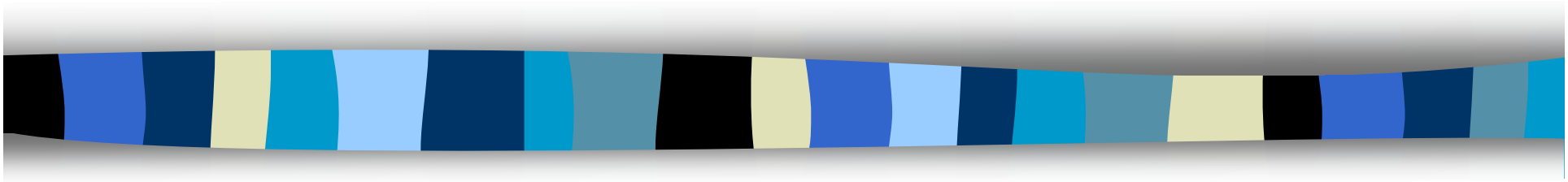
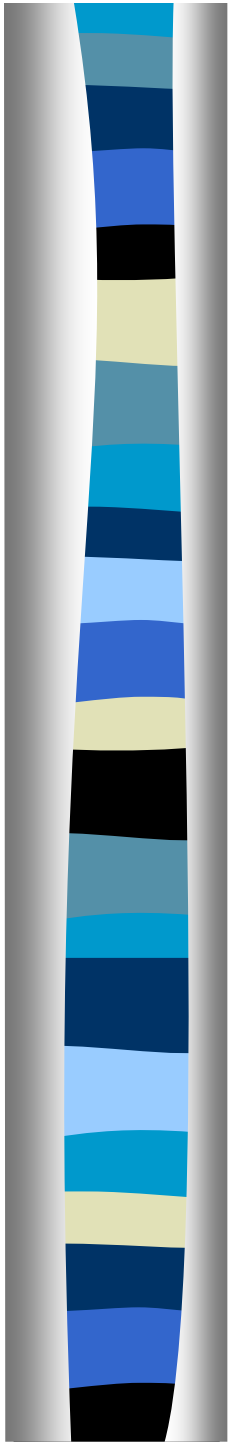
Hematology Physiology 2
Leukocytes, Coagulation



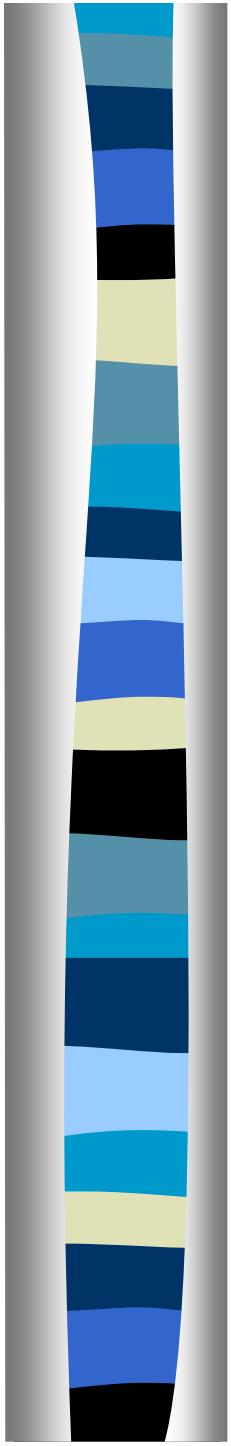
Brenda Beckett, PA-C



Terms

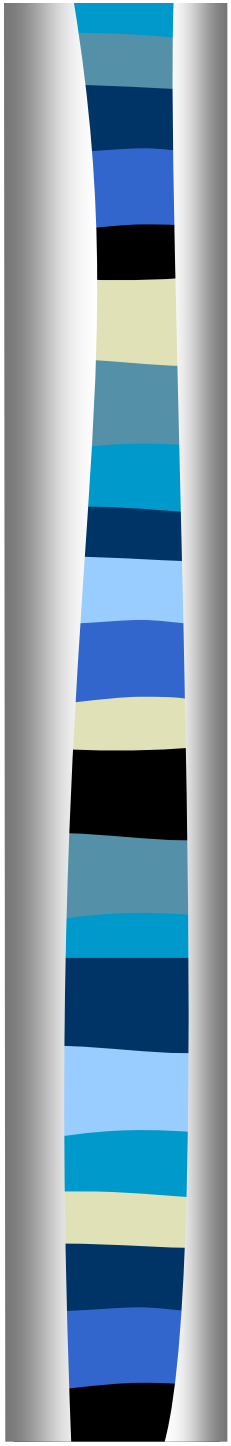
Lymphopoiesis
Granulopoiesis
Monocyte
Macrophage
Neutrophil
Phagocytosis
Acquired immunity
B lymphocyte
T lymphocyte

Thrombopoiesis
Hemostasis
Coagulation cascade
Clotting factors
Bleeding disorders
Hypercoagulation



Leukocytes

- Protective against viruses, bacteria, parasites and other invasive organisms
- Formed in bone marrow and lymph tissue
- Transported in blood to area of inflammation

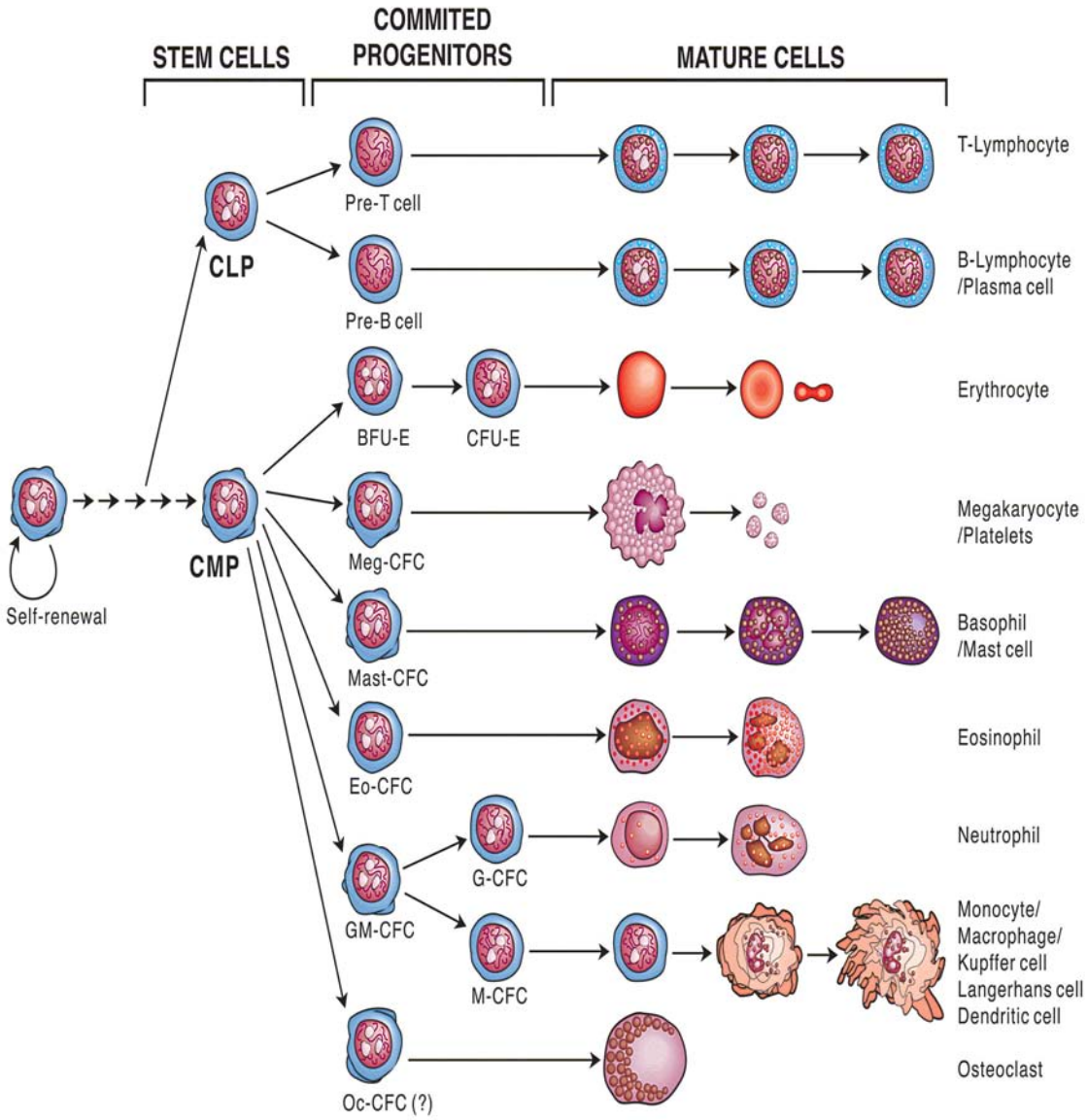


Leukocytes

- Percentages (approximate)
  - Neuts 62%
  - Eos 2.3%
  - Basos 0.4%
  - Monos 5.3%
  - Lymphs 30%

How they work

- Neutrophils and Monocytes:
  - Ingest organisms by phagocytosis
- Lymphocytes:
  - In connection with immune system, attach to organisms and destroy them


STEM CELLS
COMMITED PROGENITORS
MATURE CELLS
Self-renewal
CLP
CMP
Pre-T cell
Pre-B cell
BFU-E
CFU-E
Meg-CFC
Mast-CFC
Eo-CFC
G-CFC
GM-CFC
M-CFC
Oc-CFC (?)
T-Lymphocyte
B-Lymphocyte /Plasma cell
Erythrocyte
Megakaryocyte /Platelets
Basophil /Mast cell
Eosinophil
Neutrophil
Monocyte/ Macrophage/ Kupffer cell Langerhans cell Dendritic cell
Osteoclast

Formation

- Myelocytic (grans and monos):
  - Formed only in bone marrow
- Lymphocytic:
  - Produced mainly in lymphoid organs:
    - Spleen
    - Lymph glands
    - Thymus

Life Span Varies

- In blood mainly to be transported from marrow or lymphoid tissue to areas where needed (inflammation)
- Grans: 4-5 hrs in blood. 4-5 days in tissue. If serious infection, shortened because perform function and are destroyed.

