

INTRODUCTION

Concept

A. Tissue

1. Connective
2. Exceptional
 - a. Only liquid tissue
 - b. No intercellular fibers
3. Part of cardiovascular system

B. Body Fluid

1. Intracellular fluid (ICF) -- 2/3 of total
2. Extracellular fluids (ECF) -- 1/3 of total
 - a. Blood
 - 1/4 of ECF
 - 8% of total body fluids
 - b. Tissue (interstitial) fluid -- most of remaining 3/4
 - c. Minor (in volume) miscellaneous fluids
 - Cerebrospinal fluid
 - Intraocular fluid
 - Serous fluids -- cardiac, pleural & peritoneal

Functions

A. Transport

1. Nutrients -- organic -- e.g. sugars, amino acids, fats
2. Inorganic metabolites -- e.g. Na, Cl, H, K, Ca, OH, HCO₃, PO₄
3. Gases -- O₂ & CO₂
4. Water
5. Hormones & enzymes
6. Antibodies -- immune-related
7. Metabolic wastes -- to be excreted
8. Blood cells

B. Fluid Environment

1. Overall
 - a. Maintains all body fluid homeostatic levels
 - b. Via transport through entire body
 - c. Intimately coordinated with tissue fluid
2. Specific contexts
 - a. ph balance -- circulates H⁺ & related ions
 - b. Osmotic balance -- circulates water & Na
 - c. Electrolyte balance -- circulates all remaining ions

C. Body Temperature

1. Absorbs radiated heat from cellular respiration
2. Evenly distributes heat

3. Essential heat retained -- excess eliminated

D. Immunity

1. Microbial protection
2. Protection against other foreign material

Components

A. Formed Elements *[details later]*

1. Concept
 - a. Actually the various types of blood cells
 - b. " Element "
 - From debated status of platelets
 - Not always considered to be cells
2. Types
 - a. Erythrocytes -- red blood cells (RBC)
 - b. Leukocytes
 - White blood cells (WBC)
 - 5 distinct types
 - c. Thrombocytes -- platelets

B. Plasma

1. Concept
 - a. Liquid portion
 - b. 55% of blood volume

c. Suspends & carries formed elements

2. Water

a. About 91% of plasma volume

b. Functions

- Dispersion medium for other substances
- Blood pressure maintenance
- Heat absorption

3. Proteins

a. General

- 7% of plasma volume
- More than 100 different types
- Most conjugated -- glyco- or lipoprotein
- Most synthesized by liver

b. Albumins

- 54% of proteins
- Create proper viscosity -- main role
- Contribute to colloid osmotic pressure
- Carriers for other substances -- e.g. hormones

c. Globulins

- 40% of proteins
- Same functions as albumins -- alpha & beta
- Immune functions -- gamma globulins

- Help determine blood type -- gamma
- d. Others
 - General
 - Serum -- plasma minus these proteins
 - Both involved in coagulation
 - Fibrinogen -- 5% of proteins
 - Prothrombin -- 1% of proteins
- 4. Miscellaneous other substances
 - a. Remaining 2% of plasma volume
 - b. Organic nutrients -- e.g. glucose, cholesterol
 - c. Vitamins
 - d. Hormones
 - e. Enzymes
 - f. Electrolytes -- e.g. Na, Mg, K
 - g. Minerals -- e.g. Zn, Fe, silica
 - h. Wastes -- organic & inorganic

ERYTHROCYTES

General

- A. Features *[contrast with leukocytes]*
 - 1. Give blood red color
 - 2. Hemoglobin carrier -- most important function

3. Enucleated when mature
 - a. Unique in body
 - b. More space for hemoglobin
4. Perform completely within circulation

B. Numbers

1. Total -- $25-30 \times 10^{12}$
2. 4.5-5.5 million / mm^3 -- lower in women
3. Hematocrit
 - a. Packed volume
 - b. 47% men / 42% women

C. Appearance

1. Size -- 8 μm diameter
2. Shape
 - a. Biconcave disc
 - b. From nuclear loss
3. Flexible -- must squeeze through 7 μm capillaries

Hemoglobin

A. Location

1. Within RBC cytoplasm
2. Confined for 2 reasons

- a. Small enough molecule to escape from blood
- b. Protected from destruction

B. Amount

1. 90% of RBC volume
2. 200-300 million molecules / RBC
3. Clinical measure
 - a. 14-16 g / dl for men
 - b. 12-14 g / dl for women

