Blood and Circulatory System Disorders

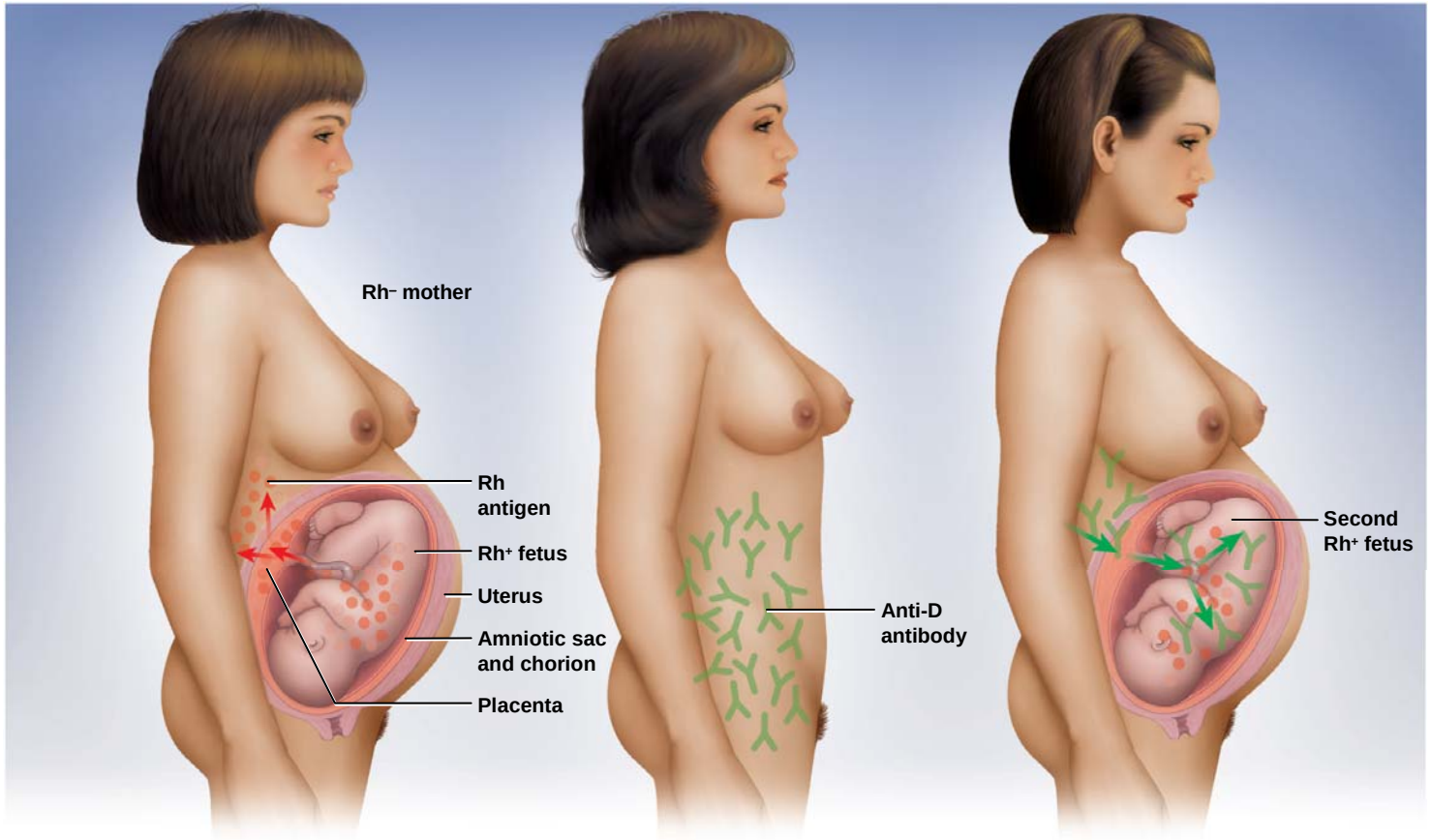
Hemolytic Disease of Newborn

- **Occurs when Rh^- woman is sensitized to form Rh-D antibodies then becomes pregnant with second fetus which is Rh+ // now her antibodies will cross placenta and attach fetal Rh- RBCs**
  - **this may happen because:**
    - **previously pregnant with Rh^+ fetus**
    - **received blood transfusion Rh+ RBC**
  - **now woman has anti-D in plasma**
    - **Anti-D antibodies can cross placenta**
    - **forms antigen-antibody complex in fetal blood / hemolyze fetal RBC**

Hemolytic Disease of Newborn

- **How to prevention**
  - **RhoGAM // given to pregnant Rh^- women before delivery**
  - **RhoGAM binds fetal agglutinogens // so Rh+ RBC can not sensitize or exposed mother to antigen (now masked by RhoGam) during delivery**
  - **Mother now will not make Anti-D antibodies**

Hemolytic Disease of Newborn



- **Rh antibodies attack fetal blood**

causing severe anemia and toxic brain syndrome // erythroblastosis fetalis

Diagnostic Tests

- Complete blood count (CBC)
  - Includes total red blood cells (RBCs), white blood cells (WBCs), and platelets
  - Leukocytosis (increased WBCs) // Associated with inflammation or infection
  - Leukopenia (decreased WBCs) // Associated with some viral infections, radiation, chemotherapy
  - Increased eosinophils // *Common in allergic responses & parasite infections*
- Differential count for WBCs

Diagnostic Tests (Cont.)

- Morphology // Observed with blood smears
  - Shows size, shape, uniformity, maturity of cells
  - Different types of anemia can be distinguished.
- Hematocrit // Percent by volume of cellular elements in blood *(benchmark 45% but variable)*
- Hemoglobin // Amount of hemoglobin per unit volume of blood
  - Mean corpuscular volume (MCV) // Indicates the oxygen-carrying capacity of blood

Diagnostic Tests (Cont.)

- Reticulocyte count // Assessment of bone marrow function
- Chemical analysis // Determines serum levels of components > such as iron, vitamin B_{12}, folic acid, cholesterol, urea, glucose
- Bleeding time // Measures platelet function
- Prothrombin time (PT) and partial thromboplastin time (PTT)
  - *Measure function of various factors in coagulation process*
  - International normalized ratio (INR) is a standardized version.

Blood Therapies

- Whole blood, packed red blood cells, packed platelets // For severe anemia or thrombocytopenia
- Plasma or colloid volume-expanding solutions // To maintain blood volume
- Artificial blood products // Compatible with all blood types // functions of normal whole blood. None of them can perform all the complex

Blood Therapies

- Epoetin alfa // Artificial form of erythropoietin
  - Before certain surgical procedures
  - Anemia related to cancer
  - Chronic renal failure
- Bone marrow or stem cell transplantation // *Close tissue match necessary*
  - Treatment of some cancers
  - Severe immunodeficiency
  - Severe blood cell diseases
- Drug treatment // Aids in the clotting process

Blood Dyscrasias

plasma cell dyscrasiasa = diverse group of neoplastic diseases

involving proliferation of a single clone of cells producing a serum M component (a monoclonal immunoglobulin or immunoglobulin fragment)

usually having a plasma cell morphology

Note: dyscrasias is an “old term” not often used today / formerly used to indicate an abnormal mixture of the four humors

The Anemias

- Anemia causes a reduction in oxygen transport.
- Basic problem is hemoglobin deficit
- Oxygen deficit leads to: // Less energy production in all cells // Cell metabolism and reproduction diminished
  - Compensation mechanisms // Tachycardia and peripheral vasoconstriction
  - General signs of anemia // Fatigue, pallor (pale face), dyspnea, tachycardia