Life Span

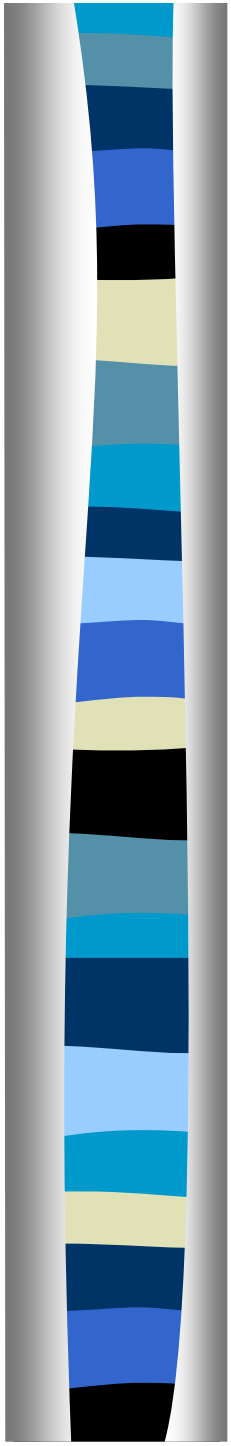
- Monos:
  - 10-12 hrs in blood, to tissue
  - Swell to larger size, become tissue macrophage
  - Live for months unless destroyed while performing phagocytosis

Life Span

- Lymphs:
  - Enter blood continuously with lymph drainage, where they stay for a few hrs
  - Pass back into tissue by diapedeis, re-enter lymph.
  - Return to blood again and again
  - Life span of months to years depending on need

Defensive properties: Neutrophils & Macrophages

- Attack & destroy invading cells
- Neuts can do this in circulating blood
- Monos: immature. As macrophage, combat disease
- Both move thru tissue via ameiod motion when stimulated by products of inflammation



Defense

- Phagocytosis
  - Selective
  - Most natural substances have protective protein – repels phagocytosis
  - Dead tissues & foreign particles: No protective coat, can lead to phagocytosis

Phagocytosis, cont.

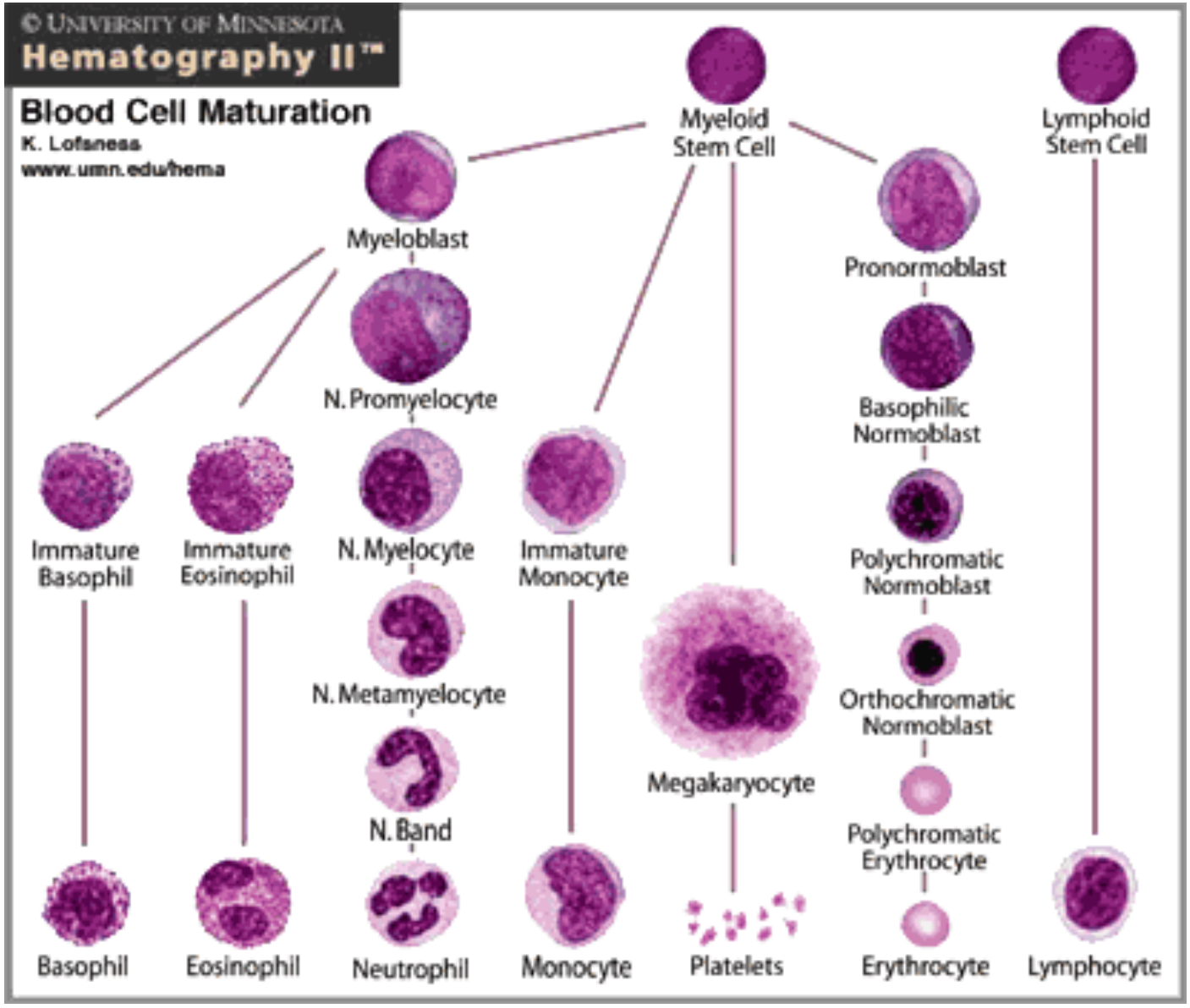
- Enhanced by binding of antibody to foreign particles
- Once phagocytized, lysosomes and cytoplasmic granules dump digestive enzymes and bactericidal agents into vesicle

Inflammation

- After tissue injury, substances released, change is tissue.
- Increased blood flow & permeability of capillaries, fluid into interstitial spaces, migration of grans & monos, swelling
- “wall off” area of injury: decreases spread of infection

