becomes **activated** by chemotactic factors
- **Tightly adheres** through the integrin family of proteins.
- **Migrates** across the endothelial cell wall.
- **Phagocytizes** organisms so that they are contained within a vesicle or phagosome.
- **Releases granule products** and reduced oxygen species (e.g. hydrogen peroxide and superoxide) to kill organisms

Function of the Circulating Neutrophil

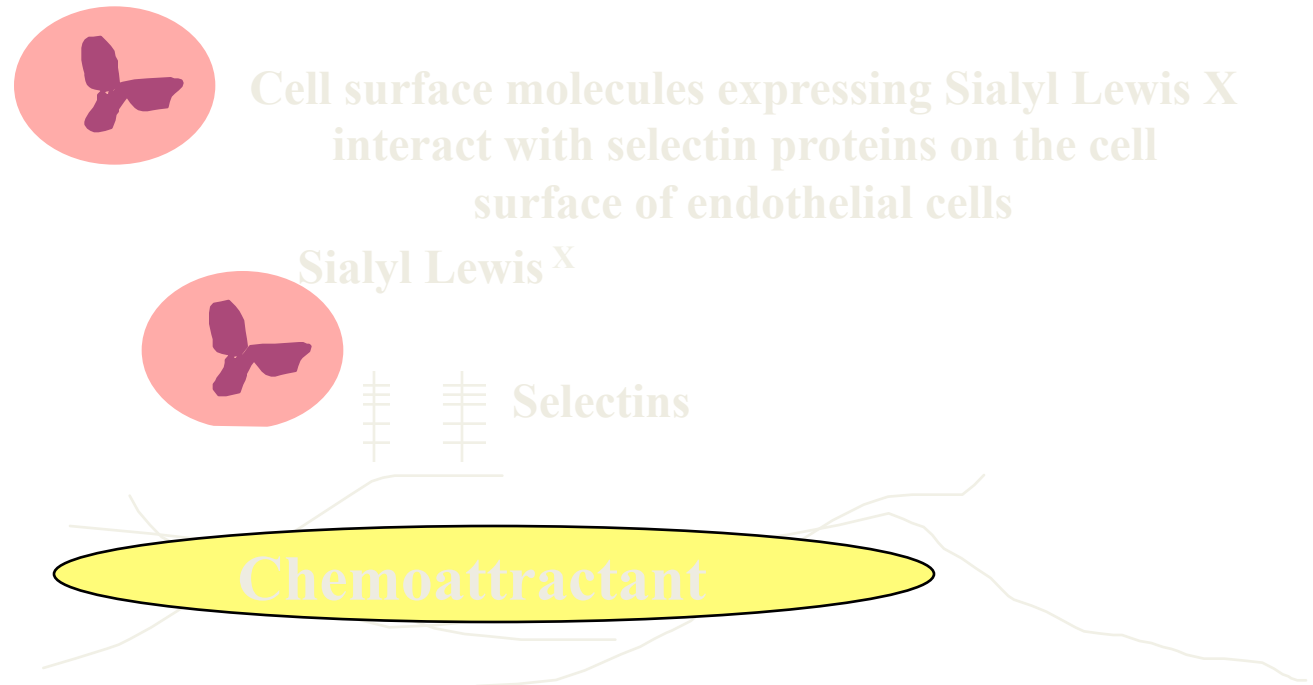


Disruption of Neutrophil Function

- Steps where defects in structural components of neutrophils results in impaired ability to fight infection
 - Recruitment from the circulation
 - Adhesion and subsequent migration
 - Defective production in active oxygen metabolites
 - Deficiency in granules