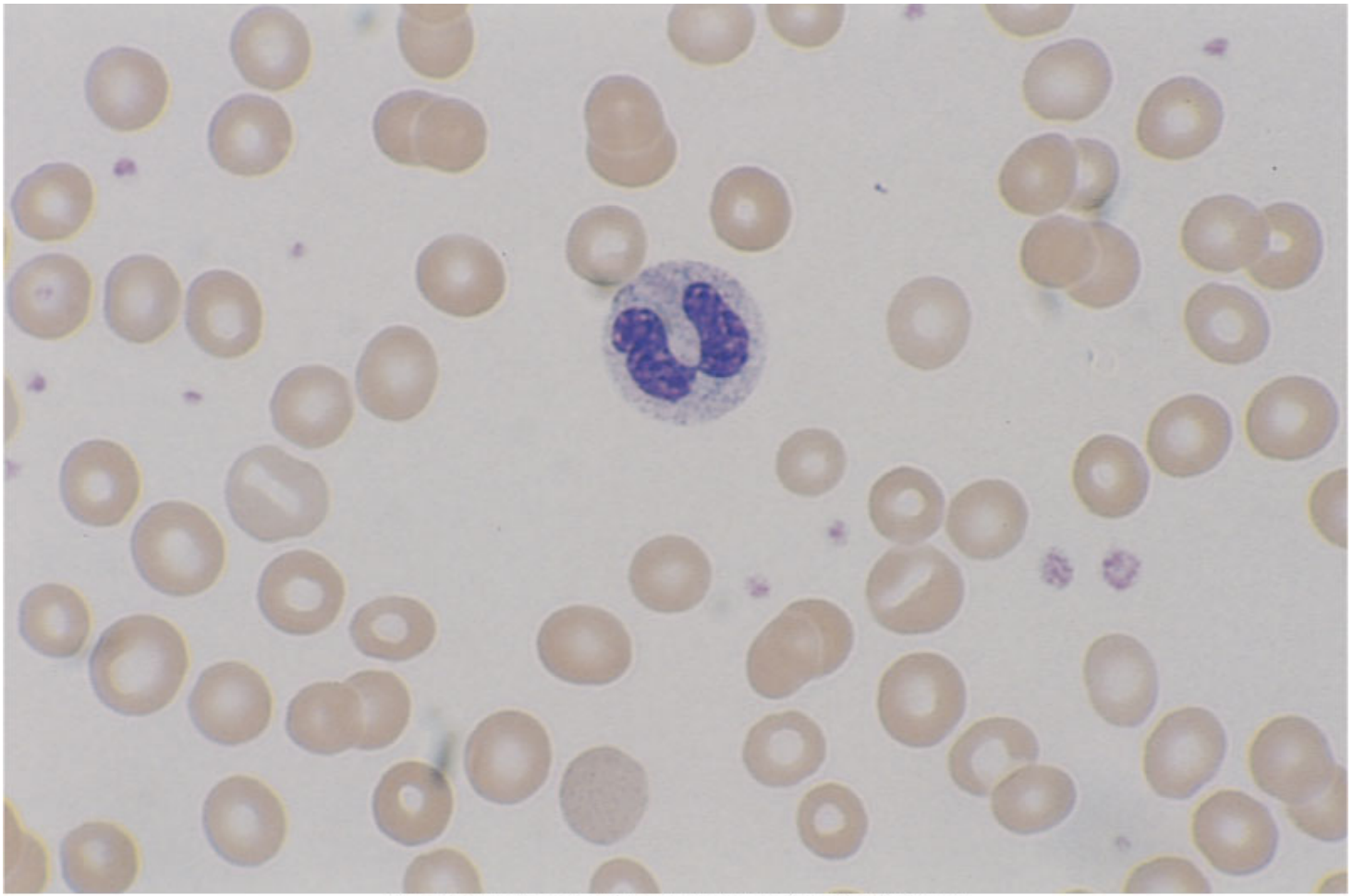
The Anemias

- Oxygen deficit leads to:
  - Decreased regeneration of epithelial cells
    - Digestive tract becomes inflamed and ulcerated, leading to stomatitis
    - Inflamed and cracked lips
    - Dysphasia
    - Hair and skin may show degenerative changes.
  - Severe anemia may lead to angina or congestive heart failure (CHF).

Iron Deficiency Anemia

- Insufficient iron impairs hemoglobin synthesis. // Microcytic, hypochromic RBCs
  - Result of low hemoglobin concentration in cells
- Very common
  - Ranges from mild to severe
  - Occurs in all age groups, but more common in women of childbearing age
  - Estimated that one in five women is affected // Proportion increases for pregnant women
- Frequently sign of an underlying problem

Iron Deficiency Anemia - Blood Smear



From Stevens ML: Fundamentals of Clinical Hematology, *Philadelphia, 1997, Saunders.*

Iron Deficiency Anemia: Causes

- Dietary intake of iron below minimum requirement
- Chronic blood loss // As from bleeding, ulcer, hemorrhoids, cancer
- Impaired duodenal absorption of iron // In many disorders, malabsorption syndromes
- Severe liver disease // May affect iron absorption as well as storage

Iron Deficiency Anemia: Signs and Symptoms

- Pallor of skin and mucous membranes
- Fatigue, lethargy, cold intolerance
- Irritability
- Degenerative changes
- Stomatitis and glossitis
- Menstrual irregularities
- Delayed healing
- Tachycardia, heart palpitations, dyspnea, syncope

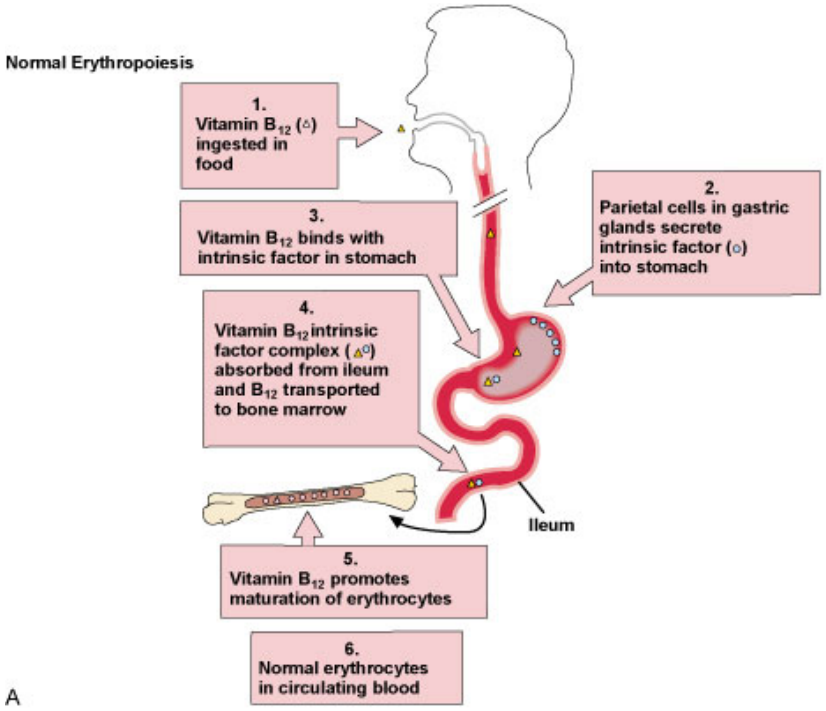
Pernicious Anemia Due to a Lack of Intrinsic Factor

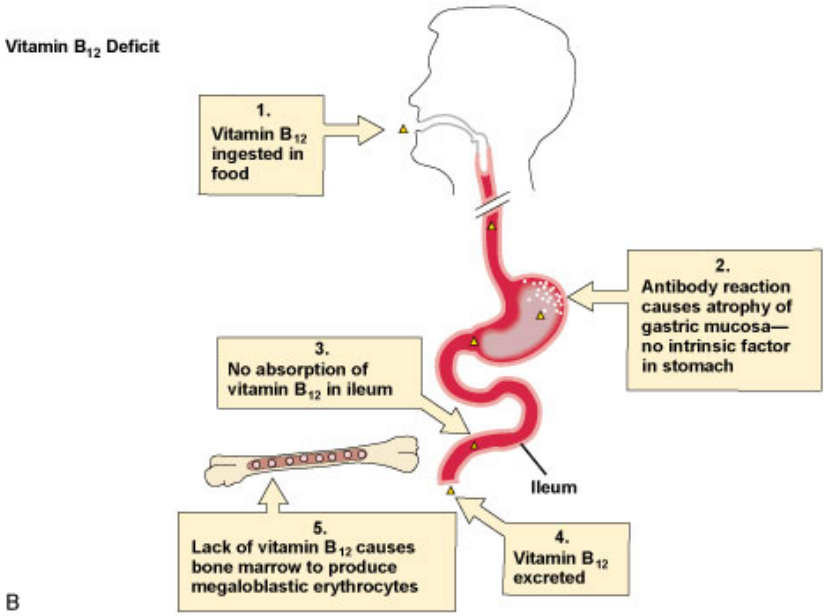
- Basic problem is lack of absorption of vitamin B_{12} because intrinsic factor is not available to transport B12 across gastric mucosa
  - Intrinsic factor secreted by gastric mucosa // parietal cells of gastric pit
  - Required for intestinal absorption of vitamin B_{12}
- Characterized by very large, immature, nucleated erythrocytes
  - Carry less hemoglobin
  - Shorter life span

Pernicious Anemia: Vitamin B_{12} Deficiency (Cont.)