Inflammation: Role of Neuts & Macrophages

- 1. Tissue macrophages become mobile, migrate to area (minutes)
- 2. Neutrophil invasion (hours). Causes increased production in bone marrow
- 3. Monos from blood enter tissue, become macrophages (days to wks)
- 4. Increased production of grans & monos by marrow (3-4 days). Early forms in blood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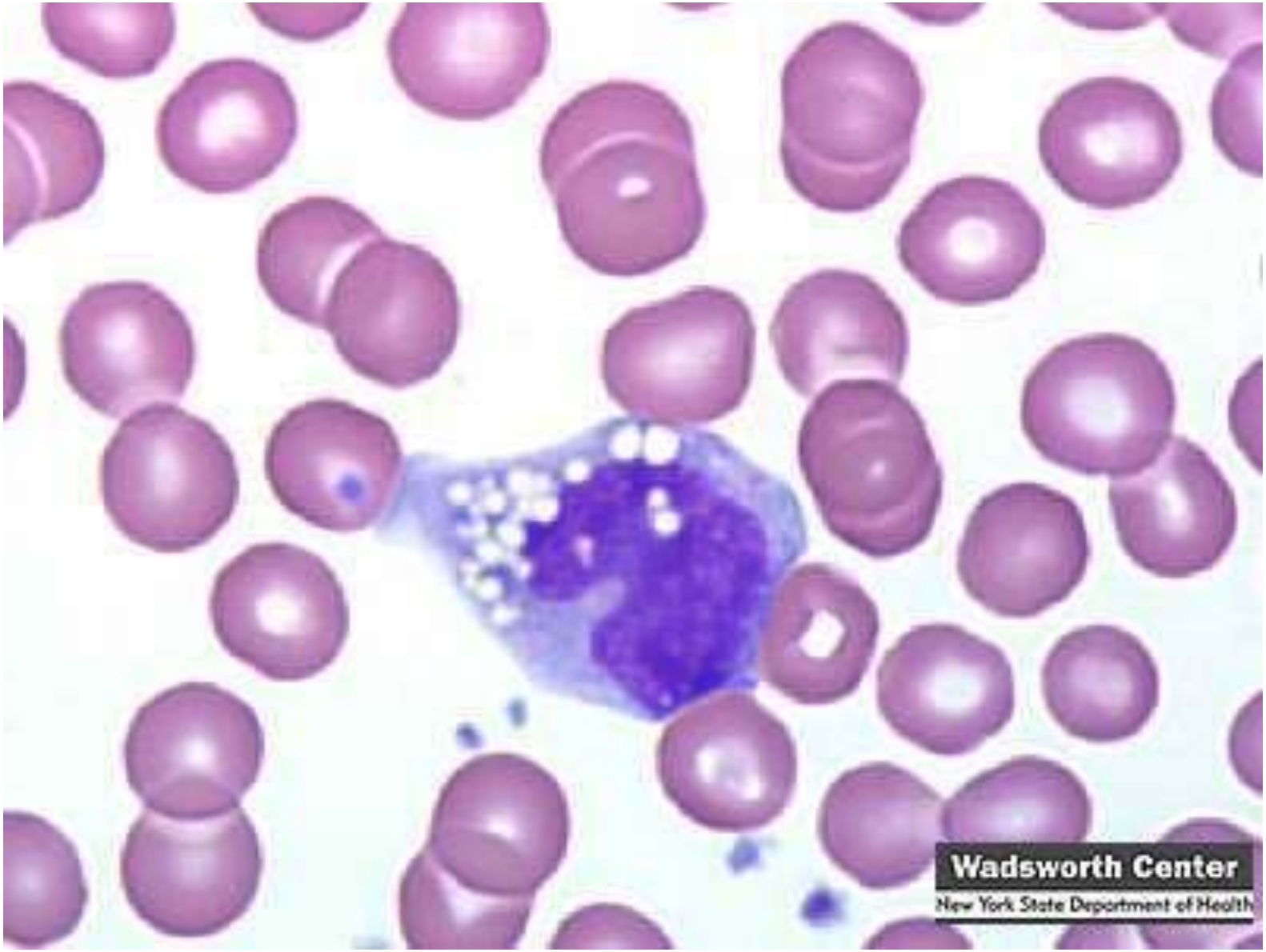
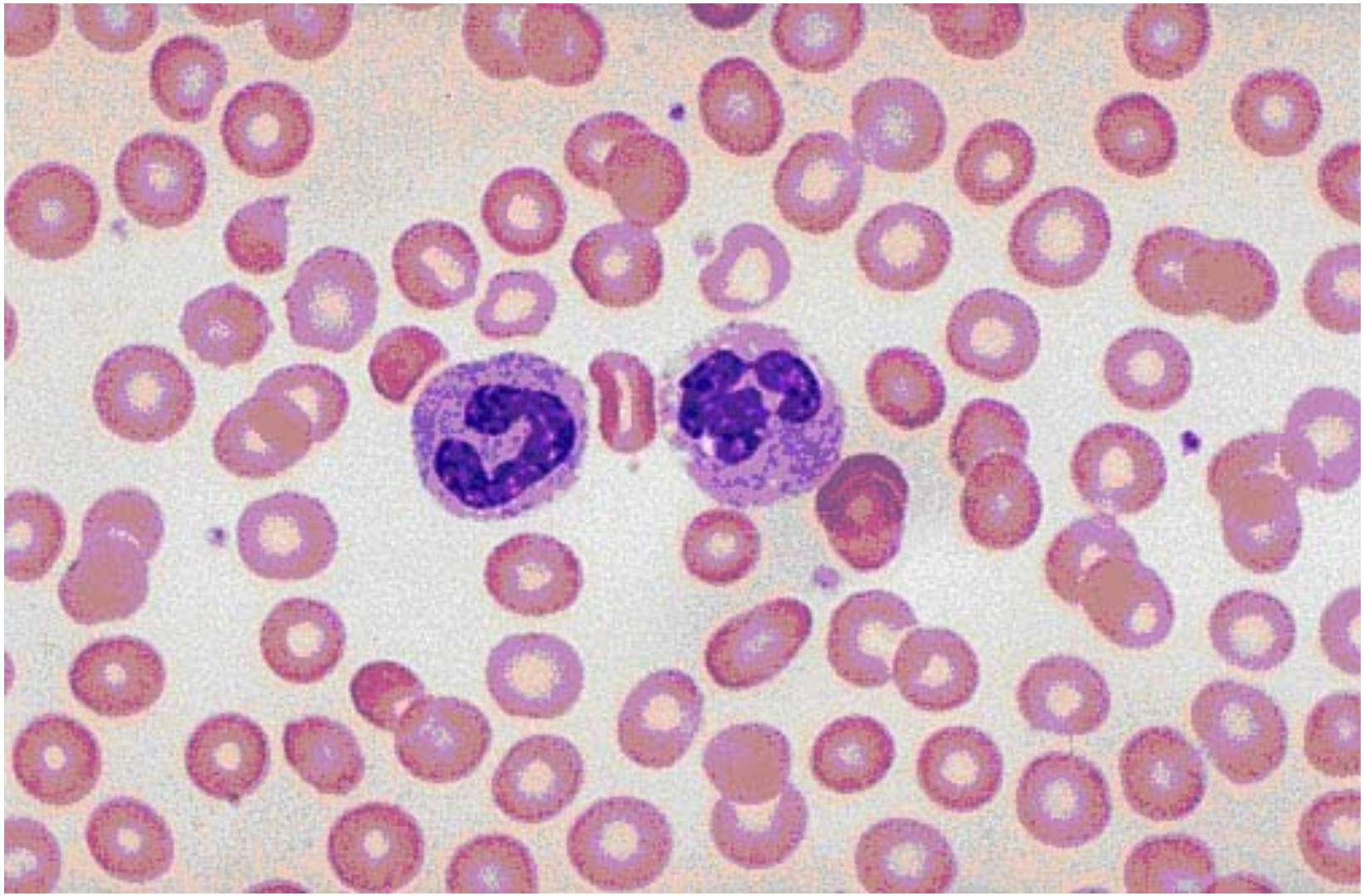
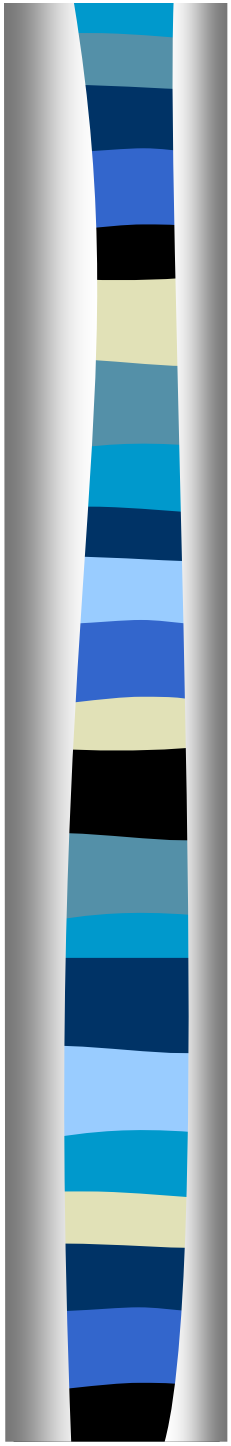
Hematography II™
Blood Cell Maturation
K. Lofsness
www.umn.edu/hema
Myeloid Stem Cell
Lymphoid Stem Cell
Myeloblast
Pronormoblast
N. Promyelocyte
Basophilic Normoblast
Immature Basophil
Immature Eosinophil
N. Myelocyte
Immature Monocyte
Polychromatic Normoblast
N. Metamyelocyte
Orthochromatic Normoblast
Megakaryocyte
N. Band
Polychromatic Erythrocyte
Basophil
Eosinophil
Neutrophil
Monocyte
Platelets
Erythrocyte
Lymphocyte