C. Structure

1. Conjugated protein
2. Protein component
 - a. Globin
 - b. Polypeptide -- about 143 amino acid residues
 - c. 4 polypeptide subunits per molecule
 - d. Variant forms -- occur within same molecule
3. Prosthetic component
 - a. Heme
 - b. Amino acid derivative
 - c. Iron held at center
 - d. 4 hemes per molecule -- 1 for each globin subunit
4. Function
 - a. Heme

- Oxygen transport
- O₂ bonds with Fe
- *[details later -- respiratory system]*

b. Globin

- Stabilizes molecule
- Aids reversibility of O₂ - heme reaction

D. Formation

1. Synthesized within RBC's
2. During erythropoiesis

Erythropoiesis

A. Introduction

1. Concept -- erythrocyte production
2. Locations
 - a. Before 5 years old
 - Red bone marrow -- within all bones
 - Liver
 - Spleen
 - Lymph nodes
 - b. After 5 years old
 - Red bone marrow only
 - Not all bones now contain red marrow

B. The process [condensed version]

1. Stem (myeloid or hematopoietic) cells
 - a. Differentiated mesenchymal cells
 - b. Always present -- perpetuated by mitotic division
2. Erythroblasts
 - a. Differentiated stem cells
 - b. Several different types -- each leads to next
 - c. Hemoglobin synthesis during this stage
 - d. Nucleus shrinks & ejected from cell
3. Reticulocyte
 - a. Reticulated dark staining material
 - b. Remnants of various organelles
 - c. Released into general circulation in this stage
4. Mature erythrocyte -- several days later

C. Essential Nutrients

1. Fe
 - a. 50% within hemoglobin
 - b. Remainder stored extensively in body
 - c. Some loss daily -- 1-2 mg (men-women)
2. Vitamin B₁₂ -- essential for DNA synthesis during mitosis
3. Folic acid -- essential for DNA synthesis

D. Lifespan

1. Approximately 120 days -- because enucleated

2. Destruction
 - a. Liver & spleen
 - b. Phagocytes
 - c. Iron reused
 - d. Remaining heme
 - Converted to bilirubin
 - Excreted in bile
 - e. Globin -- back to general amino acid pool
3. Turnover rate -- about 1% destroyed / day

E. Regulation

1. PO_2 of blood gauge for determining rate
2. Erythropoietin (erythropoiesis-stimulating hormone)
 - a. Blood hormone -- glycoprotein
 - b. Secreted in inverse proportion to O_2 level
 - c. Stimulates stem cells to become Erythroblasts
 - d. Sources
 - Kidneys mostly
 - Liver
 - Possibly other regulators of kidneys & liver

Abnormalities

- A. Polycythemia

1. Elevated RBC count from increased erythropoiesis
2. Normal cause
 - a. High altitude
 - b. Response to low PO_2
3. Pathological cause
 - a. Any condition which lowers PO_2
 - b. e.g. emphysema, asthma, cardiac failure

B. Anemia

1. Lowered RBC count
 - a. Always abnormal
 - b. Not always life-threatening -- if moderate
 - c. 2 possible reasons
 - Too few RBC's with normal Hemoglobin (Hb)
 - Normal RBC number with defective Hb
2. Hemorrhage -- plasma replaced relatively quickly
3. Diminished erythropoiesis -- from PO_2 elevation
4. Low level of exercise -- from diminished need for O_2
5. Hemolysis
 - a. Concept
 - Splitting (lysis) of RBC membranes
 - From weakened membranes
 - b. Causes -- various types

- Aplastic -- from bone marrow destruction
- Pernicious -- inadequate vitamin B₁₂
- Sickle cell -- defective Hb & weakened RBC's

LEUKOCYTES

General

A. Features

1. Colorless & clear if isolated & concentrated
2. Various immune-related functions
3. Most phagocytic & mobile
4. Have nucleus
5. Most function out of circulation in tissue fluid
6. 5 distinct types

B. Numbers

5,000 - 10,000 / mm³

C. Movements

1. Amoeboid
 - a. Autonomous movement
 - b. Used for phagocytosis & diapedesis
 - c. Not all 5 types -- neutrophils & monocytes best
2. Diapedesis

- a. Enter & leave circulation
 - b. Squeeze between lining cells of capillaries
3. Chemotaxis
- a. Follow chemical trail to site of injury
 - b. Attractant chemical from injured cells

Types & Functions

A. General

1. Only generalized types to be presented
2. Variants exist
 - a. Structural & functional
 - b. Some covered later -- e.g. under immunity
 - c. *[structural details in lab]*

