

SIGNS AND SYMPTOMS OF BLOOD DISORDERS

(accents on anemia, polycythemia, leukopenia, leukocytosis, hemorrhagic syndrome, leukemia)

LECTURE IN INTERNAL MEDICINE PROPAEDEUTICS

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Plan of the lecture

- Blood
- Spectrum of Blood Disorders
- Blood System' Methods of Examination
- Blood System' Signs and Symptoms
- Glossary of Terms referred to Endocrine Diseases and Metabolic Disorders

Hematopoiesis

Myeloid tissue

Bone marrow

Erythrocytes

Platelets

Granulocytes

Monocytes

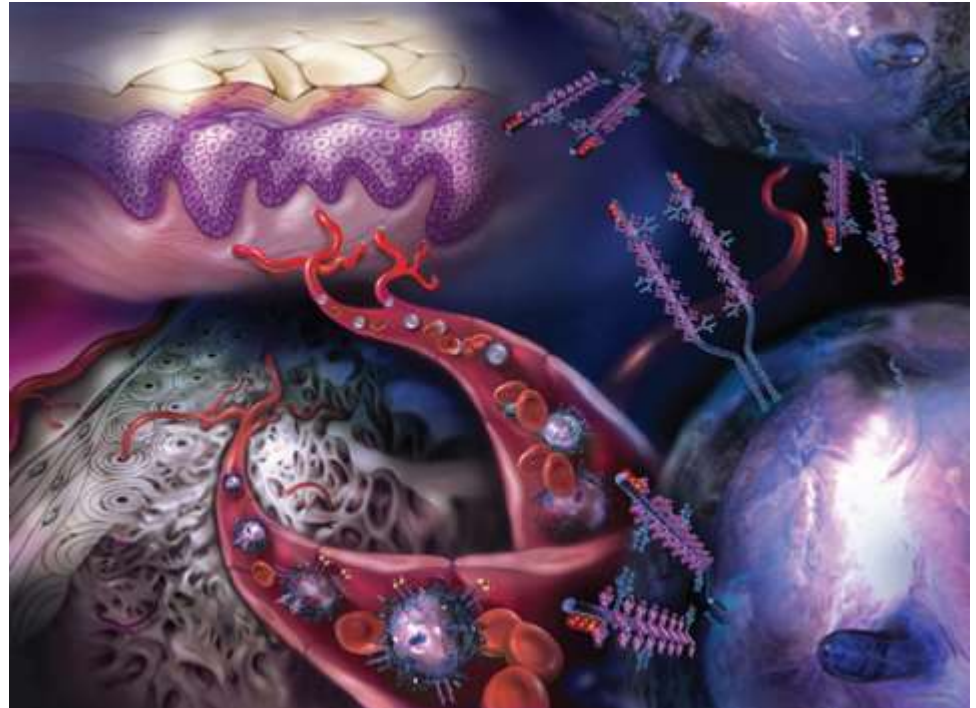
Lymphocytes