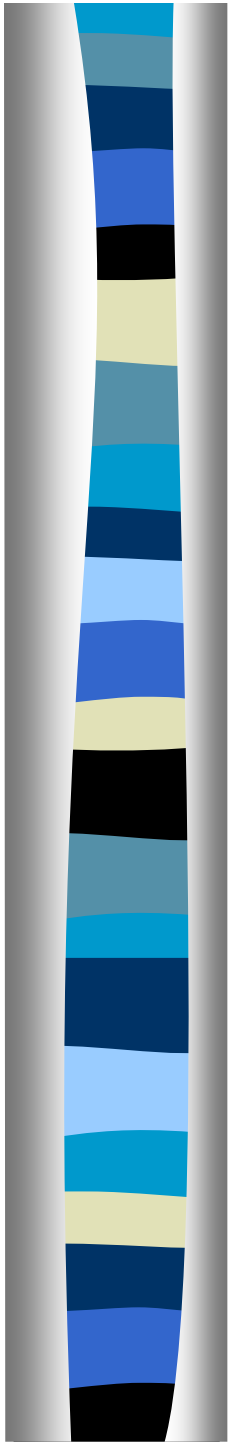

Wadsworth Center
New York State Department of Health





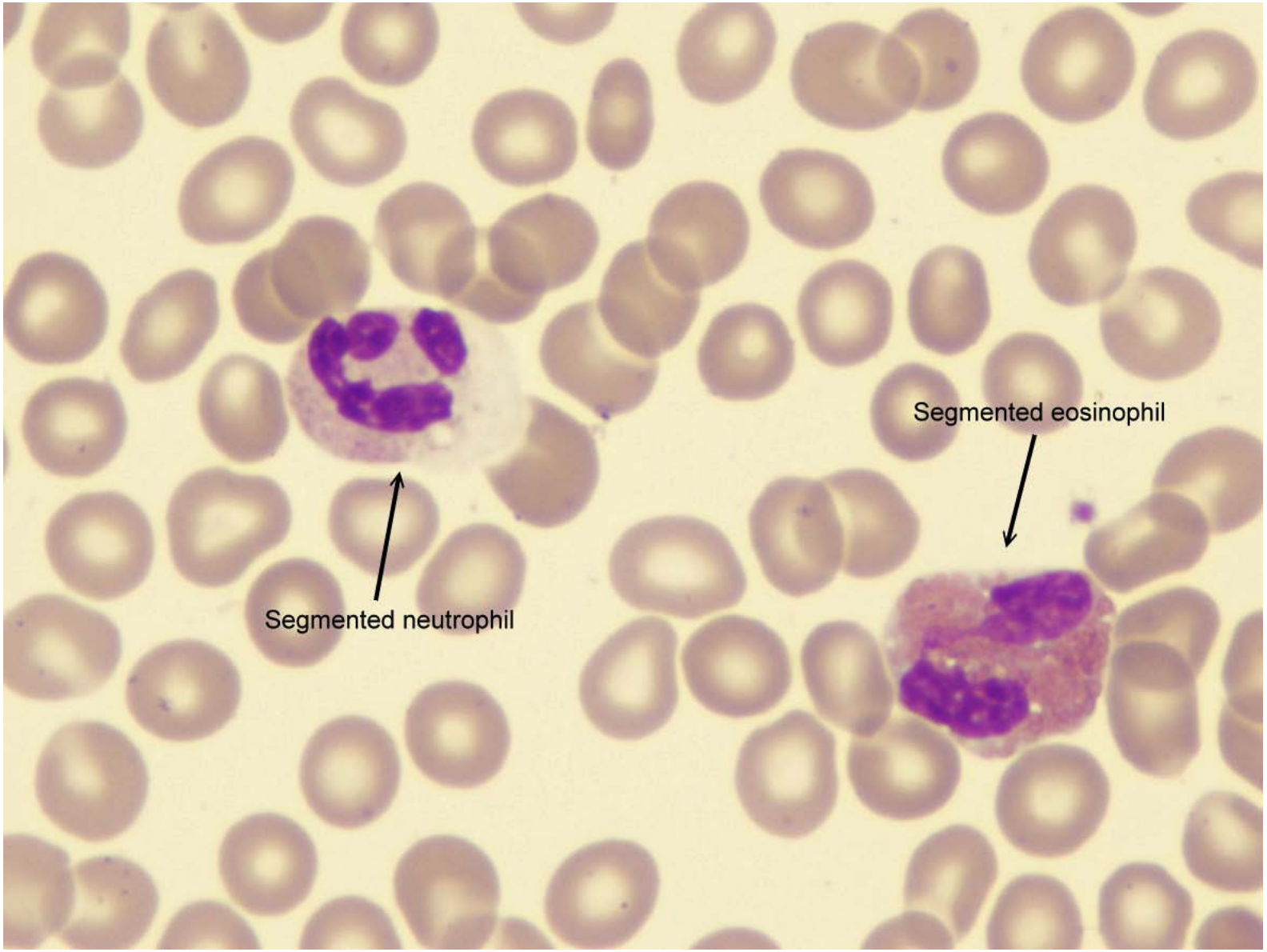
Feedback Control

- > 2 dozen factors. Major are:
  - TNF: Tumor necrosis factor
  - IL-1: Interleukin-1
  - GM-CSF: Granulocyte-monocyte colony stimulating factor
  - G-CSF: Granulocyte colony stim factor
  - M-CSF: Monocyte colony stim factor



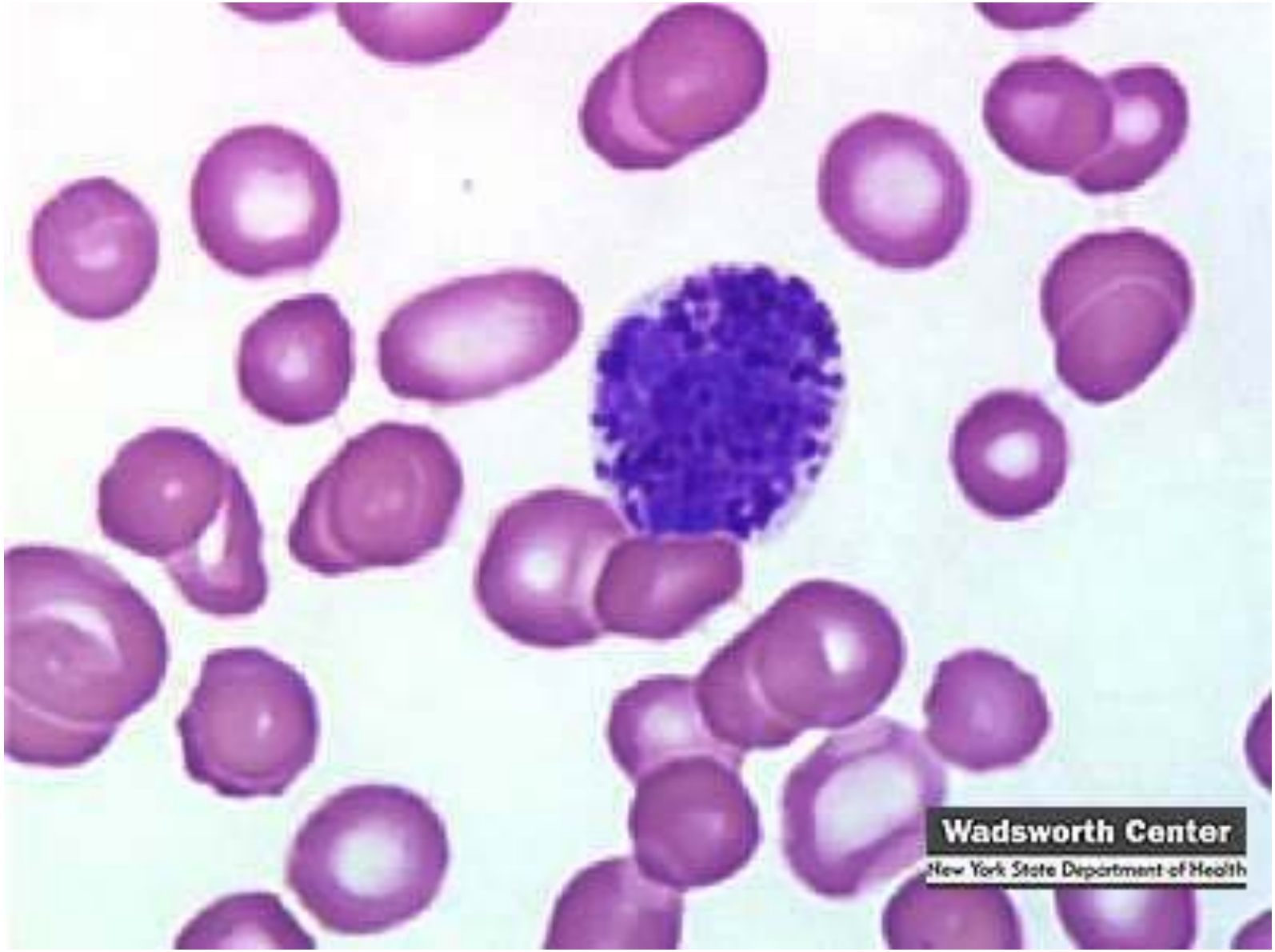
Eosinophils

- Increased in parasitic infection
- Parasites too large to be phagocytized
- Eos attach to surface, release substances that kill parasites
- Also collect in tissue with allergic reaction