Defect in Attachment/Rolling

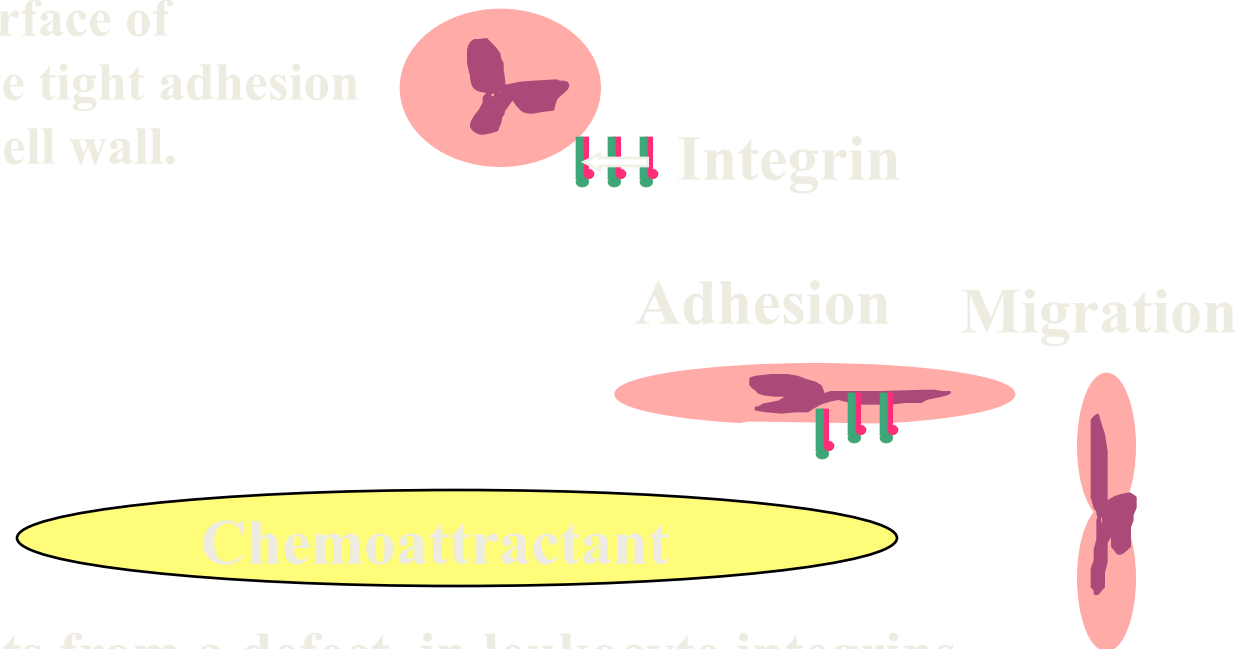
Attachment/rolling



LAD-2 Impaired expression of sialyl LewisX -
Neutrophils do not attach and are not recruited to the site of inflammation

Defect in Adhesion

Integrins on the surface of neutrophils mediate tight adhesion to the endothelial cell wall. Cells then migrate.



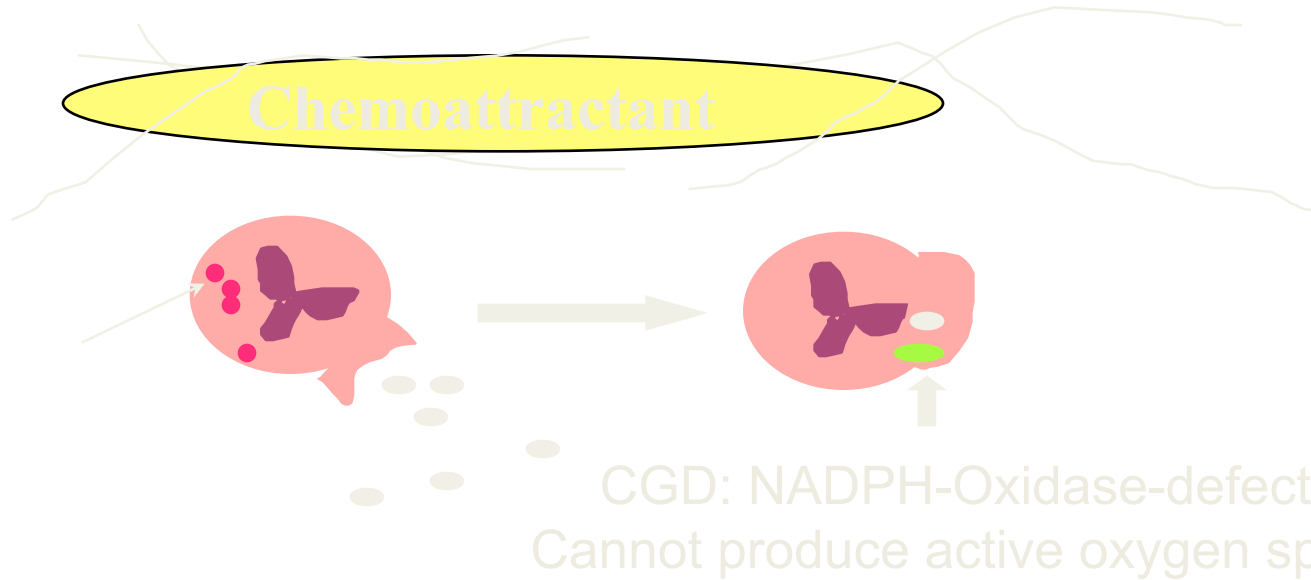
LAD-1 results from a defect in leukocyte integrins. Decreased to absent expression on the cell surface. Cells can not adhere and subsequently cannot migrate.

