CARDIOVASCULAR PHYSIOLOGY

Lecture Outline

- General Functions
- Components
- Production & Function of Formed Elements
- RBC specialized functionality
  - Anemia
- Hemostasis
  - Platelets & Coagulation

General Functions

- Functions as:
  - a transport medium
  - a protective medium
  - a regulatory medium
  - a hydraulic medium

Gases
Nutrients
Chemical messengers
Heat
Wastes

Platelet activation
Coagulation
Adaptive Immunity
Non-specific defenses

pH
Temperature
Volume/Cell Count

Movement of tissues
Filtration force

Components

- Whole blood is divided into
  - Formed elements (45%)
    - Erythrocytes
    - Leukocytes
    - Thrombocytes
  - Plasma (55%)
    - Extracellular matrix composed of
      - Water
      - Ions
      - Organic molecules
      - Trace elements and vitamins
      - gases

Neutrophils
Eosinophils
Basophils
Lymphocytes
Monocytes

Amino acids
Proteins
Glucose
Lipids
Nitrogenous wastes

Albumins
Globulins
fibrinogens

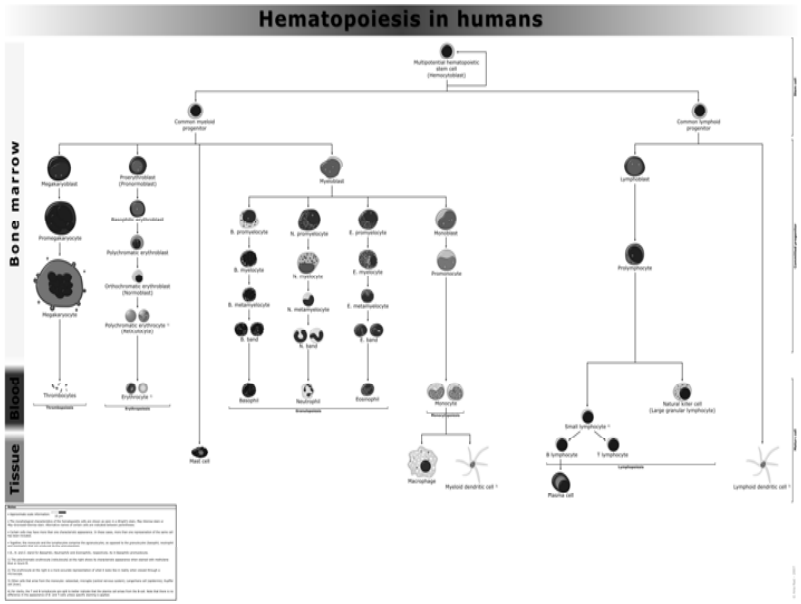
CO_2
O_2

Production & Function of Blood Cells

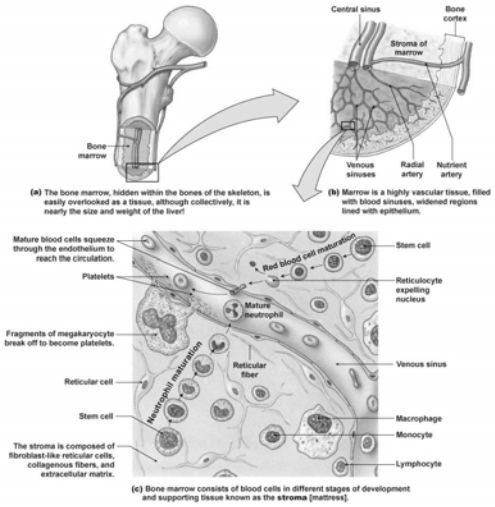
- Production of blood cells is called hematopoiesis
  - Is initiated by week three of embryonic development
  - Rate is influenced by cytokines
    - EPO (erythropoietin)
      - Produced in the kidney
      - Targets bone marrow & increases production of erythrocytes
    - TPO (thrombopoietin)
      - Produced in the liver
      - Targets bone marrow & increases production of megakaryocytes
    - CSFs, IL's, SCF (stem cell factor)
      - Produced by the endothelium and fibroblasts of bone marrow and by leukocytes
      - targets all blood cell types & increases activity of hematopoietic stem cells