Lymphoid tissue

Thymus

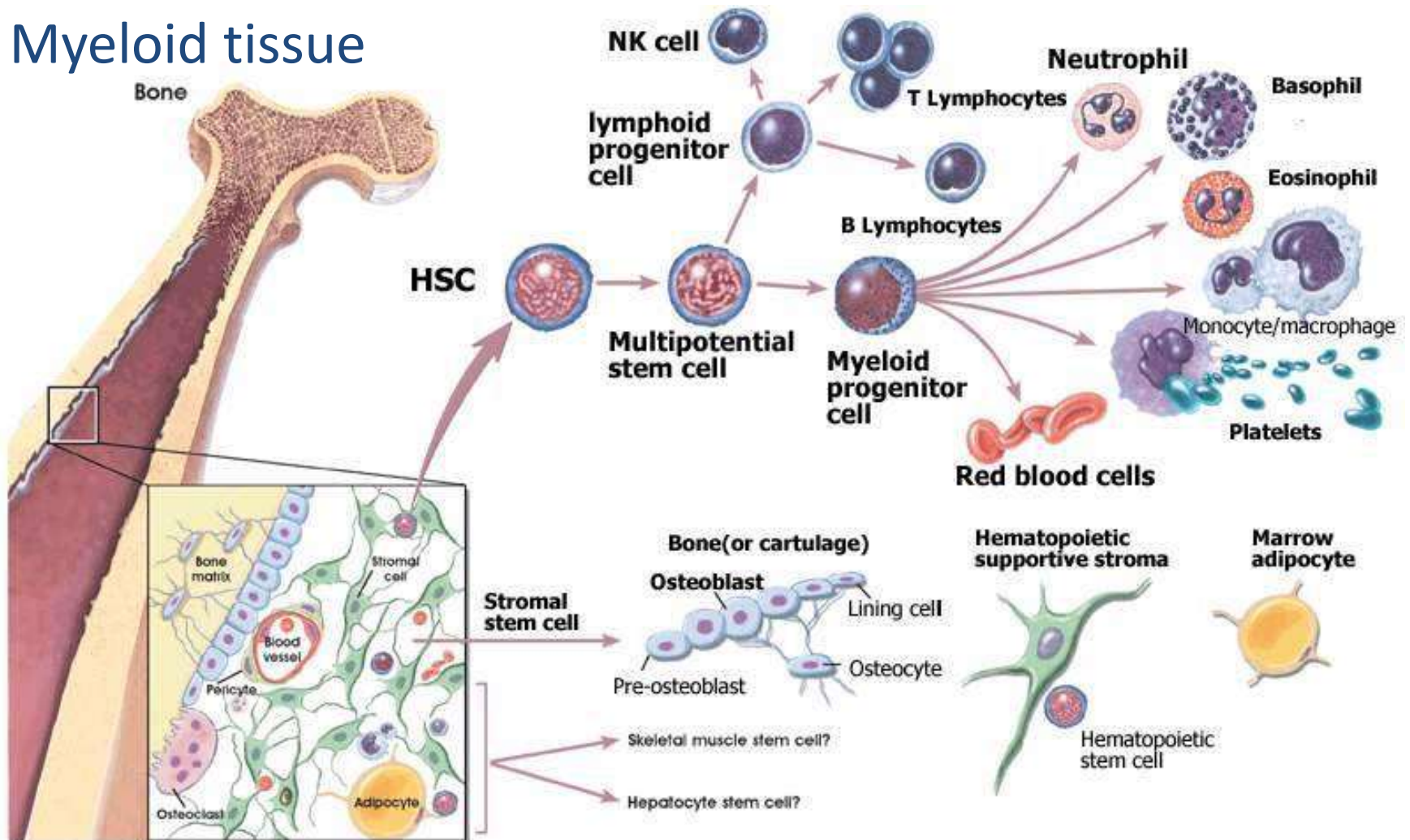
Lymph nodes

Spleen



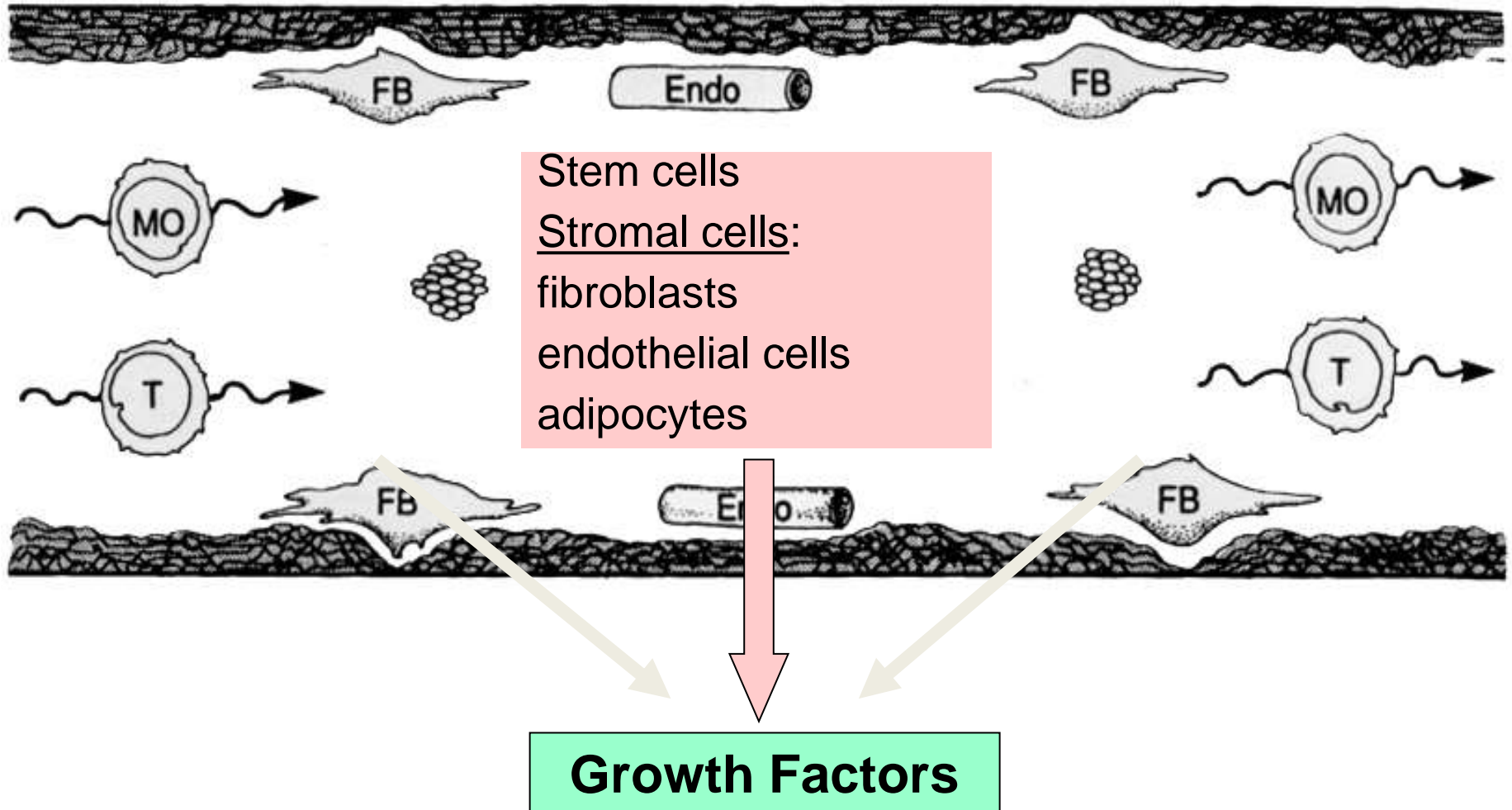
Hematopoiesis

Myeloid tissue



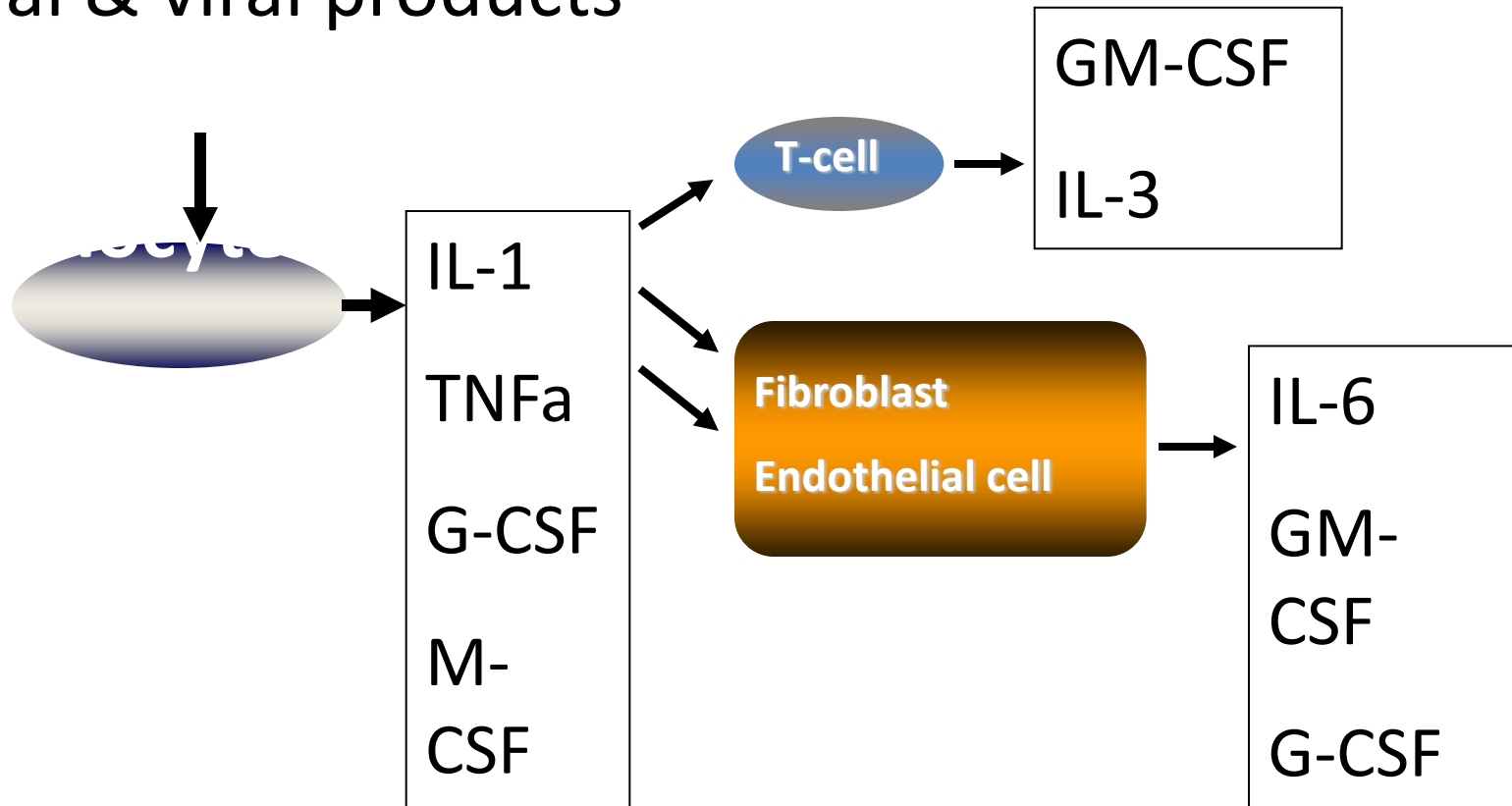
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Hematopoietic Microenvironment