Clinical manifestations: LAD

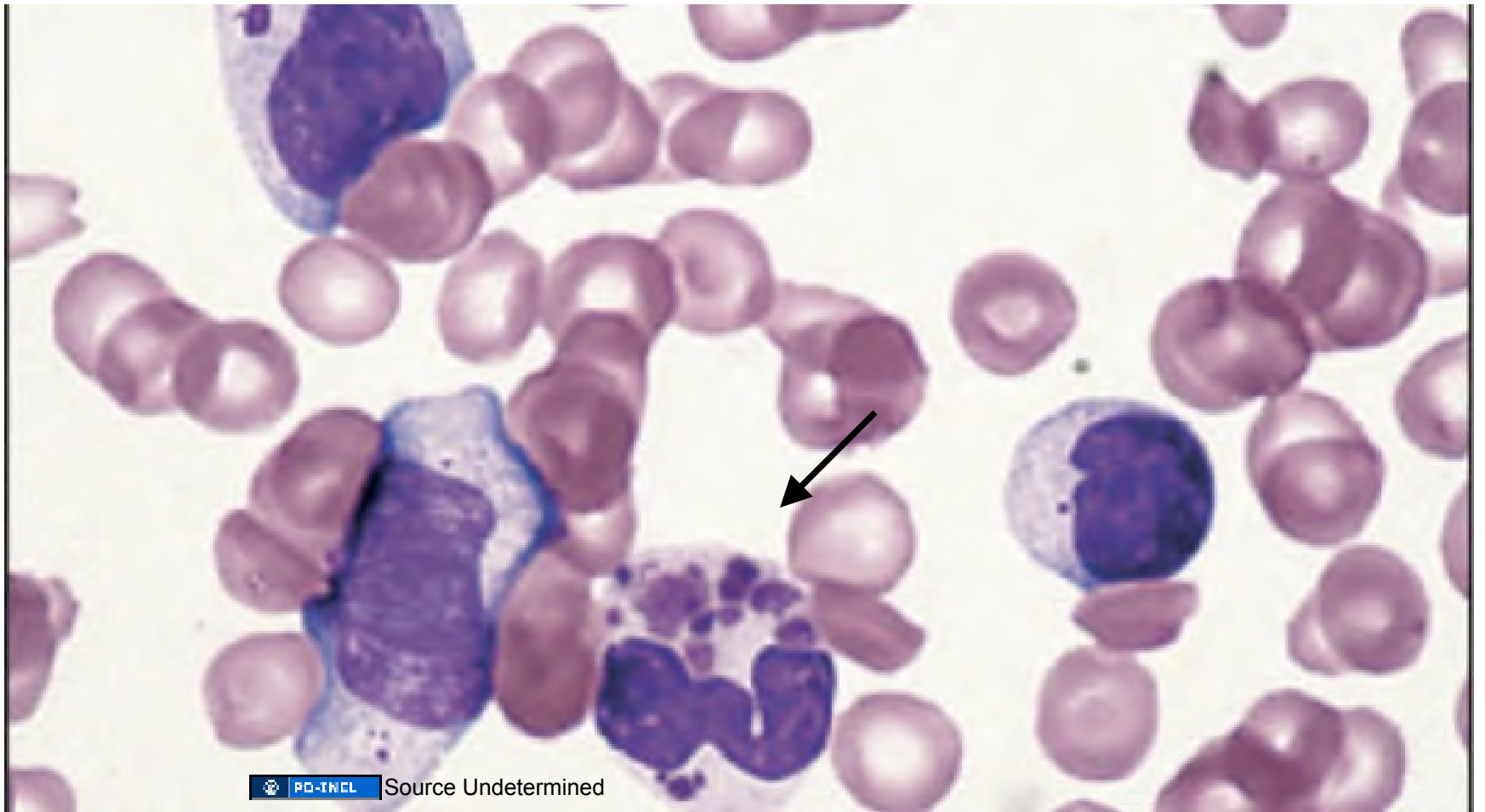


Phagocytosis

Chediak-Higashi Syndrome: Defect in granule formation



Bacteria are engulfed and contained in a phagosome.
Contents of the granules are released.
Oxygen metabolites (superoxide and H_2O_2) kill bacteria