Production & Function of Blood Cells

- All blood cells differentiate from a pluripotent stem cell
  - The Hematopoietic stem cell is
    - Pluripotent because it is already partially differentiated… won't produce anything else but blood cell types
  - This process occurs in bone marrow
    - Mainly in the epiphyses (ends) of long bones and in the flat bones (sternum, ribs, ilium)



Production & Function of Blood Cells

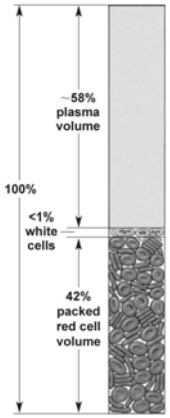


Production & Function of Blood Cells

- Red Blood Cell Production
  - Low O_2 levels initiate synthesis of hypoxia-inducible factor-1 (HIF-1)
  - HIF-1 turns on EPO gene and synthesis of EPO is on!
  - Turns off as hypoxia is corrected due to the increase in O_2 carrying RBCs.
  - Today EPO is produced by recombinant DNA technology and other CSFs for WBCs
    - Benefits?
      - Cancer patients and
      - athletes! (illegally)

Production & Function of Blood Cells

- Blood Cell Levels



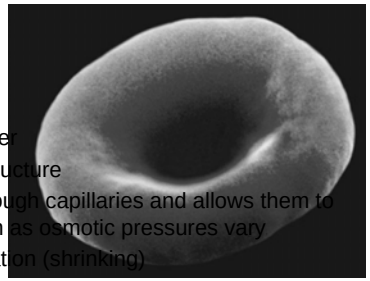
	MALES	FEMALES
Hematocrit	40%–54%	37%–47%
Hemoglobin (g Hb/dL* blood)	14–17	12–16
Red cell count (cells/μL)	$4.5–6.5 \times 10^6$	$3.9–5.6 \times 10^6$
Total white cell count (cells/μL)	$4–11 \times 10^3$	$4–11 \times 10^3$
Differential white cell count		
Neutrophils	50%–70%	50%–70%
Eosinophils	1%–4%	1%–4%
Basophils	<1%	<1%
Lymphocytes	20%–40%	20%–40%
Monocytes	2%–8%	2%–8%
Platelets (per μL)	$150–450 \times 10^3$	$150–450 \times 10^3$

Production & Function of Blood Cells

- Colony-Stimulating Factors (CSFs)
  - Regulate wbc production and development = leukopoiesis
    - Rate must be able to be quickly amped up as a mature leukocyte no longer undergoes mitosis
      - Any additional wbcs must come from stem cell activity
    - Production of a specific type is controllable by the mature population of its type
      - This ensures the correct leukocyte production for the demand

RBC Specialized Function

- Red Blood Cells
  - Specialized aspects:
    - Biconcave shape
      - Approx 7um in diameter
      - Due to cytoskeletal structure
      - Aids in movement through capillaries and allows them to maintain integrity even as osmotic pressures vary
        - » Swelling vs. crenation (shrinking)
    - Anucleate condition in mature rbcs
      - Implications?
      - Life span?



RBC Specialized Function

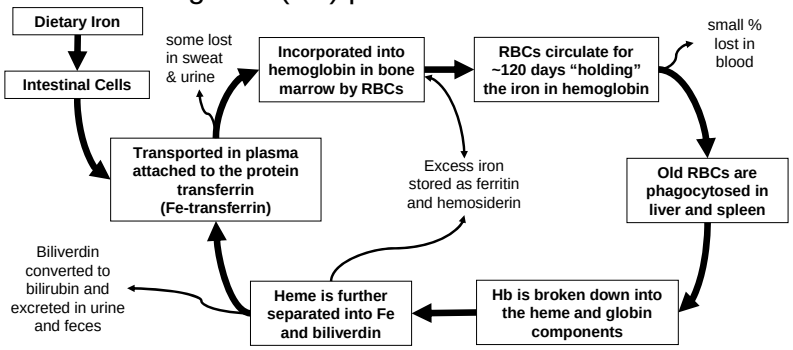
- Red Blood Cells
  - Specialized aspects:
    - The last stage (immature form) of the production process is called a reticulocyte
      - Significant as a little bit of ER remains and is visible upon microscopic evaluation
        - » The ratio of reticulocytes to erythrocytes is used to monitor production rates
    - Production and transport of hemoglobin (Hb) which accounts for 97% of the content of a mature rbc!
      - This comes to approximately 280 million hemoglobin molecules/cell!
      - Each Hb molecule carries 4 oxygen molecules
      - Increases the O_2 carrying capacity of blood by about 70 times!