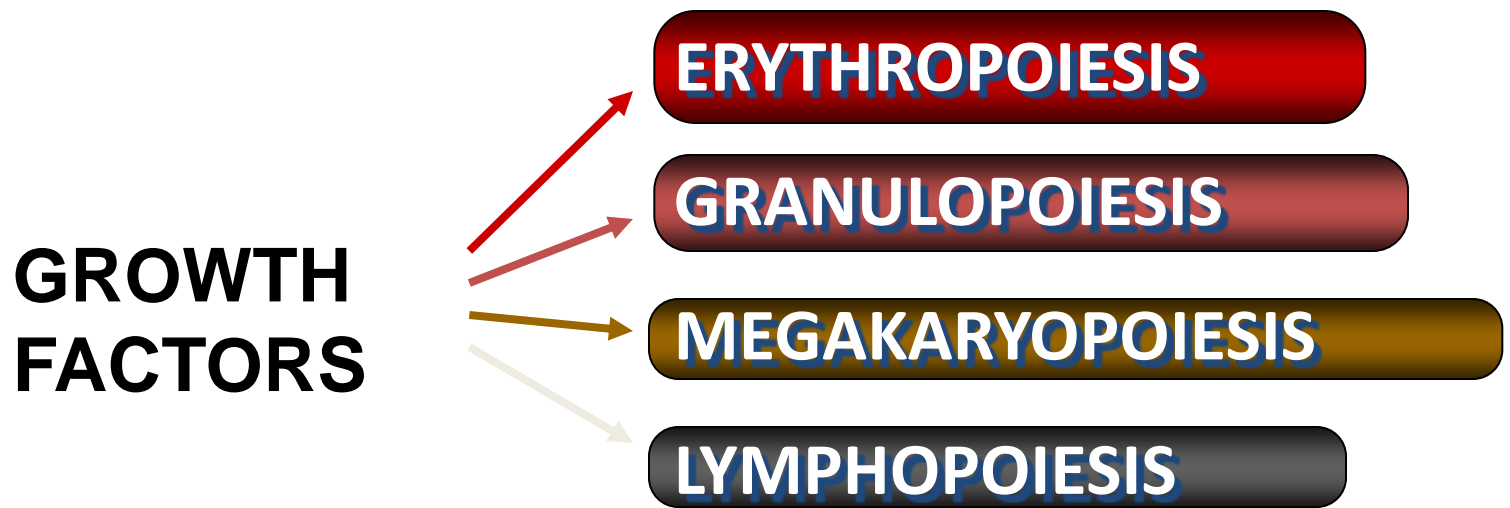


Hematopoietic Growth Factors

Bacterial & viral products