- Dietary insufficiency is very rarely a cause.
- Genetic factors have been implicated.
  - More common in light-skinned women of northern European ancestry
- Often accompanies chronic gastritis
- May also be an outcome of gastric surgery

Development of Pernicious Anemia

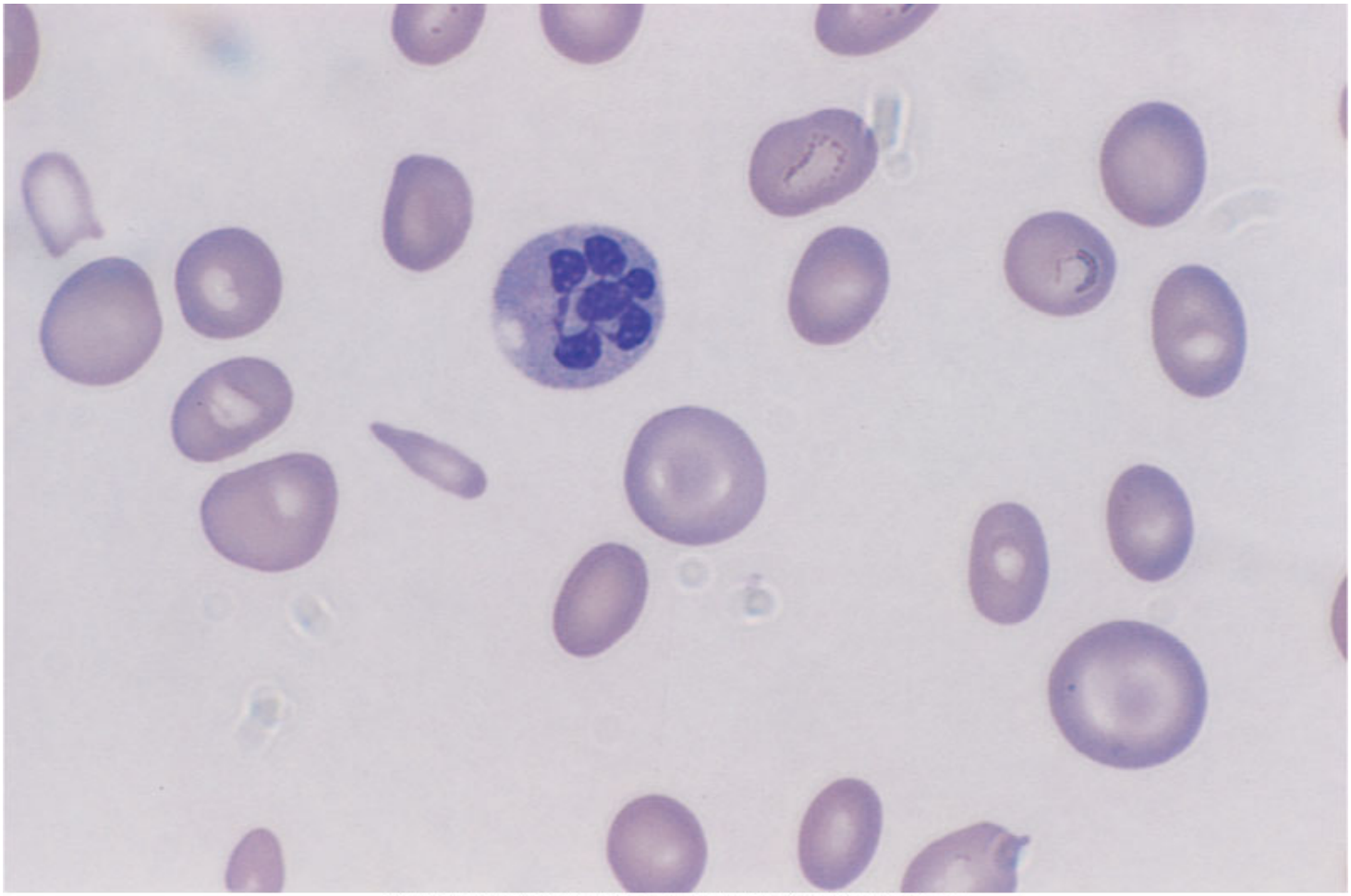




Vitamin B_{12} and Nerve Cells

- Vitamin B_{12} is needed for the function and maintenance of neurons.
- Significant deficit of the vitamin will cause symptoms in the peripheral nerves.
- These may be reversible.

Vitamin B_{12} Deficiency



From Stevens ML: Fundamentals of Clinical Hematology, *Philadelphia, 1997, Saunders.*

Pernicious Anemia: Vitamin B_{12} Deficiency (Cont.)

- Manifestations in addition to those typical for anemias
  - Tongue is typically enlarged, red, sore, and shiny.
  - Digestive discomfort, often with nausea and diarrhea
  - Feeling of pins and needles, tingling in limbs

Pernicious Anemia: Vitamin B_{12} Deficiency (Cont.)

- Diagnostic tests
  - Microscopic examination (erythrocytes)
  - Bone marrow examination (hyperactive)
  - Vitamin B_{12} serum levels below normal
  - Presence of hypochlorhydria or achlorhydria (low concentration of HCl – also produced by parietal cells) // Presence of gastric atrophy

Aplastic Anemia

- Impairment or failure of bone marrow
- May be temporary or permanent
- Often idiopathic but possible causes include:
  - Myelotoxins // Radiation, industrial chemicals, drugs
  - Viruses // Particularly hepatitis C
  - Genetic abnormalities // Myelodysplastic syndrome & Fanconi's anemia

Aplastic Anemia

- Blood counts indicate pancytopenia.
  - Anemia, leukopenia, thrombocytopenia
  - Bone marrow biopsy may be required.
  - Erythrocytes often appear normal.