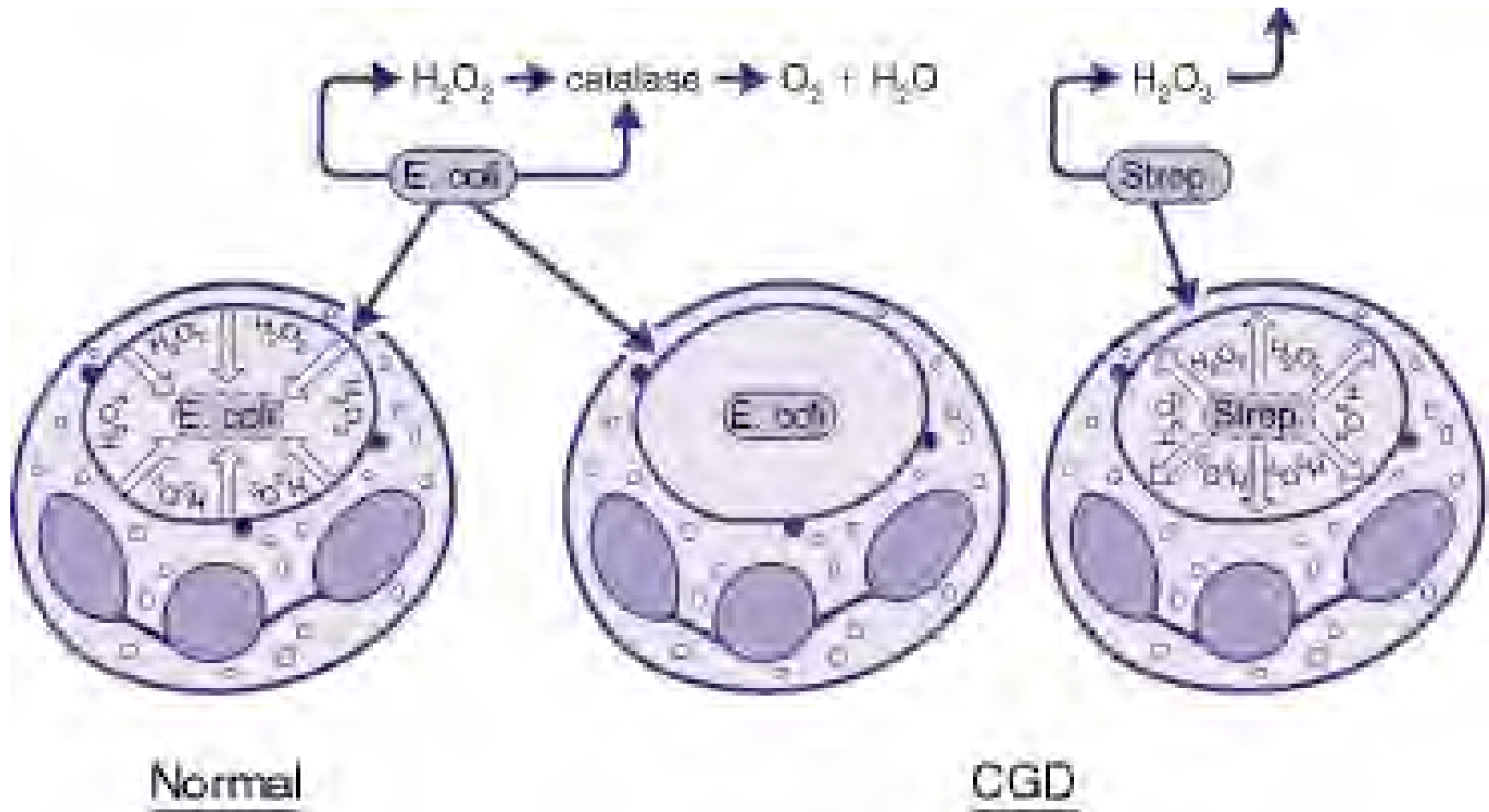
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- Oculocutaneous albinism
 - Photophobia
 - Sun sensitivity
- Neuropathy
- Infections, esp Staph aureus

- TX: BMT

Chronic granulomatous disease (CGD)



Chronic granulomatous disease: CGD

- Catalase positive organisms
 - Staph aureus
 - Serratia marcescens
 - Burkholderia cepacia
 - Fungal
- Skin, lungs, bones, abscesses
- Granuloma formation from chronic infection

Myeloperoxidase deficiency

- One of the more common disorders
 - 1: 4000
- Decreased production of hypochlorous acid (HOCl)
- Killing takes longer than normal
- Clinically silent for most people