B. Granulocytes

1. Concept
 - a. Cytoplasmic granules
 - b. Characteristic for each type
 - c. Different size, number &/or color
2. Neutrophils (polymorphonucleocytes)
 - a. 60 - 65% of all WBC's -- most numerous
 - b. Medium-large
 - c. One of 2 principal phagocytes
 - Mainly bacteria

- Usually die from toxicity of effort

3. Eosinophils (acidophils)

- 2 - 4 % of all WBC's
- Large
- Phagocytic -- parasites
- Detoxify substances from other WBC's

4. Basophils (Mast Cells -- ?)

- 0.5 - 1 % of all WBC's -- least numerous
- Medium
- Mast cell

- Very similar to basophil
- Probably different cell type -- same function
- Not in blood -- in various connective tissues
- d. Not phagocytic -- release several substances
 - Histamine -- inflammatory responses
 - Heparin -- anticoagulant
 - Serotonin & bradykinin -- vasodilators

C. Agranulocytes

1. Concept

No regular (size & shape) cytoplasmic granules

2. Lymphocytes (plasma cells)

- 20 - 35 % of all WBC's
- Very small - medium

- c. Plasma cell
 - Derived from lymphocyte
 - Outside of circulation
- d. Central, controlling role in immunity
- e. Many specific sub-types [*details later*]

3. Monocytes (macrophages)

- a. 3 - 8% of all WBC's
- b. Large - very large
- c. Macrophage
 - Outside of circulation
 - Very large
- d. Most important phagocyte
 - Phagocytizes every category
 - Bacteria
 - Viruses
 - Parasites
 - Old RBC's
 - General debris
 - Hardy -- fairly long life span

Leukopoiesis

- A. Concept -- leukocyte formation

B. Locations

1. Red bone marrow
 - a. Chief site
 - b. All Granulocytes & monocytes
2. Lymphoid tissues
 - a. Lymph nodes, spleen, tonsils, thymus, nodules
 - b. Lymphocytes only

B. The Process

1. Basically same as erythropoiesis
 - a. Stem (myeloid) cells
 - Differentiate into several distinct groups
 - Generally termed colony forming units (CFU's)
 - Further differentiation within each CFU
 - Produce precursors (progenitors)
 - [details -- b-e below]
 - b. Proerythroblast
 - Precursor for RBC
 - Stage before erythroblast
 - c. Myeloblast
 - Precursor of all Granulocytes
 - Separate directions for the 3 types
 - d. Monoblast -- monocyte precursor
 - e. Lymphoblast

- Lymphocyte precursor
- Different stem cell sub-family from others

C. Life span

1. Great variation
 - a. Longer lived types -- mono- / lymphocytes
 - b. Hazards of phagocytic activity
2. From minutes to many years

D. Regulation

1. No one determining factor, due to varied functions
2. Factor sources
 - a. Damaged tissues
 - b. Some leukocytes -- macrophages & lymphocytes
3. Factors
 - a. Interleukin-1 -- general leukopoietic role
 - b. Tumor necrosis factor (TNF) -- general role
 - c. Specific colony stimulating factors (CSF's)
 - GM-CSF -- for Granulocytes & monocytes
 - G-CSF -- for Granulocytes only
 - M-CSF -- for monocytes
 - d. Others -- e.g. other interleukins

Abnormalities

A. Leukocytosis

1. Elevated WBC count -- above 10,000 / mm³
2. Inflammation & allergic reactions
 - a. 35,000 - 100,000 / mm³
 - b. From increased leukopoiesis
 - c. Normal (?) -- part of immune response
3. Leukemia
 - a. 250,000 + / mm³
 - b. Due to abnormal production of WBC's
 - c. Many immature & incompletely formed cells
 - d. Symptoms & death from various causes
 - Severe anemia
 - Coagulation problems
 - Immune suppression
 - Nutritional diversion of metabolic resources
 - e. Lymphogenic
 - Originates in lymphoid tissues
 - Spreads to non-lymphoid tissues
 - f. Myelogenic
 - Begins in bone marrow
 - Spreads widely
 - g. Chronic leukemias
 - Longer duration -- years

- Some differentiation to nearly normal types

h. Acute leukemias

- Rapidly severe -- months to death
- Mostly abnormal, non-functional cells

B. Leucopenia (Agranulocytosis)

1. WBC count below $5,000 / \text{mm}^3$
 - a. Low / no leukopoiesis
 - b. Too rapid turnover of mature WBC's
2. Nutritional deficiencies -- similar to anemia
3. Marrow damage from drugs or radiation
4. Acute stage of some infections -- e.g. influenza

THROMBOCYTES (PLATELETS)