Aplastic Anemia

- Identification of cause and prompt treatment needed for bone marrow recovery
  - Removal of any bone marrow suppressants
  - Failure to identify cause and treat effectively is **life-threatening**

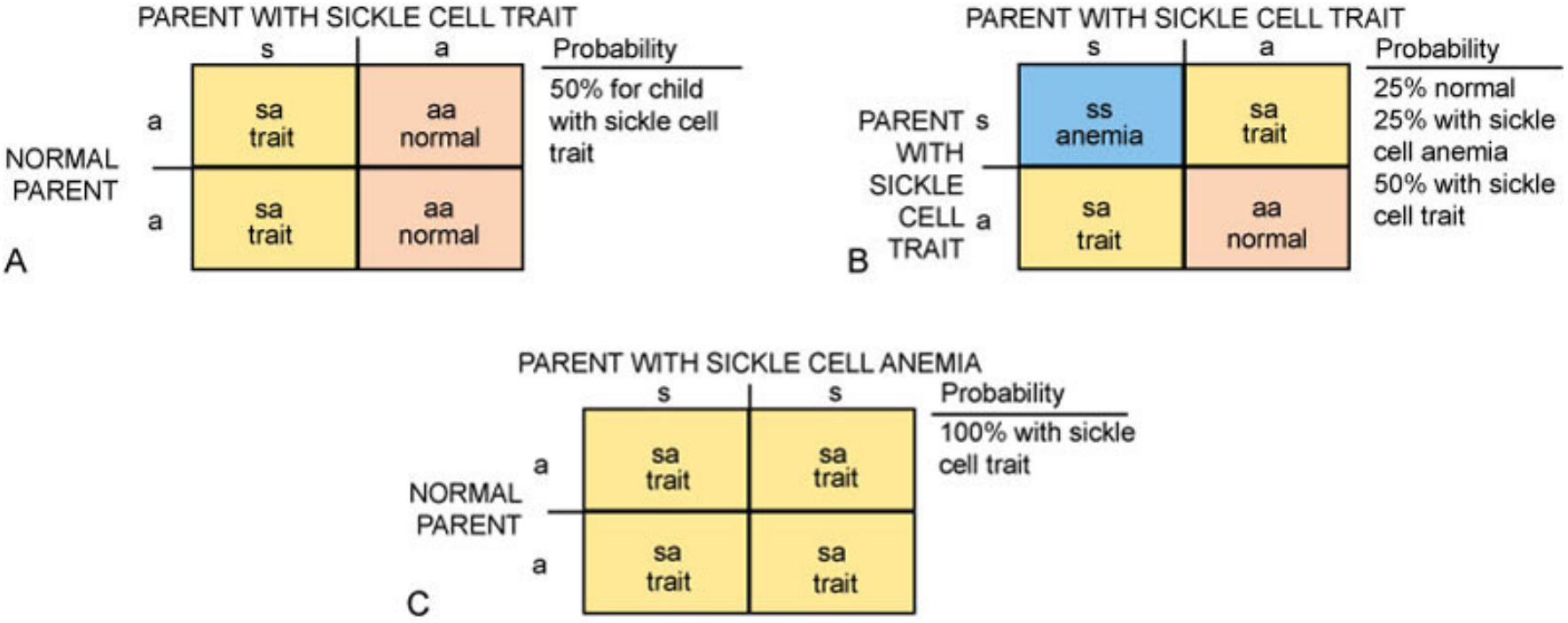
Hemolytic Anemia

- Results from excessive destruction of RBCs
- Causes
  - Genetic defects
  - Immune reactions
  - Changes in blood chemistry
  - Infections such as malaria
  - Toxins in the blood
  - Antigen-antibody reactions // Incompatible blood transfusion // Erythroblastosis fetalis

Sickle Cell Anemia

- Genetic condition
  - Autosomal
  - Incomplete dominance
  - Anemia occurs in homozygous recessive.
  - Diagnostic testing is available.
  - More common in individuals of Mediterranean
  - Including African ancestry // Heterozygous condition is somewhat protective against malaria.
  - One in ten African Americans is heterozygous for the trait.

Sickle Cell Anemia

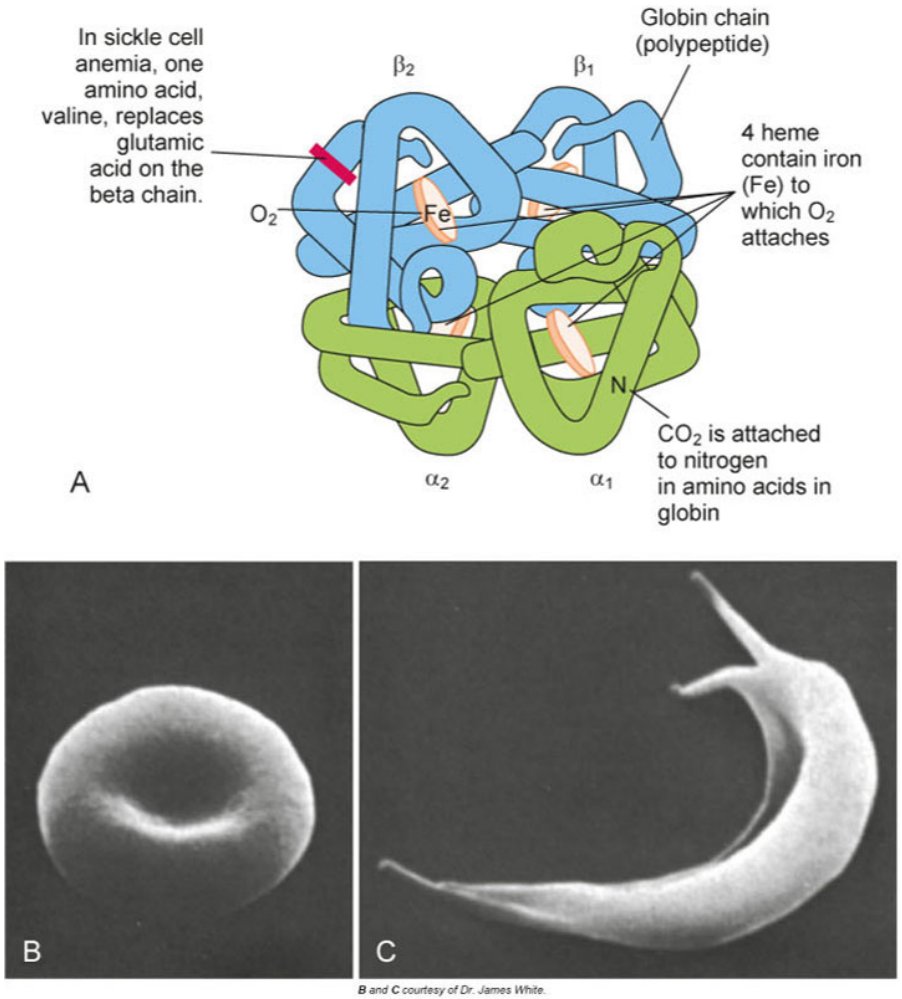


KEY
aa = normal: HbA
ss = sickle cell anemia: HbS
sa = sickle cell trait: mixed HbA and HbS

Sickle Cell Anemia

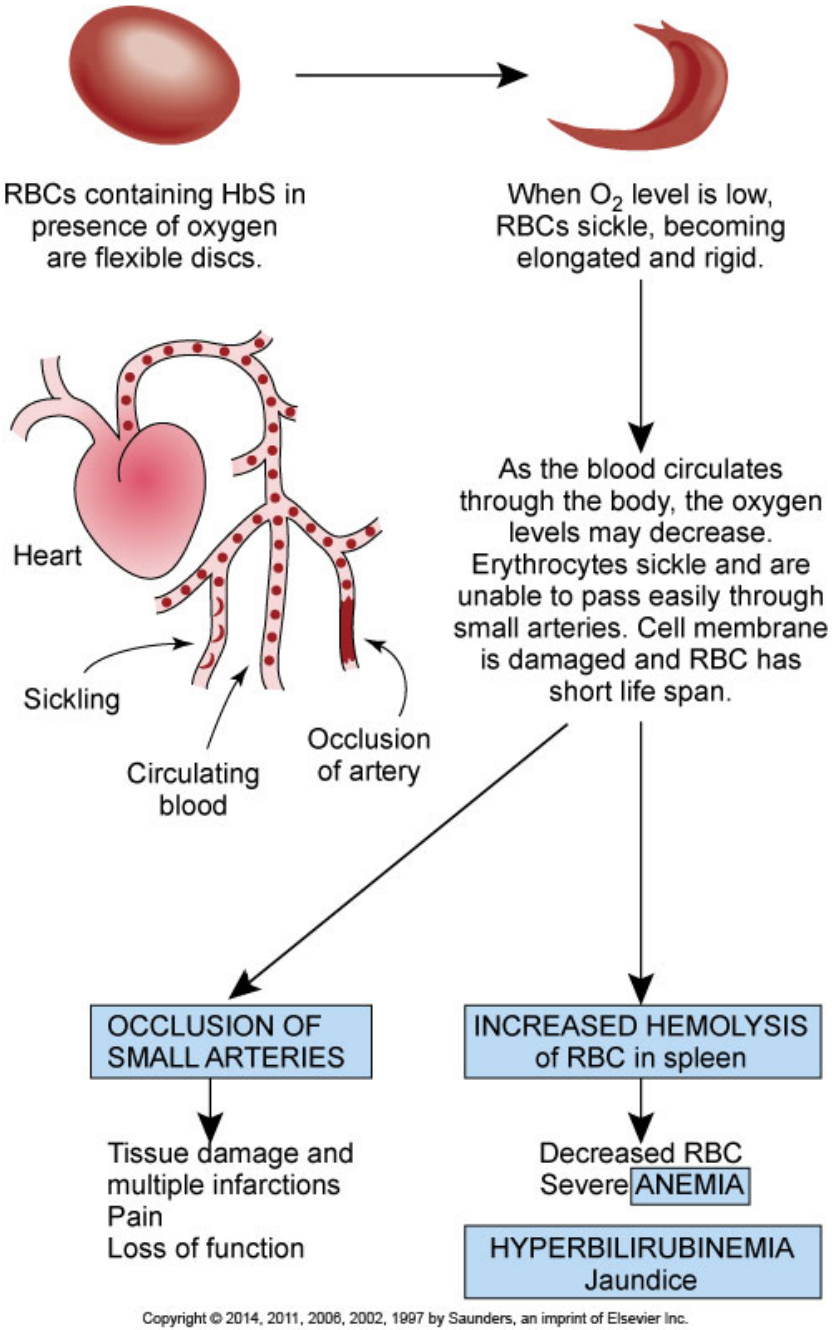
- Abnormal hemoglobin (HbS)
- Sickle cell crisis occurs whenever oxygen levels are lowered.
- Altered hemoglobin is unstable and changes shape in hypoxemia.
- Sickle-shaped cells are too large to pass through the microcirculation.
- Obstruction leads to multiple infarctions and areas of necrosis.