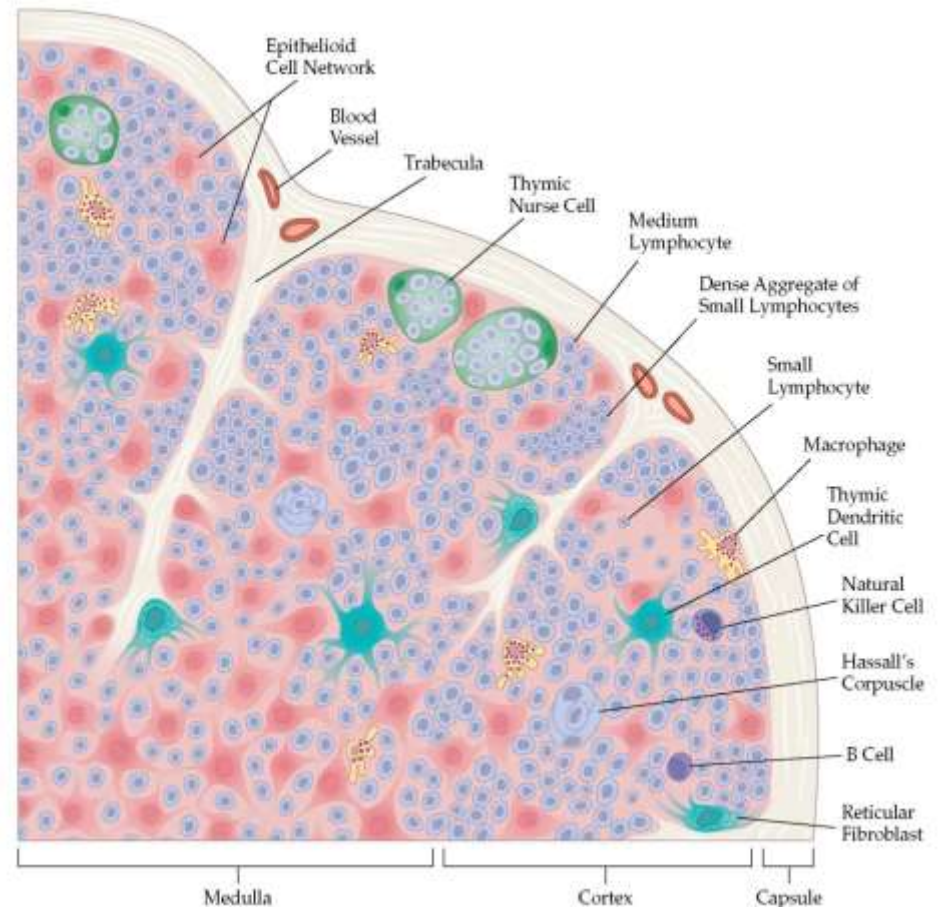
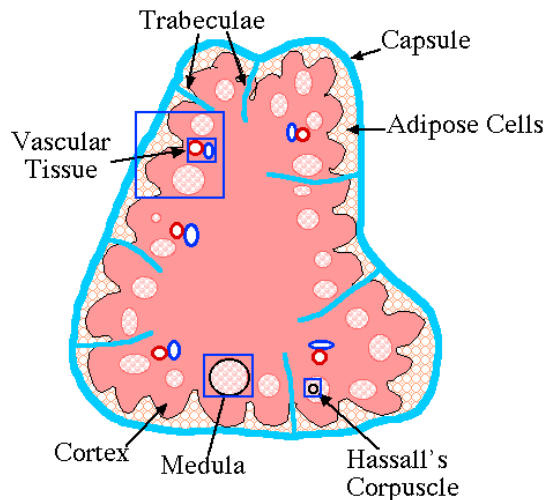
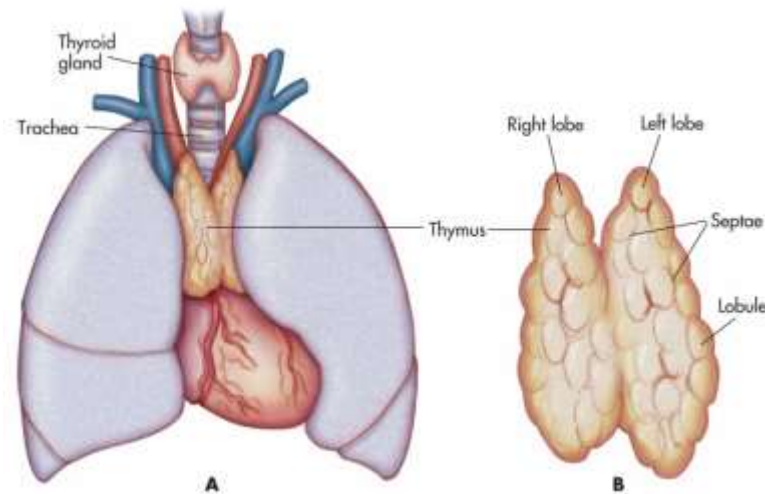
Hematopoiesis