Diseases with Neutrophil Defects

Disease	Step	Molecular Defect
LAD-2	Rolling	Sialyl Lewis X Carbohydrate
LAD-1	Adhesion Phagocytosis	Integrin expression
Chediak- Higashi Syndrome	Migration Degranulation	Vacuolar sorting protein (large granules interfere with traversing endothelial wall)

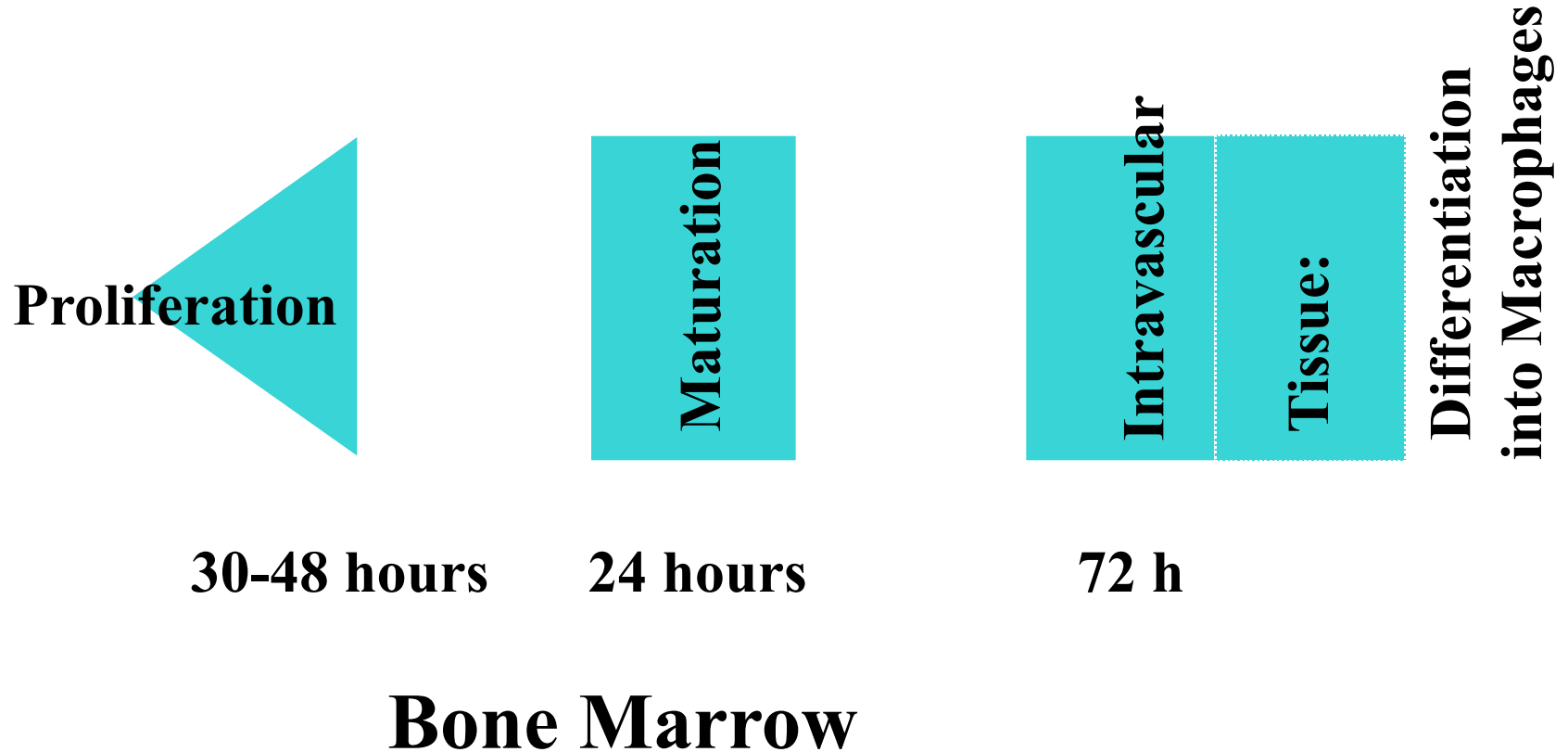
Diseases with Neutrophil Defects

Disease	Step	Molecular Defect
CGD	Oxidative burst	NADPH oxidase
Myeloperoxidase Deficiency	Oxidative burst	HOCl Production