Sickle Cell Anemia



B and *C* courtesy of Dr. James White.

Sickle Cell Anemia



Sickle Cell Anemia

- Multiple infarctions affect brain, bones, organs
- In addition to basic anemia: // Hyperbilirubinemia, jaundice, gallstones // Caused by high rate of hemolysis
- Clinical signs // *Do not usually appear until the child is about 12 months old*

Sickle Cell Anemia: Signs and Symptoms

- Severe pain because of ischemia of tissues and infarction
- Pallor, weakness, tachycardia, dyspnea
- Hyperbilirubinemia—jaundice
- Splenomegaly
- Vascular occlusions and infarctions
  - In lungs // Acute chest syndrome
  - Smaller blood vessels // Hand-foot syndrome
- Delay of growth and development
- Congestive heart failure

Sickle Cell Anemia

- Diagnostic tests
  - Blood test // Hemoglobin electrophoresis
  - Prenatal DNA analysis
- Treatment
  - Hydroxyurea has reduced the frequency of this crisis.
  - Dietary supplementation with folic acid
  - Bone marrow transplantation
  - Immunization in children // Against pneumonia, influenza, meningitis

Comparison of Selected Anemias

TABLE 10-2 Comparison of Selected Anemias

Anemia	Characteristic RBC	Etiology	Additional Effects
Iron deficiency anemia	Microcytic, hypochromic Decreased hemoglobin production	Decreased dietary intake, malabsorption, blood loss	Only effects of anemia
Pernicious anemia	Megaloblasts (immature nucleated cells) Short lifespan	Deficit of intrinsic factor owing to immune reaction	Neurologic damage Achlorhydria
Aplastic anemia	Often normal cells Pancytopenia	Bone marrow damage or failure	Excessive bleeding and multiple infections
Sickle cell anemia	RBC elongates and hardens in "sickle" shape when O_2 levels are low—short lifespan	Recessive inheritance	Painful crises with multiple infarctions Hyperbilirubinemia

Polycythemia

- Primary polycythemia also referred to as polycythemia vera
  - Increased production of erythrocytes and other cells in the bone marrow
  - Neoplastic disorder (cancer)
  - Serum erythropoietin levels are low.

Polycythemia

- Secondary polycythemia – erythrocytosis caused by anything other than cancer
  - Increase in RBCs in response to prolonged hypoxia
  - Increased erythropoietin secretion
  - Compensation mechanism to provide increased oxygen transport
- Note: anything that increases hematocrit increases blood viscosity // makes heart work harder to pump blood // leads to heart failure

Polycythemia: Signs and Symptoms

- Distended blood vessels, sluggish blood flow
- Increased blood pressure
- Hypertrophied heart
- Hepatomegaly
- Splenomegaly
- Dyspnea
- Headaches
- Visual disturbances
- Thromboses and infarctions

Polycythemia

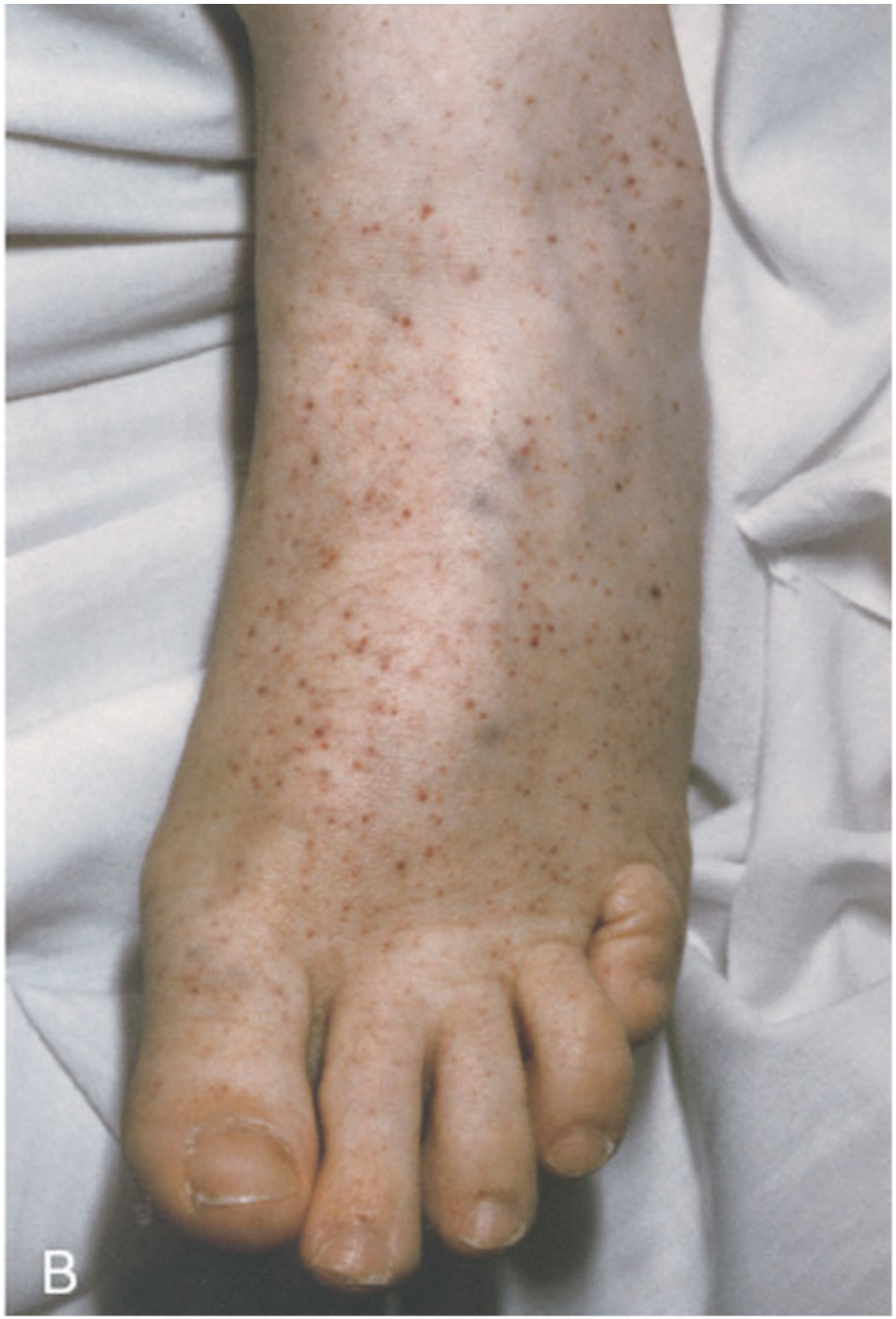
- Diagnostic tests
  - Increased cell counts
  - Increased hemoglobin and hematocrit values
  - Hypercellular bone marrow
  - Hyperuricemia
- Treatment
  - Identify cause
  - Drugs or radiation // Suppression of bone marrow activity
  - Periodic phlebotomy