Segmented eosinophil
Segmented neutrophil

Basophils

- Similar to mast cells
- Liberate heparin into blood, prevents coagulation
- Release histamine, contributes to inflammatory process
- Role in some types of allergic reactions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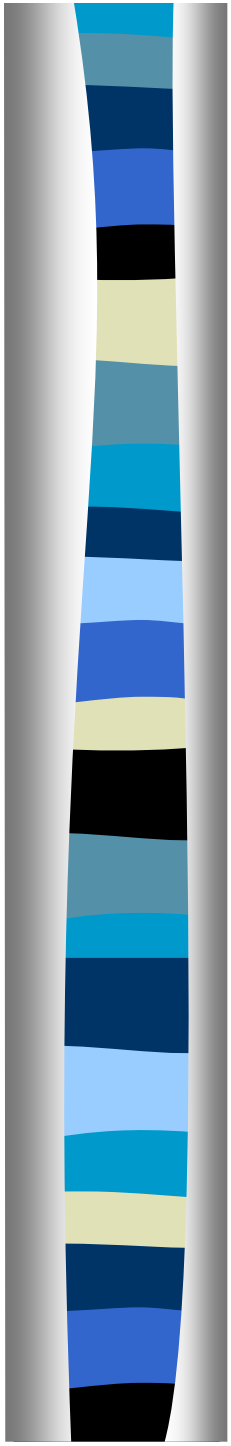
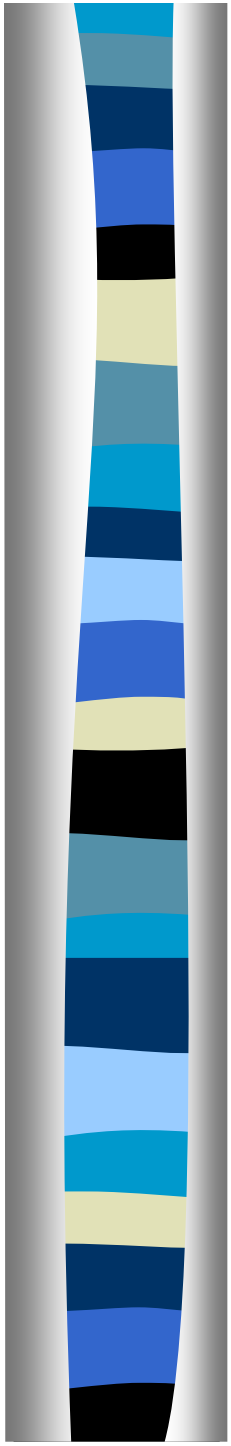


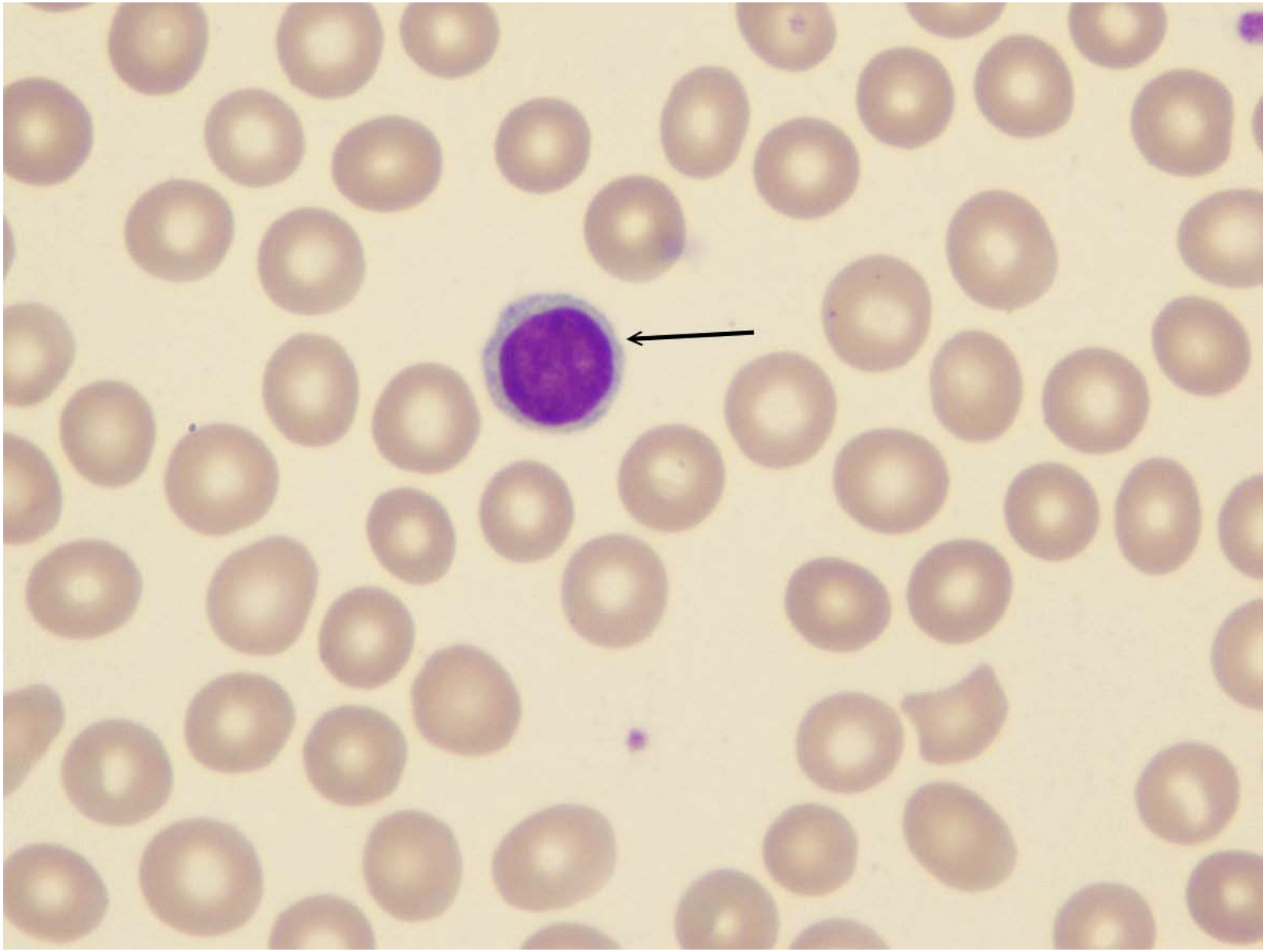
Acquired Immunity

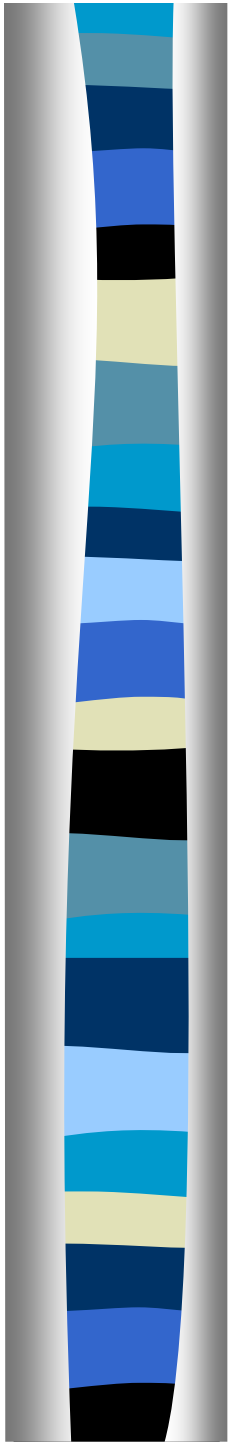
- Protective mechanism against invading agent
- Initiated by antigens
- Humoral (B cell) – circulating antibodies
- Cell mediated (T cell) – activated lymphs destroy foreign agent



Lymphocytes

- Basis of acquired immunity
- Derived from pleuripotent stem cells
  - T lymphs
  - B lymphs



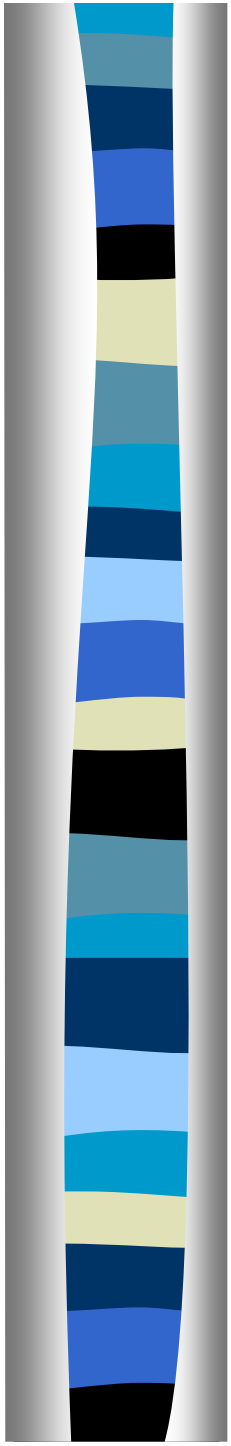


T Lymphocytes

- Cell mediated immunity
- Mostly produced in thymus gland
- Divide and develop diversity
- Leave thymus, go to lymphoid tissue
- Mostly occurs before & right after birth

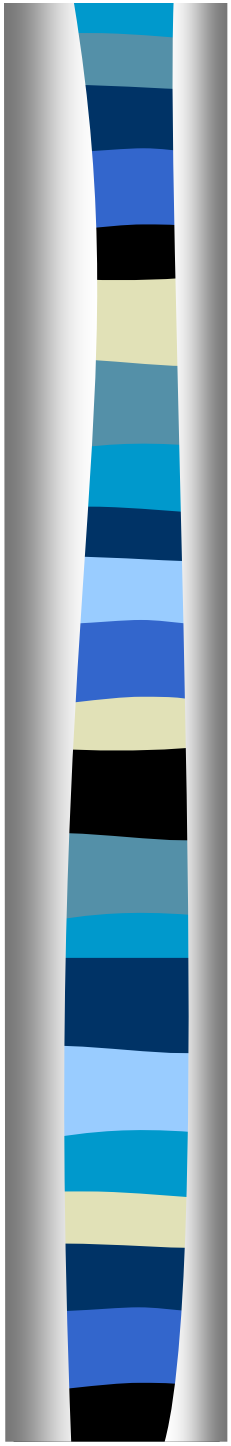
B Lymphocytes

- Humoral immunity
- Production in fetal liver, bones after birth
- Actively secretes antibodies, combine with and destroy substances
- Diverse
- Travel to lymphoid tissue