Monocyte-Macrophages

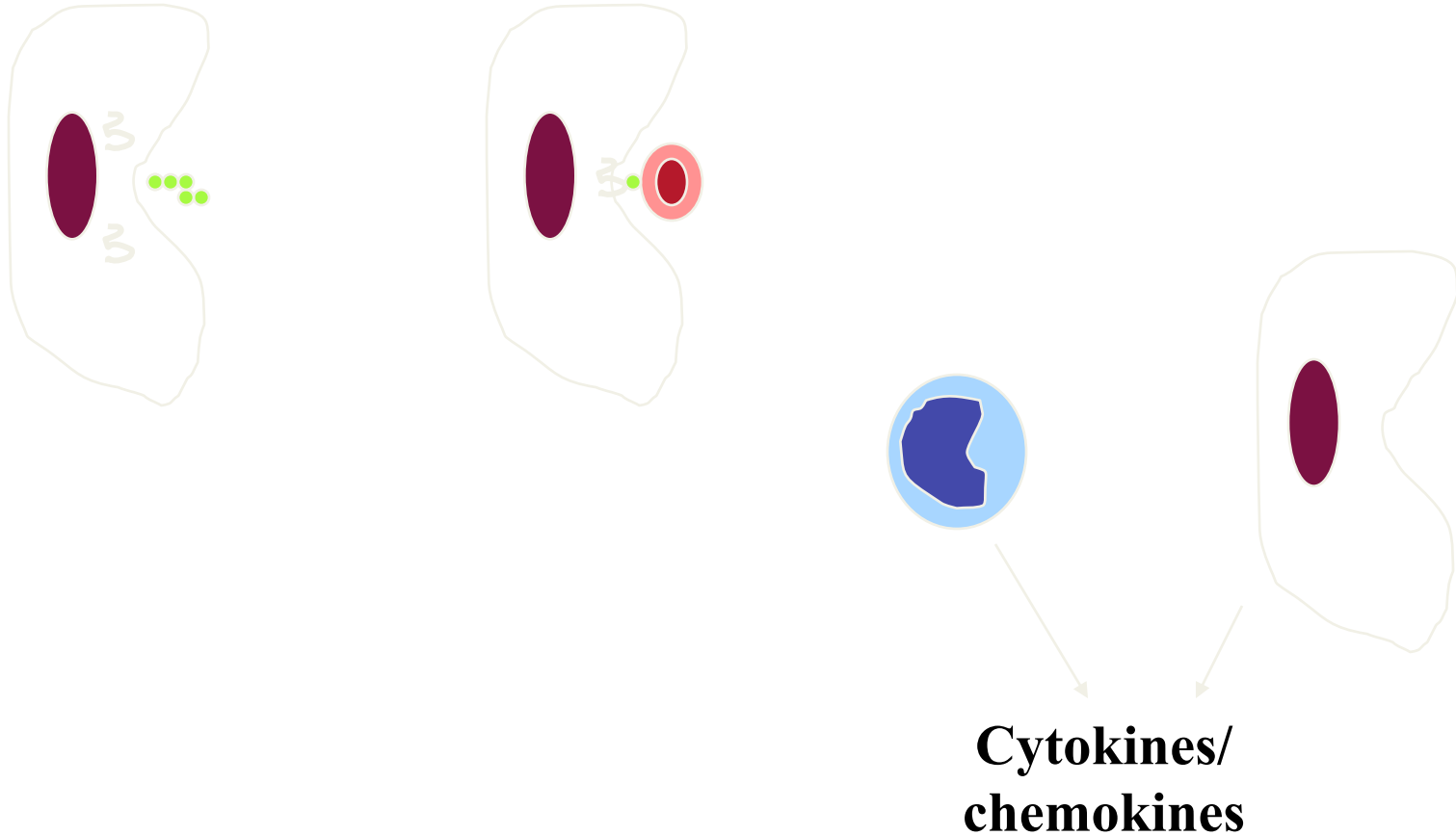
- **Monocytes: circulating precursor of the tissue macrophage.**
- **Also known as the reticuloendothelial system**
- **Average count 300 cells / μ l**
- **Range 0-800 cells/ μ l**