Generation of each specific lineage of mature blood cells is regulated by a specific set of hematopoietic growth factors

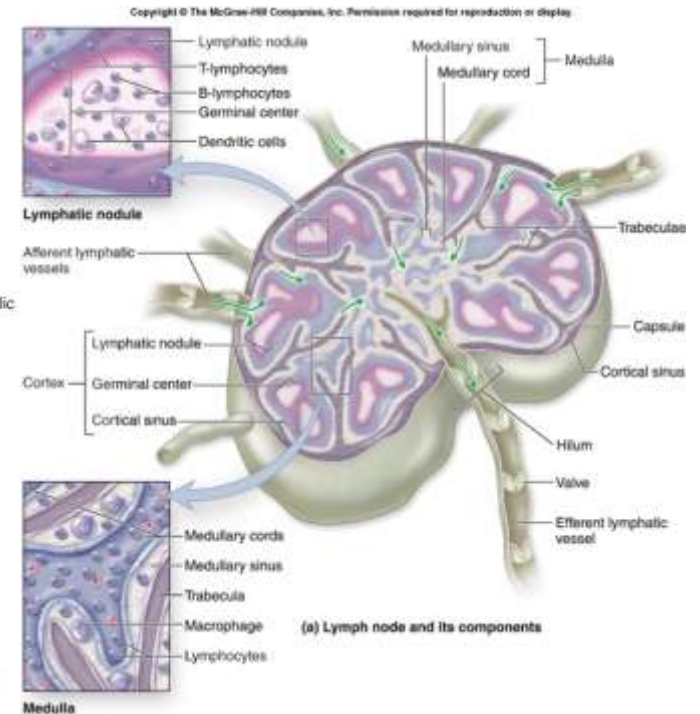
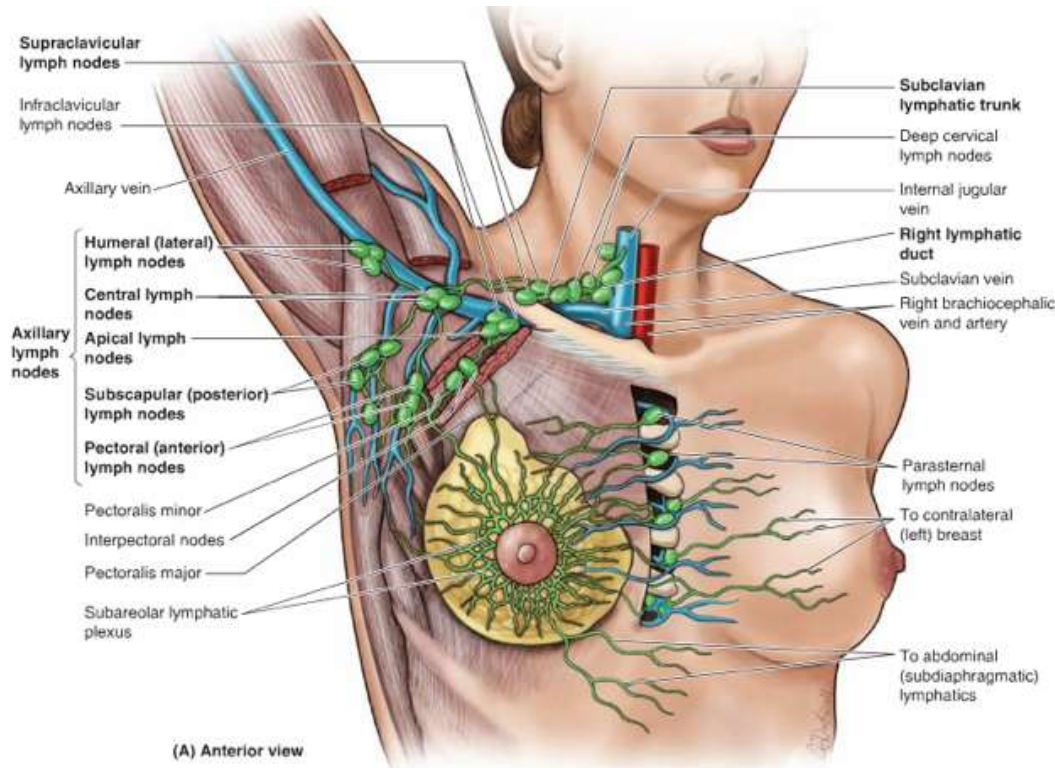
Hematopoiesis