RBC Specialized Function

- Red Blood Cells
  - Hemoglobin (Hb)
    - A quaternary protein (2 alpha & 2 beta units)
    - Hb exhibits plasticity in its shape
      - When O_2 binding sites are fully loaded it is in its "tense" configuration
        - » Holds onto O_2 with more tenacity
        - » *Where does this happen?*
      - When O_2 binding sites are less than fully loaded it enters a "relaxed" configuration
        - » Makes binding and releasing O_2 easier
        - » *Where does this happen?*

RBC Specialized Function

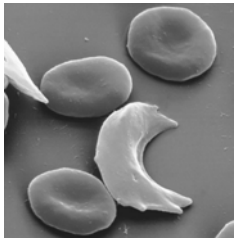
- Red Blood Cells
  - Hemoglobin (Hb) production & iron conservation



RBC Specialized Function

Anemia

- Reduction in O2 carrying capacity in blood because of low Hb content.
- RBC damage and loss from
  - Blood loss
  - Hemolytic anemia – cells bursting, may be
    - Hereditary such as
      - Sickle cell anemia
      - Spherocytosis
    - Aquired
      - Parasitic issue – malaria, dengue fever
      - Drugs
      - autoimmune issues
- Reduced capacity for RBC production
  - Aplastic anemia – cells don't form correctly
  - Loss/lack of iron (needed for Hb synthesis)
  - Deficiency in folic acid (needed for DNA production)
  - Deficiency of Vit B_{12} (needed for DNA production)
    - May be a result of lack of intrinsic factor – needed for B_{12} absorption
  - Low EPO production



RBC Specialized Function

Polycythemia

- Too many RBCs (and WBCs too)
  - May be due to stem cell dysfunction
  - May be relative polycythemia
    - The hematocrit is high but volume is normal
    - Dehydration reduces plasma volume and therefore increases relative cell count.
  - Why is polycythemia bad?

Hemostasis

- Preventing blood loss occurs in a few steps
  1. Vasoconstriction
     - Reduces blood flow and pressure in damaged vessel
       - Damage releases paracrines that cause immediate constriction of smooth muscle
  2. Platelet Plug Formation
     - The process of forming a physical plug to stop blood loss
  3. Clot formation (coagulation cascade)
     - Forms a clot (fibrin polymer)

Hemostasis

Platelet Plug Formation

- Platelets stick to damaged vessel
  - Release cytokines which initiate further vasoconstriction and additional platelet adhesion
  - Sets up a cascading effect
  - Leads to a loose plug being formed
- The damaged vessel at the same time with collagen exposed and tissue factor released starts the coagulation cascade

TABLE 16-4 Factors Involved in Platelet Function

CHEMICAL FACTOR	SOURCE	ACTIVATED BY OR RELEASED IN RESPONSE TO	ROLE IN PLATELET PLUG FORMATION	OTHER ROLES AND COMMENTS
Collagen	Subendothelial extracellular matrix	Injury exposes platelets to collagen	Binds platelets to begin platelet plug	N/A
von Willebrand factor (vWF)	Endothelium, megakaryocytes	Exposure to collagen	Links platelets to collagen	Deficiency or defect causes prolonged bleeding
Serotonin	Secretory vesicles of platelets	Platelet activation	Platelet aggregation	Vasoconstrictor
Adenosine diphosphate (ADP)	Platelet mitochondria	Platelet activation, thrombin	Platelet aggregation	N/A
Platelet-activating factor (PAF)	Platelets, neutrophils, monocytes	Platelet activation	Platelet aggregation	Plays role in inflammation; increases capillary permeability
Thromboxane A_2	Phospholipids in platelet membranes	Platelet-activating factor	Platelet aggregation	Vasoconstrictor; eicosanoid
Platelet-derived growth factor (PDGF)	Platelets	Platelet activation	N/A	Promotes wound healing by attracting fibroblasts and smooth muscle cells