Indications of Blood-Clotting Disorders

- Persistent bleeding from gums
- Repeated epistaxis
- Petechiae // Pinpoint, flat, red spots on skin and mucous membrane
- Frequent purpura and ecchymosis
- More than normal bleeding in trauma
- Bleeding into joint—hemarthroses // Swollen, red, painful
- Hemoptysis

Blood-Clotting Disorders

- Hematemesis // Coarse brown particles (coffee ground emesis)
- Blood in feces // Black or occult
- Anemia
- Feeling faint and anxious
- Low blood pressure
- Rapid pulse



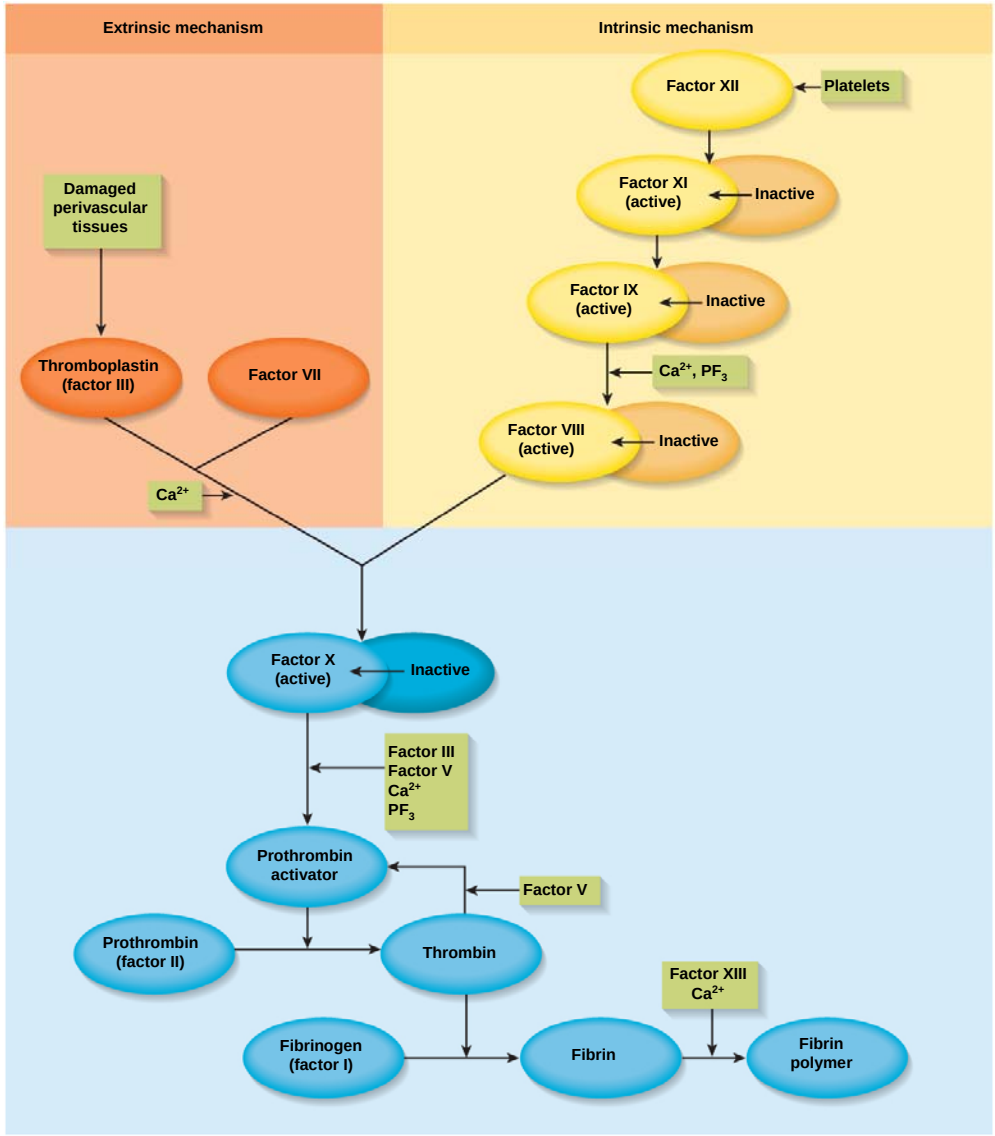
From Young NS: *Bone Marrow Failure Syndromes*, Philadelphia, 2000, Saunders.

Petechiae

Hemophilia A

- Classic hemophilia // Deficit or abnormality of clotting factor VIII
- Most common inherited clotting disorder
  - X-linked recessive trait // Manifested in men, carried by women
- Varying degrees of severity
- Prolonged bleeding after minor tissue trauma
- Spontaneous bleeding into joints
- Possible hematuria or blood in feces

Coagulation Pathways



Hemophilia A (Cont.)

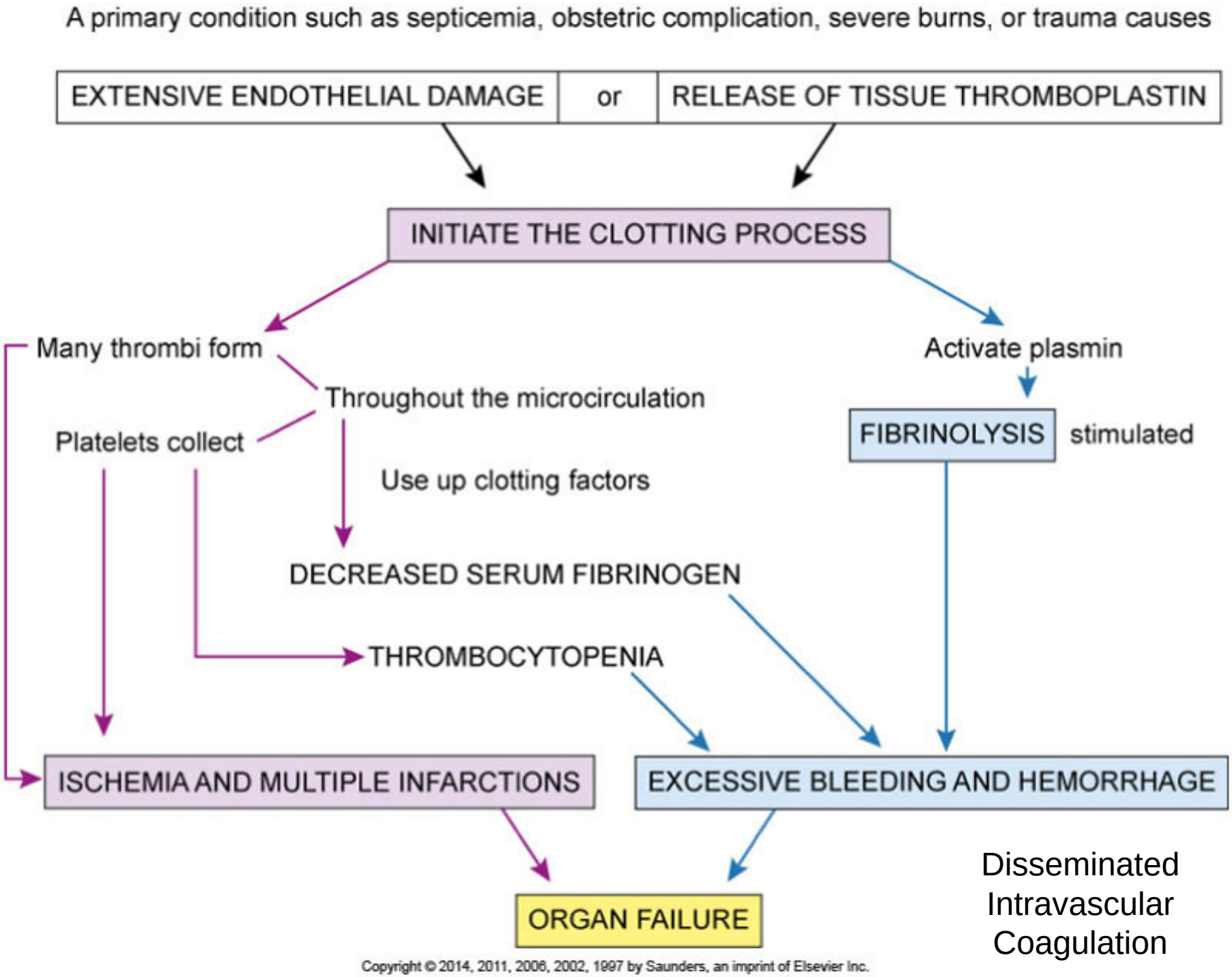
- Diagnostic tests
  - Bleeding time and PT normal
  - PTT, activated PTT (aPTT), coagulation time prolonged
  - Serum levels of factor VIII are low.
- Treatment
  - Desmopressin (DDAVP)
  - Replacement therapy for factor VIII

