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. Tissue (interstitial) fluid -- ¾ of ECF
    b. Blood –- ¼ of ECF
    c. Minor (in volume) miscellaneous fluids
        - Cerebrospinal fluid
        - Intraocular fluid
        - Serous fluids -- cardiac, pleural & peritoneal
        - Joint fluid (synovial)

Functions

A. Transport

1. Nutrients -- organic -- e.g. sugars, amino acids, fats

2. Inorganic metabolites -- e.g. Na, Cl, H, K, Ca, OH, HCO_3, PO_4
3. Gases -- O_2 & CO_2
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
- Enzymes –- very small percentage

4. Miscellaneous other substances
    a. Remaining 2% of plasma volume
    b. Organic nutrients -- e.g. glucose, cholesterol
    c. Vitamins
    d. Hormones (non-protein)
    e. Electrolytes -- e.g. Na, Mg, K
    f. Minerals -- e.g. Zn, Fe, silica
    g. 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 x 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
        - O_2 bonds with Fe
        - *[details later -- respiratory system]*

    b. Globin

        - Stabilizes molecule
        - Aids reversibility of O_2 - 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. Iron

a. 50% within hemoglobin

b. Remainder stored extensively in body

c. Some loss daily -- 1-2 mg (men-women)

2. Vitamin B_{12} -- essential for DNA synthesis during mitosis

3. Folic acid -- essential for DNA synthesis

4. Copper – essential for iron absorption

5. Cobalt – part of Vitamin B_{12} molecule

6. Niacin – coenzyme

7. Ascorbic acid (Vitamin C) – essential for iron absorption

8. Vitamin B_6 (pyridoxine) – coenzyme for amino acid metabolism

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. Usually 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 <u>need</u> 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 B_{12}
- 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 all their life
5. Most function out of circulation in tissue fluid
6. 5 distinct types

B. Numbers

5,000 - 10,000 / mm^3

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)
    a. 2 - 4 % of all WBC's
    b. Large
    c. Phagocytic -- parasites
    d. Detoxify substances from other WBC's

4. Basophils (Mast Cells -- ?)

    a. 0.5 - 1 % of all WBC's -- least numerous

    b. Medium

    c. 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)

    a. 20 - 35 % of all WBC's

    b. 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-d below]
    b. Myeloblast
        - Precursor of all Granulocytes
        - Separate directions for the 3 types
    c. Monoblast -- monocyte precursor
    d. 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 / mm^3

2. Inflammation & allergic reactions

a. 35,000 - 100,000 / mm^3

b. From increased leukopoiesis

c. Normal (?) -- part of immune response

3. Leukemias

a. 250,000 $^+$ / mm^3

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. Origin

- Lymphogenic
  - Originates in lymphoid tissues
  - Spreads to non-lymphoid tissues
- Myelogenic
  - Begins in bone marrow
  - Spreads widely

f. Severity

- Chronic
  - Longer duration -- years
  - Some differentiation to nearly normal types
- Acute leukemias
  - Rapidly severe -- months to death
  - Mostly abnormal, non-functional cells

B. Leucopenia (Agranulocytosis)

1. WBC count below 5,000 / 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 – aplastic "anemia"

4. Acute stage of some infections -- e.g. influenza

THROMBOCYTES (PLATELETS)

General

A. Features

1. Very small -- 2-4 μm diameter

2. Not cellular -- just irregular-shaped fragments

B. Numbers

150,000 - 300,000 / 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 / mm^3
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 / mm^3

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. Significance (Causes)

1. Injuries

2. Spontaneous

C. Steps

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 $\rightarrow$ 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. **[refer to handout in packet of diagrams]**
   b. Mostly know general products formed & order
   c. Know all details of reactions #3 and 4

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 – I (rare), V, VII, VIII, IX, X, XI, or XII
3. Liver disease and Vitamin K deficiency can produce insufficient factor II

C. Intravascular Clotting

1. Thrombus
   a. Induced by foreign material
      - Dislodged lining epithelial cell
      - Air or other foreign material
      - Very slow blood flow
   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. Plasmin (Fibrinolysin) -- enzymatically dissolves fibrin and fibrinogen