General

A. Features

1. Very small -- $2-4 \mu\text{m}$ diameter
2. Not cellular -- just irregular-shaped fragments

B. Numbers

$150,000 - 300,000 / \text{mm}^3$

C. Functions

Various aspects of hemostasis -- prevention of bleeding

- a. Plug holes in damaged vessels
- b. Release chemicals to initiate clotting process

[details later]

Thrombopoiesis

A. Introduction

1. Concept -- platelet production
2. Location -- red bone marrow

B. The Process

1. Stem cells
 - a. Same ones which lead to RBC & WBC
 - b. Differentiation sequence already described
 - c. Specific CFU type
2. Precursor (progenitor) -- megakaryoblast
3. Last stage
 - a. Megakaryocyte
 - b. Platelets split off from this parent cell

C. Life Span

1. Approximately 10 days, maximum
2. Phagocytized by spleen

Abnormalities

A. Thrombocythemia (Thrombocytosis)

1. Count 750,000 - 1,000,000 / mm³
2. Spontaneous proliferation of megakaryoblasts
 - a. Can occur after 50 years of age
 - b. Normal, except combined with other disorders
3. Secondary reaction to various diseases / disorders
 - a. Acute infections
 - b. Hemorrhage
 - c. Hemolysis

B. Thrombocytopenia

1. Count below 50,000 / mm³
2. Causes
 - a. Low thrombopoiesis
 - b. Excessive destruction by spleen
 - c. Over utilization
 - d. Dysfunctional platelets
3. Symptoms
 - a. Spontaneous hemorrhaging from small vessels
 - b. Increased bleeding time

HEMOSTASIS

Introduction

- A. Concept -- cessation of bleeding
- B. Causes
 - 1. Vascular spasm
 - a. Wall of blood vessel cut
 - b. Smooth muscle contracts forcefully
 - c. Can stop / severely limit bleeding
 - d. Lasts at least 30 min.
 - 2. Platelet plug
 - a. Injured vessel wall becomes sticky
 - b. Lining cells help block opening
 - c. Platelets stick to wall
 - d. Platelets release thromboxane A_2
 - Other platelets attracted -- plug formed
 - Helps promote vasoconstriction
 - 3. Clot
 - a. Needed if vessel spasm & platelet plug inadequate
 - b. *[details below]*

Coagulation (Clotting)

A. General

1. Physical cause
 - a. Interwoven threads -- fibrin
 - b. Platelets & cells trapped -- more stable than plug
2. Primary chemical basis
 - a. Fibrin threads -- insoluble
 - b. Fibrinogen -- soluble precursor
 - c. Thrombin -- catalyzes fibrinogen → fibrin
 - d. Prothrombin -- inactive thrombin precursor
 - e. Prothrombin → thrombin

B. Details

1. Lack of consensus -- several major theories
2. Series of enzymatic protein conversions
3. 2 basic mechanisms
 - a. Intrinsic -- platelet / plasma interactions
 - b. Extrinsic -- other than platelet initiation
4. Steps
 - a. [only know general products formed & order]
 - b. [refer to handout in packet of diagrams]

C. Reasons for Complexity

1. Insures occurrence only when necessary
2. Elaborate / interrelated series of reactions

3. Lessens chance of intravascular clotting

Clinical Factors

A. Times

1. Bleeding time
 - a. Flow cessation -- 1-4 min.
 - b. Fragile -- only from platelet plug
2. Coagulation time
 - a. 4-6 min.
 - b. Increased in malnutrition or disease

B. Hemophilia

1. More than one type -- slow coagulation or none
2. Inherited defective factor -- VIII, IX, XI (rare)

C. Intravascular Clotting

1. Thrombus
 - a. Induced by foreign material
 - Dislodged lining epithelial cell
 - Air
 - b. Thrombosis -- condition of having thrombus
2. Embolus
 - a. Dislodged thrombus
 - b. Becomes trapped -- blocks smaller vessels

- c. Embolism -- condition of having embolus

Anticoagulants

A. Need

1. Safeguard against thrombosis & embolism
2. Clotting substances abundant
In 100 ml -- enough to clot all body's blood

B. Substances

1. Antithrombin
 - a. Globulin
 - b. Neutralizes thrombin
2. Heparin
 - a. Glycoprotein
 - b. Antithrombin cofactor -- enhances action
3. Endothelial membrane
 - a. Thrombomodulin -- binds thrombin
 - b. Activates protein-C
 - Plasma protein
 - Inactivates several factors
4. Fibrin
 - a. Thrombin adsorbed to threads
 - b. More important than other thrombin inactivators
5. Fibrinolysin -- enzymatically dissolves fibrin