Von Willebrand's Disease

- Most common hereditary clotting disorder
- Three major types
- Signs and symptoms include:
  - Skin rashes
  - Frequent nosebleeds
  - Easy bruising
  - Bleeding of gums
  - Abnormal menstrual bleeding
- Treatment based on type and severity

Disseminated Intravascular Coagulation

- Involves both excessive bleeding and clotting
- Excessive clotting in circulation // Thrombi and infarcts occur.
- *Clotting factors are reduced to a dangerous level*.
- Widespread, uncontrollable hemorrhage results.
- Very poor prognosis, with high fatality rate
- Complication of many primary problems
  - Obstetrical complications, such as abruptio placentae
  - Infections
  - Carcinomas
  - Major trauma



Disseminated Intravascular Coagulation

Thrombophilia

- A disorder of the hemopoietic system in which there is an increased tendency for thrombosis.
- Group of inherited or acquired disorders
- Risk of abnormal clots in veins or arteries
- Blood testing for clotting factor levels and abnormal antibody levels
- Causative condition should be treated.

Myelodysplastic Syndromes

- Diseases that involve inadequate production of cells by the bone marrow
- Signs and symptoms include anemia; dependent on type of deficiencies that occur
- May be idiopathic or occur after chemotherapy or radiation treatment
- Treatment measures depend on deficiency type.
  - Transfusion replacement
  - Chelation therapy to reduce iron overload
  - Bone marrow transplantation

The Leukemias

- Group of neoplastic disorders involving white blood cells
- Uncontrolled WBC production in bone or lymph nodes
- Other hemopoietic tissues are reduced.
- One or more types of leukocytes are undifferentiated, immature, and nonfunctional.
- Large numbers released into general circulation
- Infiltrate lymph nodes, spleen, liver, brain, other organs

TABLE 10-3 Types of Leukemias

Type	Malignant Cell	Primary Age Group
Acute lymphocytic leukemia (ALL)	B-lymphocytes	Young children
Acute myelogenous (or myelocytic) leukemia (AML)	Granulocytic stem cells	Adults
Chronic lymphocytic leukemia	B-lymphocytes	Adults greater than 50 years
Chronic myelogenous leukemia (CML)	Granulocytic stem cells	Adults 30-50
Acute monocytic leukemia	Monocytes	Adults
Hairy cell leukemia	B-lymphocytes	Males greater than 50 years

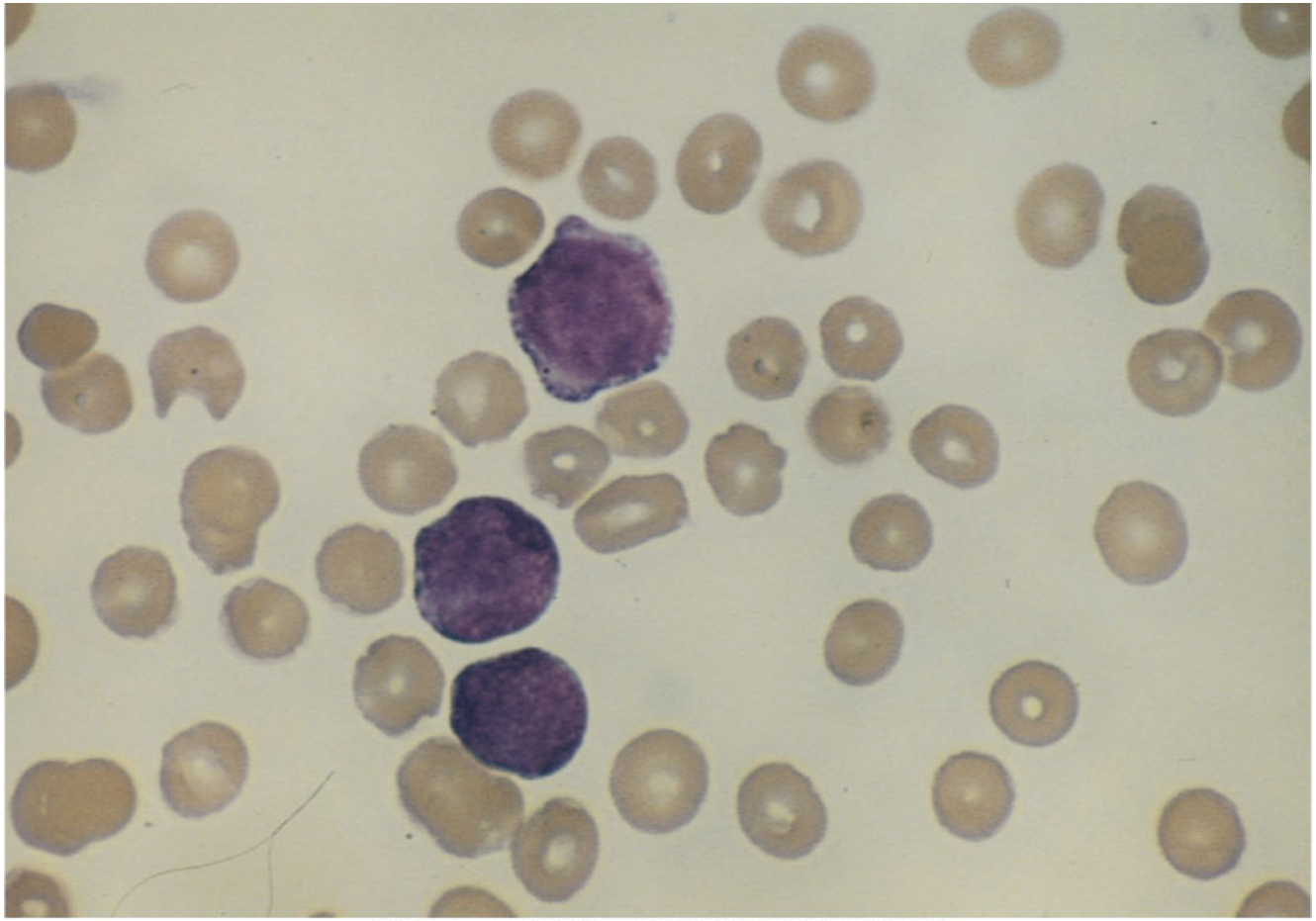
The Leukemias

- Acute leukemias (ALL and AML)
  - High proportion of immature nonfunctional cells in bone marrow and peripheral circulation
  - Onset usually abrupt , marked signs of complications
    - Occurs primarily in children and younger adults