Lymphoctes

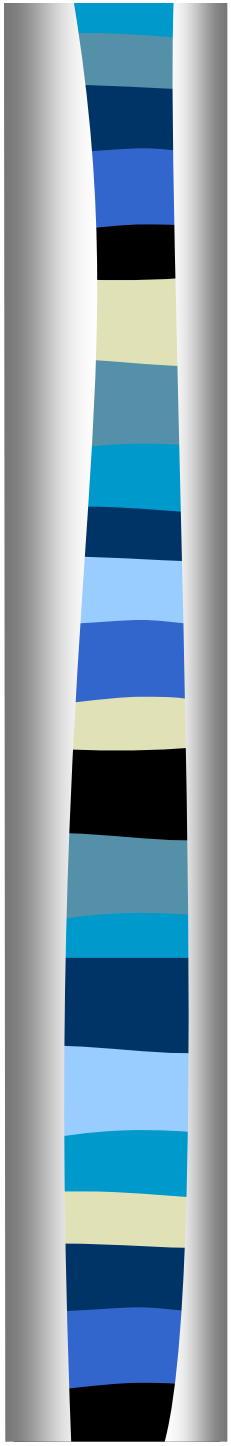
- Antigen in contact with T & B lymphs: become activated, form specific ab.
- Preformed and waiting activation
- Replicates, forms clones
  - B: secretes antibodies (plasma cell)
  - T: develops into sensitized T cell, into blood, circulates through tissues, back to lymph



B Lymphocytes

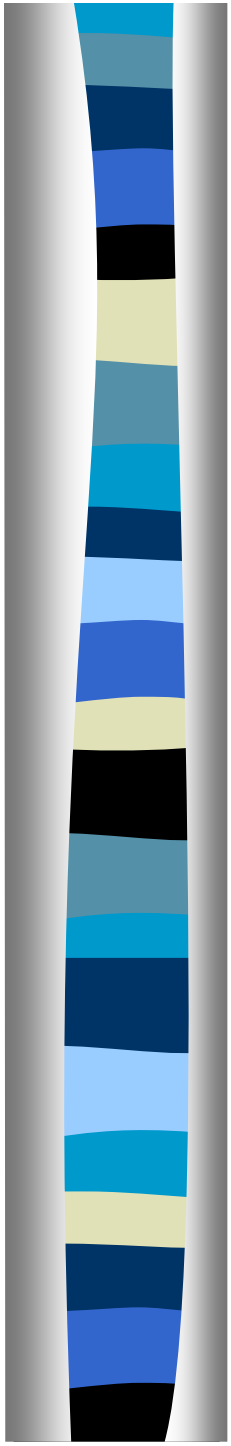
- Memory enhances response: clones remain dormant (memory cell), more rapid and potent antibody response
- Abs inactivate invading agent by:
  - Agglutination
  - Precipitation
  - Neutralization
  - Lysis

  Activates complement system



T Lymphocytes

- Activated clones circulate for months to years.
- With secondary exposure, more powerful reaction
- Antigen binds with receptor on surface of T cell

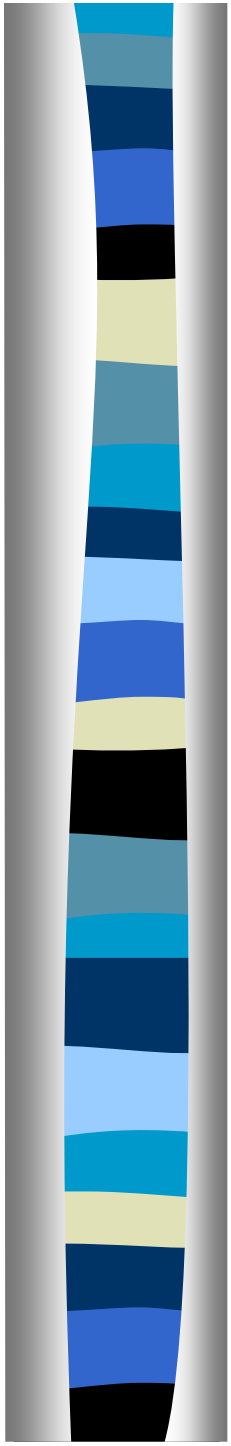


T Lymphocytes: 3 types

T helper: regulate immune fxn. Act on other cells to stimulate immune system

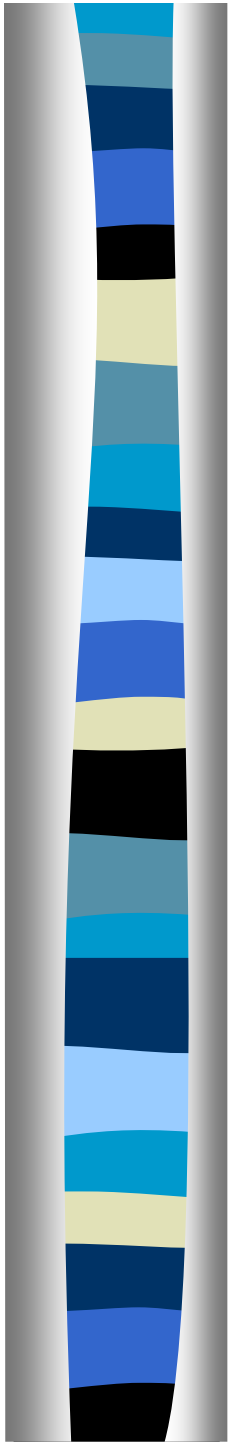
Cytotoxic T cell: “killer” Kills microorganisms in direct attack.

Suppresser T cell: Suppress function of T helper & cytotoxic T cells. Regulate immune activity.



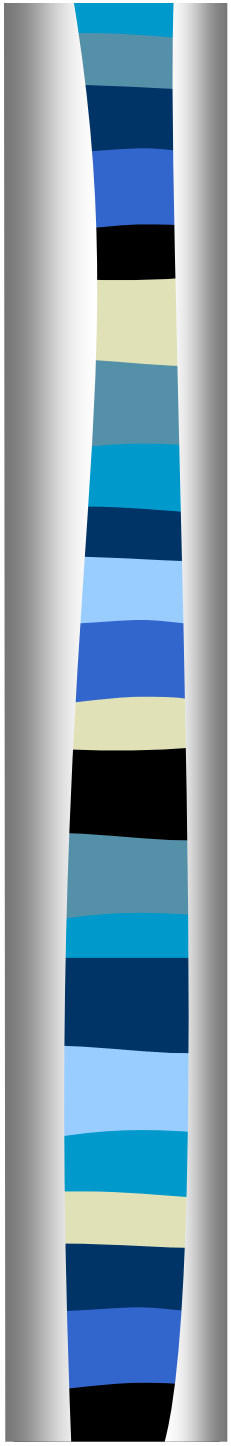
Leukemias

- Lymphogenous, myelogenous
- Uncontrolled cancerous production of one type of cells
- Leukemic cells nonfunctioning, don’t provide protection
- Almost all spread to spleen, nodes, liver



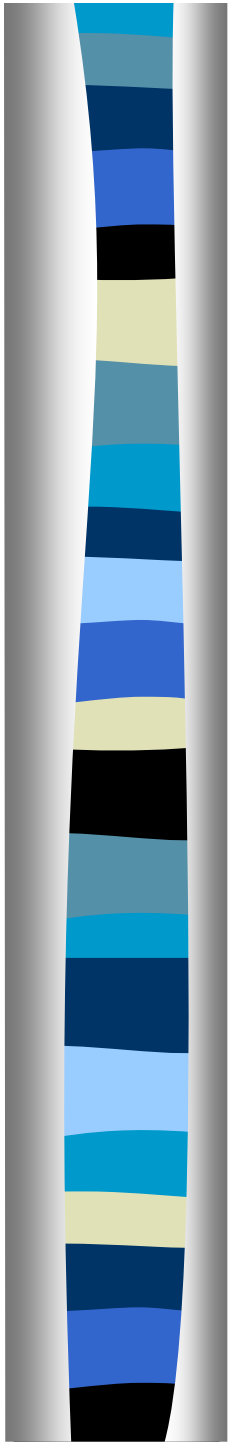
Thrombopoiesis

- Occurs in bone marrow: megakaryocytes fragment into platelets
- Important in clot formation
- Glycoprotein on cell wall adheres to injured areas, not endothelium
- Lifespan 8-12 days, removed by macrophages