Monocyte Differentiation



Function of Monocytes and Macrophages

Antigen presentation of phagocytized particles to T Cells

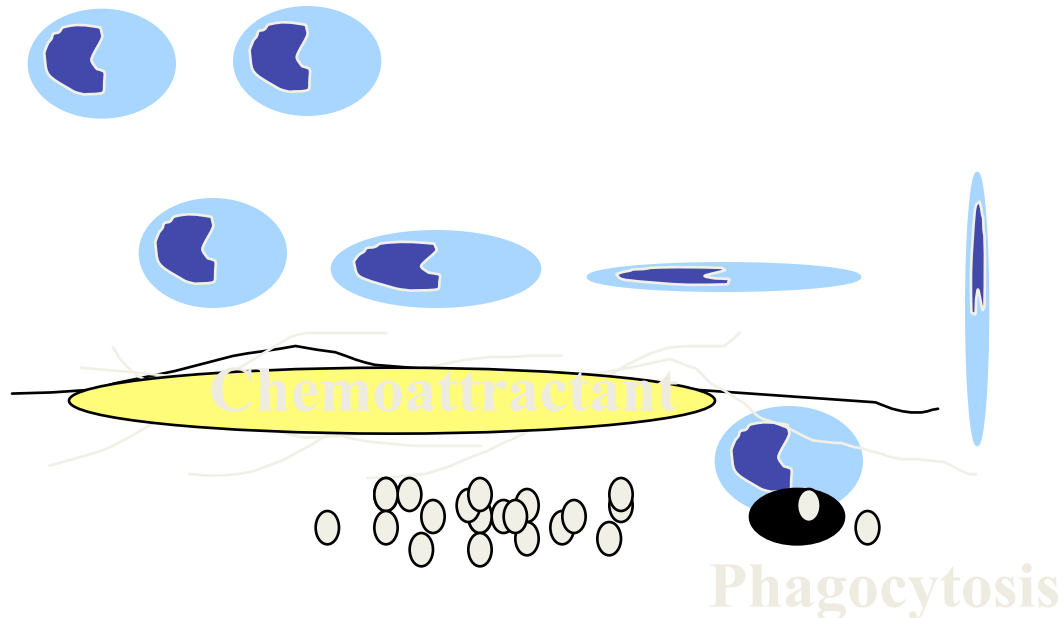


Monocyte Function

Follow neutrophils to sites of inflammation within 12-24h

Number 1/30th that of neutrophils

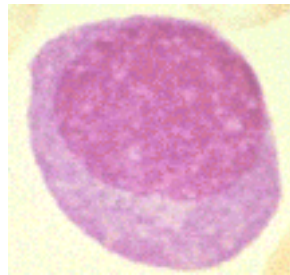
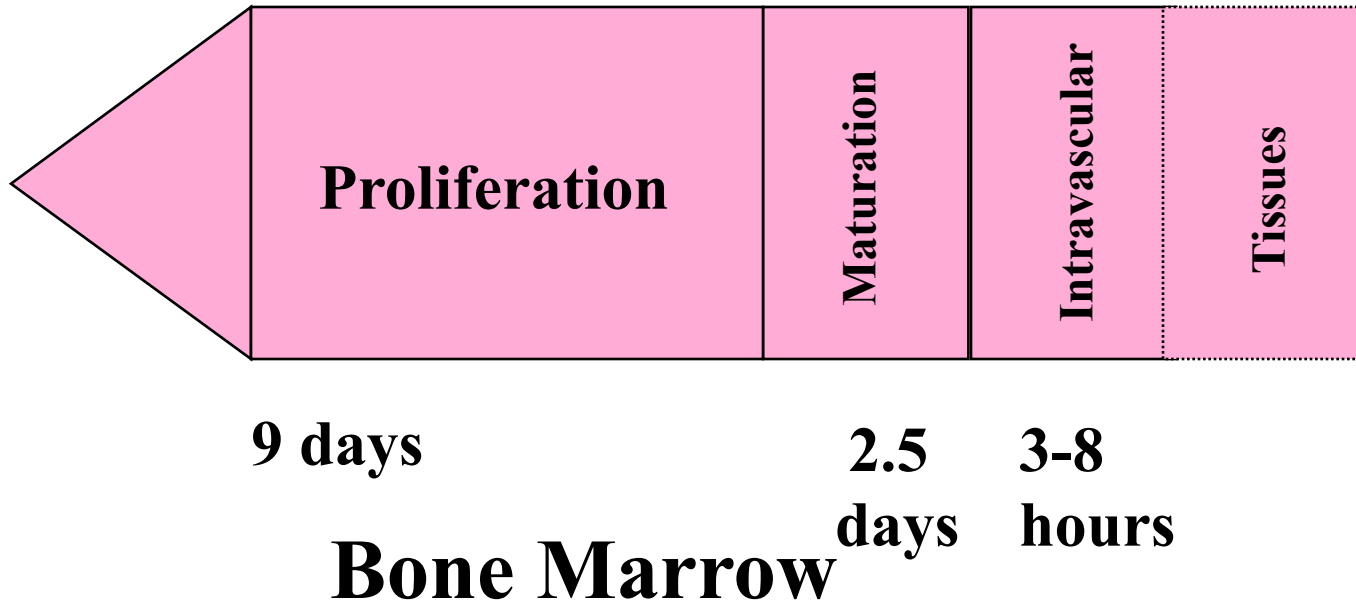
Pts w/ CGD, CHS and LAD also have defects in monocyte fxn