Hemostasis

Coagulation Cascade

- This coagulation forms a more permanent clot!
- Two pathways to achieve this
  - Intrinsic Pathway
    - Exposed collagen activates the initiating factor of the cascade event = factor XII
  - Extrinsic Pathway
    - Damaged tissues release tissue factor (factor III or tissue thromboplastin)

Hemostasis

Coagulation Cascade

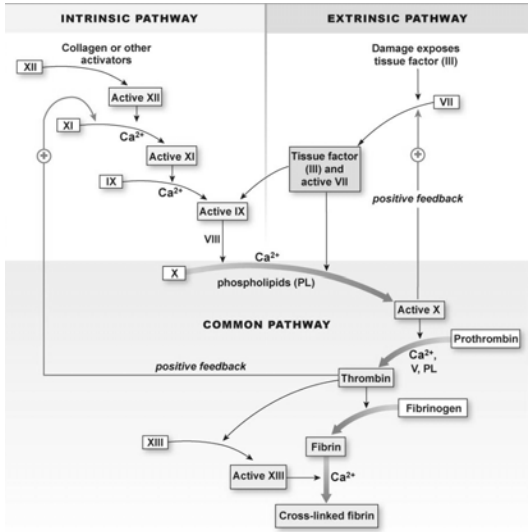


Table of Factors involved with the coagulation cascade

Number and/or name	Function
I = fibrinogen	Forms clot (fibrin)
II = prothrombin	Its active form (IIa) activates I, V, VII, VIII, XI, XIII, protein C, platelets
III* = Tissue factor	Co-factor of VIIa (formerly known as factor III)
IV* = Calcium	Required for coagulation factors to bind to phospholipid (formerly known as factor IV)
V = proaccelerin, labile factor	Co-factor of X with which it forms the prothrombinase complex
VI	*Unassigned* – old name of Factor Va
VII = stable factor	Name: Pro Convertin - Activates IX, X
VIII = Anti Hemophilic factor A	Co-factor of IX with which it forms the tenase complex
IX = Anti Hemophilic Factor B or Christmas factor	Activates X: forms tenase complex with factor VIII
X = Stuart-Prower factor	Activates II: forms prothrombinase complex with factor V
XI = plasma thromboplastin antecedent	Activates IX
XII = Hageman factor	Activates factor XI and prekallikrein
XIII = fibrin-stabilizing factor	Crosslinks fibrin

Table of other factors involved with hemostasis

prekallikrein	Activates XII and prekallikrein; cleaves HMWK
high-molecular-weight kininogen	Supports reciprocal activation of XII, XI, and prekallikrein
fibronectin	Mediates cell adhesion
antithrombin III	Inhibits IIa, Xa, and other proteases;
heparin cofactor II	Inhibits IIa, cofactor for heparin and dermatan sulfate
protein C	Inactivates Va and VIIIa
protein S	Cofactor for activated protein C
protein Z	Mediates thrombin adhesion to phospholipids and stimulates degradation of factor X by ZPI
Protein Z-related protease inhibitor	Degrades factors X (in presence of protein Z) and XI
plasminogen	Converts to plasmin, lyses fibrin and other proteins
alpha 2-antiplasmin	Inhibits plasmin
tissue plasminogen activator (tPA)	Activates plasminogen
urokinase	Activates plasminogen
plasminogen activator inhibitor-1	Inactivates tPA & urokinase (endothelial PAI)
plasminogen activator inhibitor-2	Inactivates tPA & urokinase (placental PAI)
cancer procoagulant	Pathological factor X activator linked to thrombosis in cancer

Summary

- Blood as a transport, regulative, hydraulic and protective medium
- Production of RBCs involves a recycling aspect (Fe conservation)
- Hemostasis involves
  - Vascular spasm
  - Platelet plug formation
  - Coagulation
  - Functionally a postive feedback system