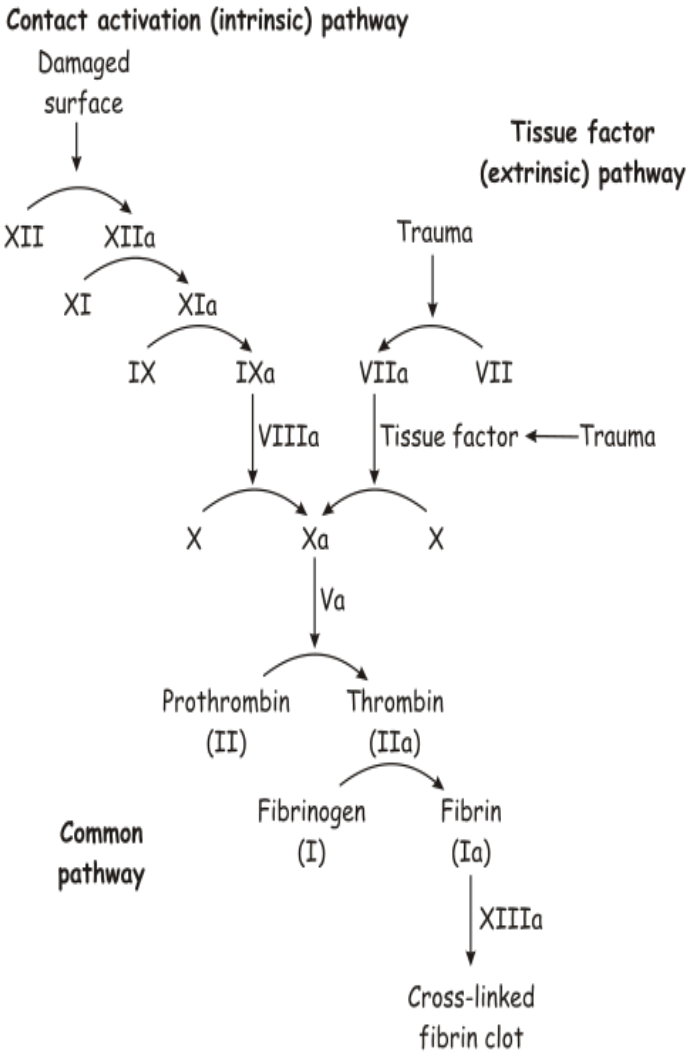
Hemostasis

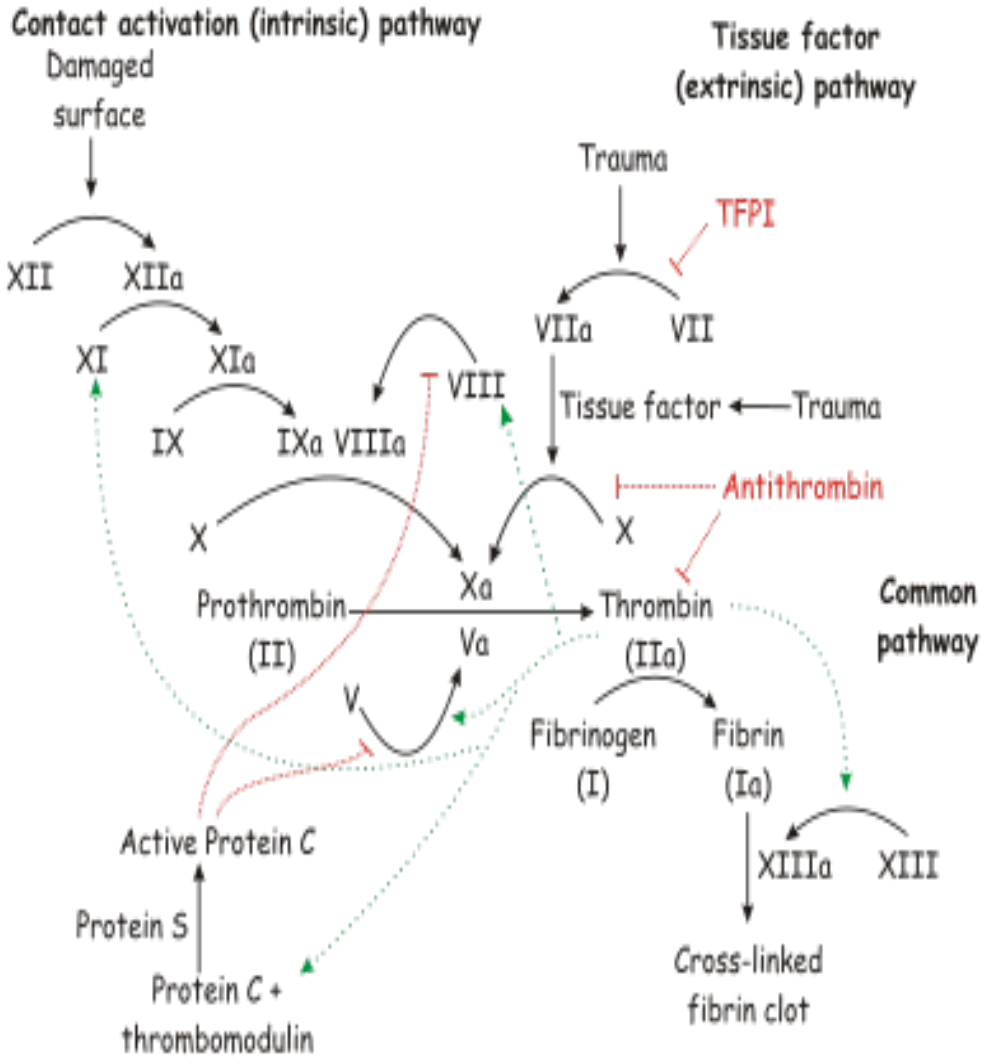
- Prevention of blood loss
- When vessel is severed or ruptured:
  - Vascular spasm (constriction)
  - Formation of platelet plug
  - Formation of blood clot (coagulation)
  - Growth of fibrous tissue to close rupture permanently

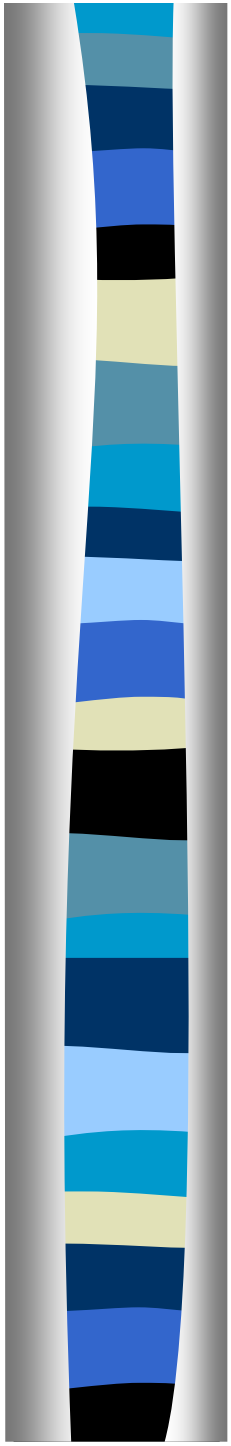


Coagulation Steps

- Formation of prothrombin activator
  - Extrinsic pathway
  - Intrinsic pathway
- Prothrombin converted to thrombin
- Fibrinogen converted to fibrin, clot forms

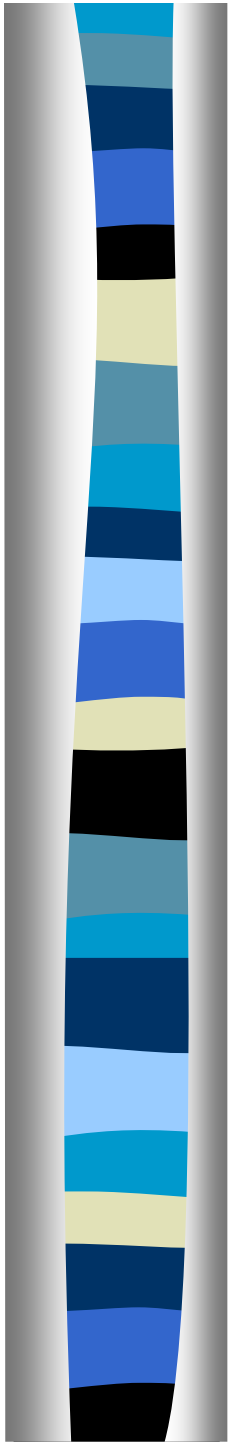

Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Tissue factor (extrinsic) pathway
Trauma
VIIa
VII
Tissue factor
Trauma
X
Xa
X
Va
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
XIIIa
Cross-linked fibrin clot
Common pathway


Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa VIIIa
VIII
X
Xa
Va
Prothrombin (II)
Thrombin (IIa)
V
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot
Active Protein C
Protein S
Protein C + thrombomodulin
Tissue factor (extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
Common pathway



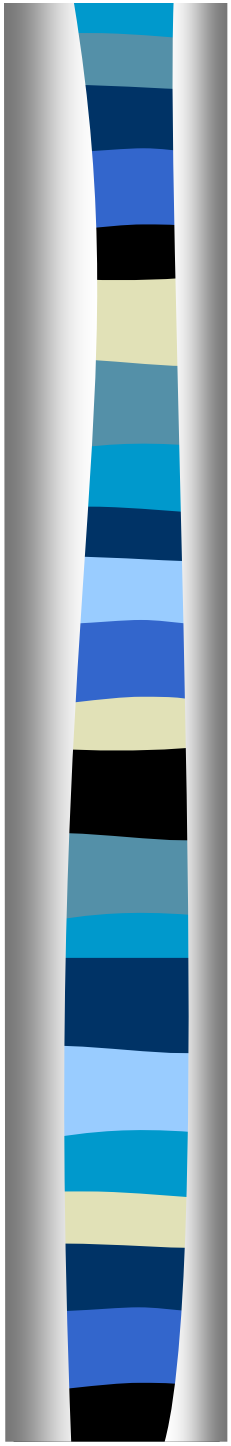
Clotting Factors

- Proteins
- Involve enzymes that cause cascading reactions
- Calcium ions are required