Lymphoid tissue: Thymus



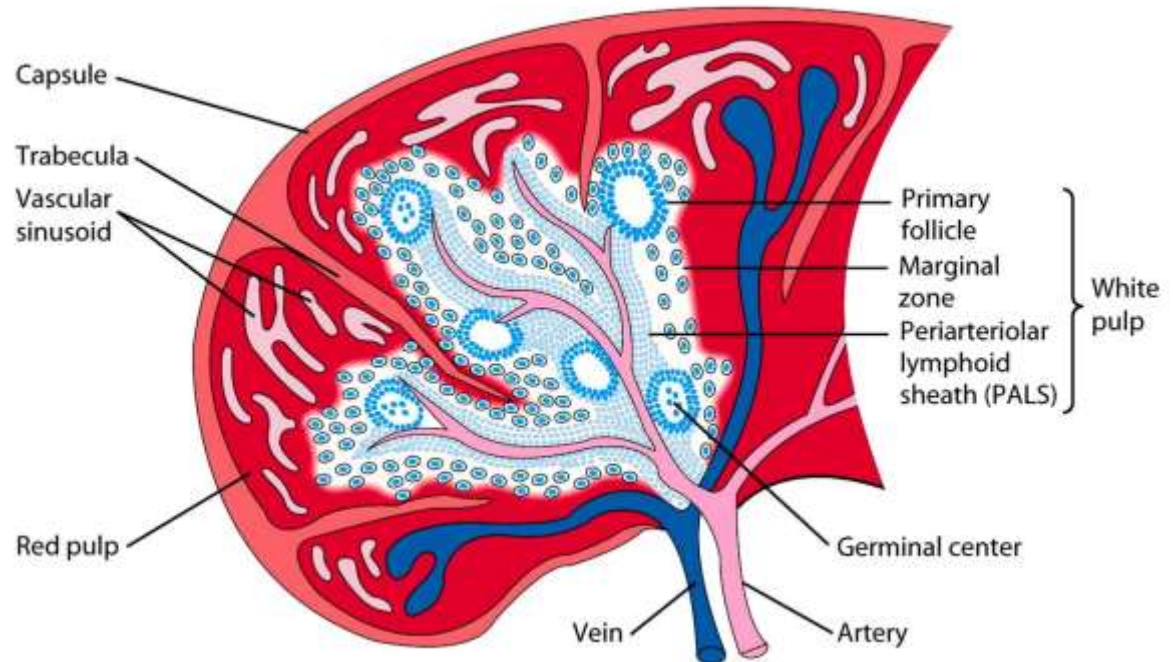
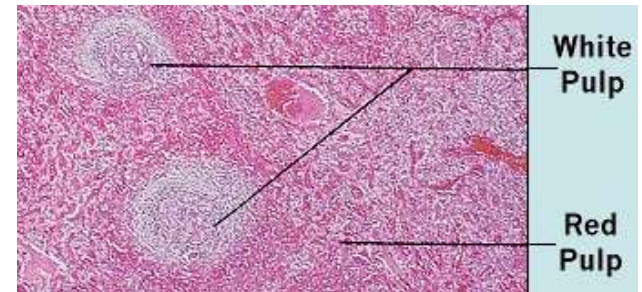
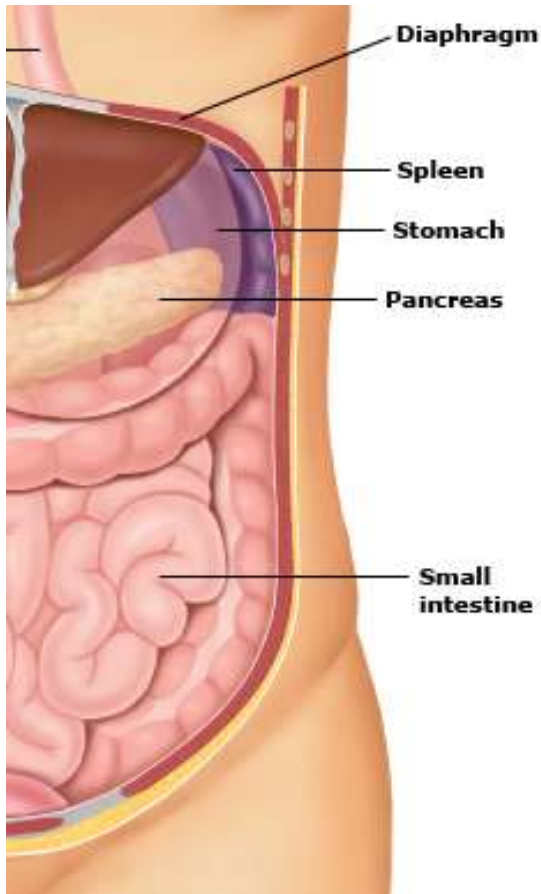
Hematopoiesis