The Leukemias

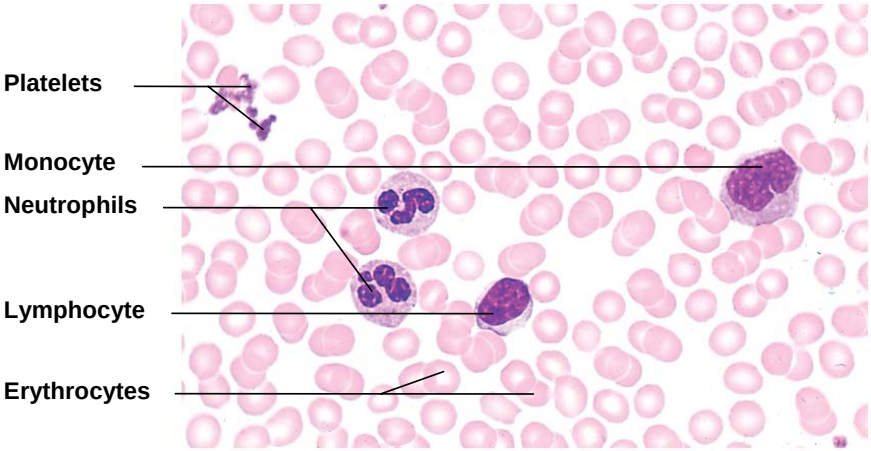
- Chronic leukemias (CLL and CML)
  - Higher proportion of mature cells
  - Insidious onset
  - Mild signs and better prognosis
    - Common in older adults

Acute Lymphocytic Leukemia



From Stevens ML: Fundamentals of Clinical Hematology, *Philadelphia, 1997, Saunders.*

Normal and Leukemic Blood



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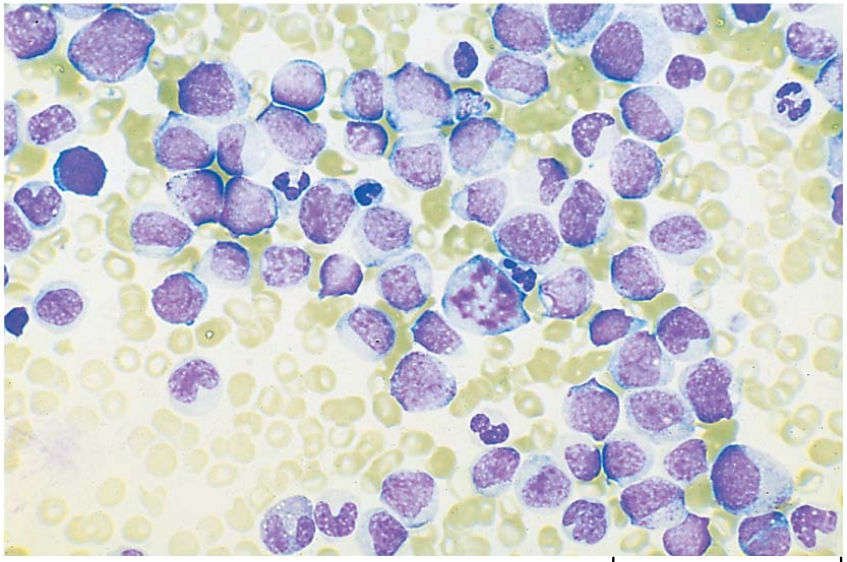


(b)

Signs and Symptoms of Acute Leukemia

- Usual signs at onset
  - Frequent or uncontrolled infections
  - Petechiae and purpura
  - Signs of anemia
- Severe and steady bone pain
- Weight loss, fatigue, possible fever
- Enlarged lymph nodes, spleen, liver
- Headache, visual disturbances, drowsiness, vomiting

The Leukemias

- Diagnostic tests
  - Peripheral blood smears
    - Immature leukocytes and altered numbers of WBCs
    - Numbers of RBCs and platelets decreased
    - Bone marrow biopsy for confirmation
- Treatment
  - Chemotherapy
  - ALL in young children responds well to drugs
  - Biological therapy (interferon) // May be used to stimulate the immune system

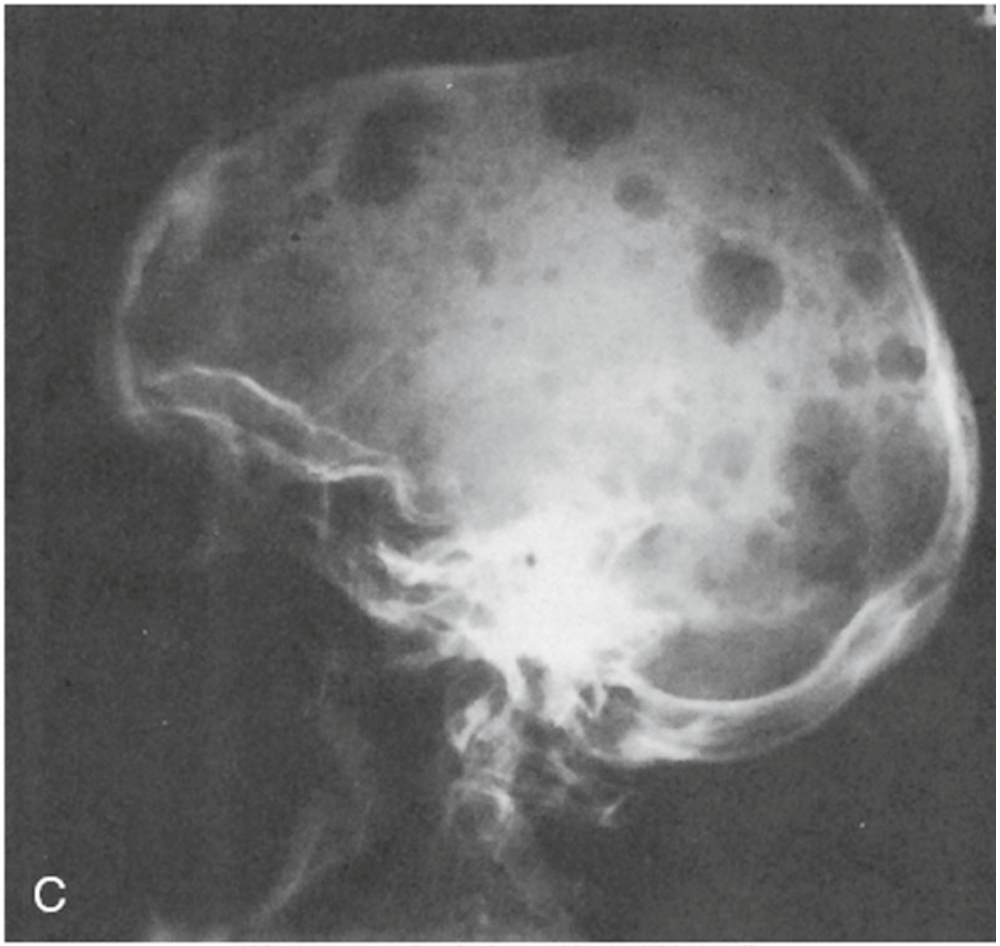
Complications of Leukemia

- Opportunistic infections, including pneumonia
- Sepsis
- Congestive heart failure
- Hemorrhage
- Liver failure
- Renal failure
- CNS depression and coma

Multiple Myeloma

- Neoplastic disease that involves increased production of plasma cells in bone marrow
- Unknown cause
- Occurs in older adults
- Production of other blood cells is impaired
- Multiple tumors in bone
  - Loss of bone
  - Severe bone pain
- Prognosis poor, with short life expectancy

Multiple Myeloma of the Skull



A,B. From Kumar V, et al, editors: Robbins Basic Pathology, *ed 8, Philadelphia, 2007, Saunders, p 455.*
C. Courtesy Marvin J. Stone, MD, Sammons Cancer Center, Baylor University Medical Center, Dallas. From Copstead LE, Banasik J: *Pathophysiology*, ed 5, St. Louis, 2013, Mosby.