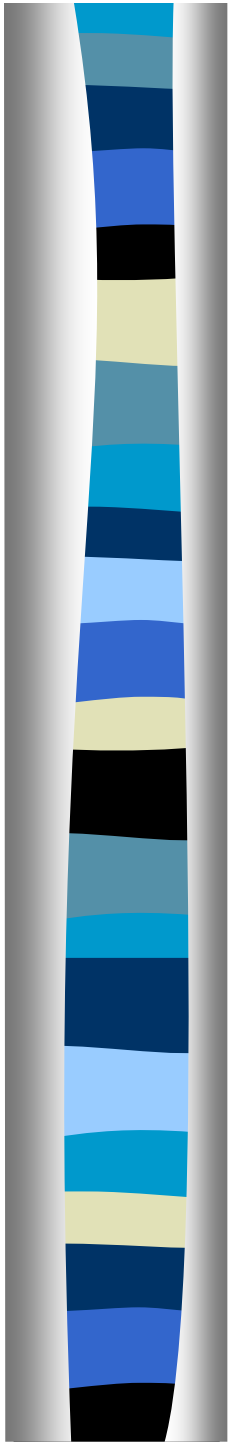
Normal Prevention of Clots

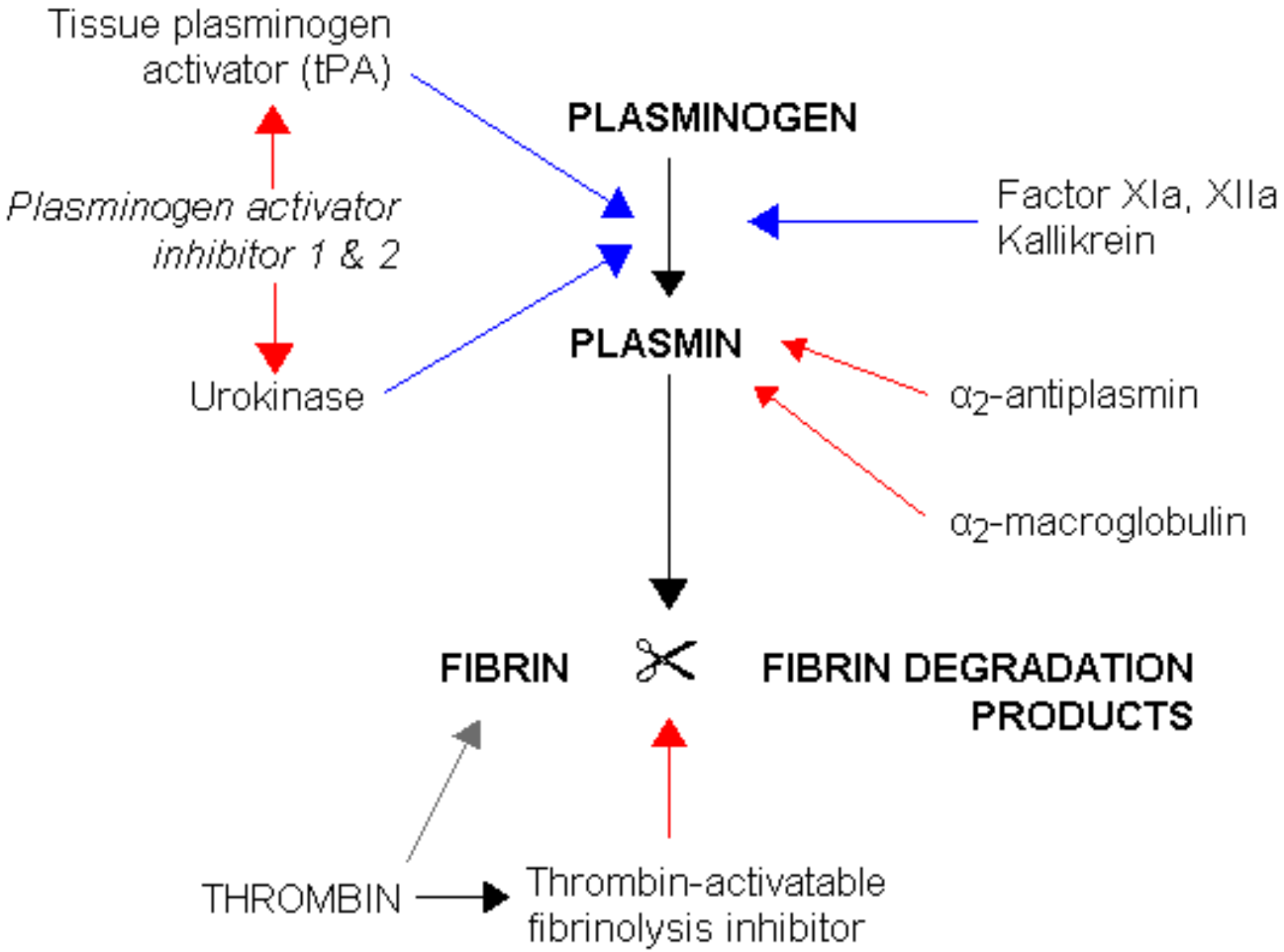
- Smooth endothelium
- Layer of glycocalyx in endothelium, repels clotting factors and platelets
- Protein bound with endothelial memb, binds thrombin, also activates Protein C, inactivates Factors V & VIII
- AT III: removes fibrin from blood – heparin increases effectiveness



Normal Prevention of Clots

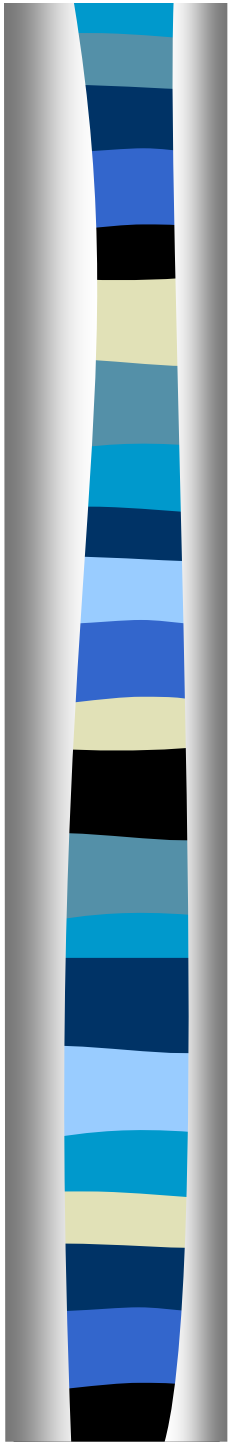
- Plasminogen becomes plasmin – lyses clots
- t-PA is released




Tissue plasminogen activator (tPA)
PLASMINOGEN
Factor XIa, XIIa Kallikrein
Plasminogen activator inhibitor 1 & 2
PLASMIN
Urokinase
α2-antiplasmin
α2-macroglobulin
FIBRIN
FIBRIN DEGRADATION PRODUCTS
THROMBIN
Thrombin-activatable fibrinolysis inhibitor

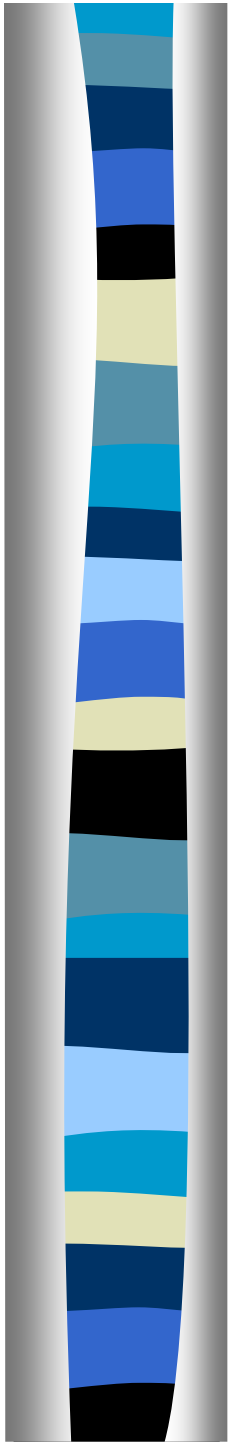
Bleeding Disorders

- Vitamin K deficiency
  - Necessary for forming some factors
- Hemophilia
  - Deficiency of F VIII (hemophilia A)
  - Deficiency of F IX (hemophilia B)
- Von Willebrand disease: affects F VIII
- Throbocytopenia
  - Bleed from small vessels, purpura



Hypercoagulation

- APC (Activated Protein C) Resistance
- Factor V Leiden gene mutation
- Protein C or S deficiency
- Antithrombin III deficiency



Anticoagulants

- Heparin
  - Increased effectiveness of AT III
  - Instantaneous effect
- Coumadin
  - Competes with Vitamin K, decreased levels of prothrombin, F VII, IX, X.