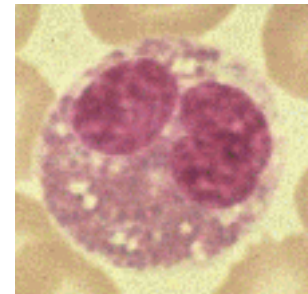
Disturbances in Monocytes

- **Low counts**
 - glucocorticoids
 - stress
- **Elevated counts**
 - Malignancy
 - Granulomatous disease
 - Marrow recovery
 - Infections
 - malaria
 - TB
 - Rocky Mountain Spotted fever
 - leishmaniasis
 - brucellosis

Eosinophils



Myelocyte



Eosinophil

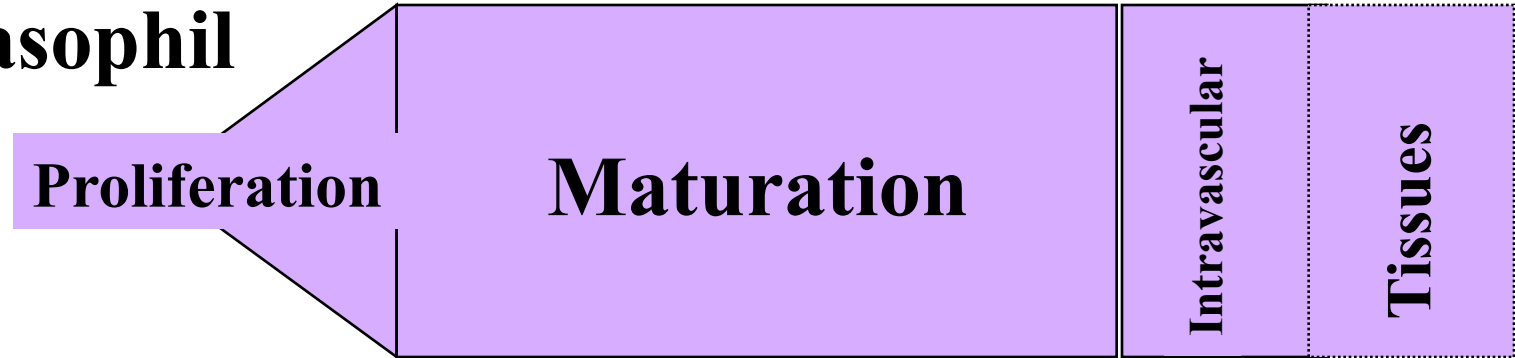
Eosinophil Function

- Bright red granules
- IgE on cell surface (not on neutrophils)
- Play a key role in killing parasites
- Average absolute count 200/ μ l
- Non allergic individuals usually <400/ μ l

Eosinophilia

- **Conditions:**
 - **N**eoplasm (Hodgkin's disease, lymphoma other tumors)
 - **A**llergies-drugs, environmental (grass, trees, dust)
 - **A**sthma
 - **C**ollagen vascular diseases-vasculitis
 - **P**arasitic infection
- **Idiopathic hypereosinophilia:** elevated eosinophil count associated with organ dysfunction (GI, skin, CNS, cardiovascular).
 - > 5000/ μ l requires treatment with immunosuppressives and antihistamines

Basophil

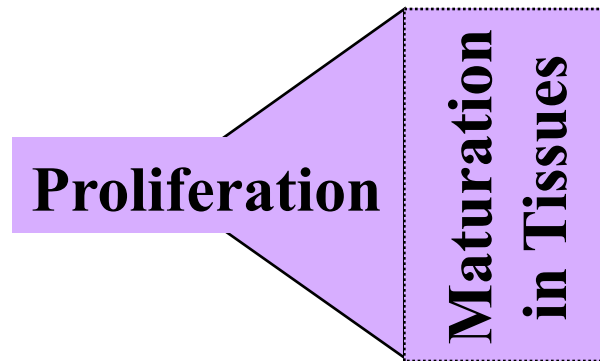


2.5
days

7 days

days

Mast Cell



Basophil Function

- **Basophils and mast cells**
 - Function remains obscure but may play a role in host defense against certain parasites

Disturbances in Basophil Count

- Low count
 - hypersensitivity
 - glucocorticoids
- High count
 - Allergies
 - infection
 - endocrinopathies
 - myeloproliferative disorders
 - Systemic mastocytosis
 - symptoms due to excess histamine release

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