Lymphoid tissue: Lymph nodes



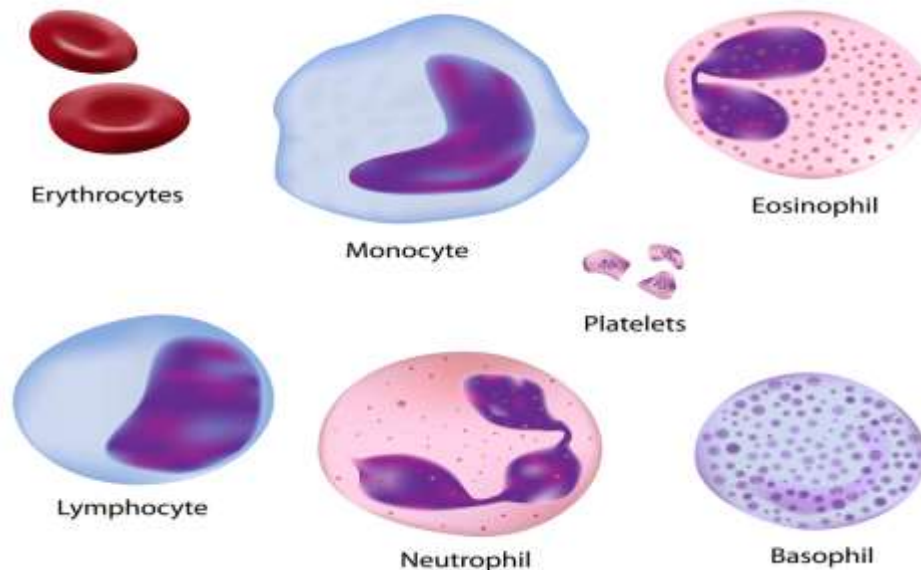
Hematopoiesis

Lymphoid tissue: Spleen



Lifespan of Blood Cells

| | |
|--------------|--|
| RBC | 120 days |
| Platelet | 10 days |
| Granulocytes | circ. : 9 hours; tissue : days |
| Lymphocyte | circ. : hours to years; tissue: weeks to years |



Red Blood Cells Functions

- Red blood cells (erythrocytes) are the most abundant cells in the bloodstream and contain hemoglobin, the compound that carries oxygen through the body
- Apart from carrying oxygen they also release the enzyme carbonic anhydrase which allows water in the blood to carry carbon dioxide to the lungs where it is expelled, and control the pH of the blood by acting as an acid-base buffer


Platelets Functions

- Platelets (thrombocytes) contribute to the hemostatic process in two different ways
 - First, through their adhesive and cohesive functions that lead to the formation of a hemostatic plug
 - Second, they can activate coagulation mechanisms through the exposure of an adequate phospholipidic surface, acting as a catalytic site for the development of coagulation and the consolidation of the hemostatic plug


White Blood Cells Functions

- Neutrophils defend against bacterial & fungal infection as the first responders to it
- Eosinophils primarily deal with parasitic infections and allergic reactions
- Basophils promote blood flow and prevent coagulation, they release heparin and histamine
- Monocytes phagocytize pathogens and they present antigens to T cells
- Lymphocytes refer to a group of cells consisting of B cells, T cell and natural killer (NK) cells and are the major components of the body's adaptive immunity

Hematopoietic Response

Hypoxia  RBCs

Infection  Granulocyte/Monocyte

Antigen  Lymphocyte

Hemorrhage  Platelet

Spectrum of Blood Disorders

- Blood Disorders Affecting Red Blood Cells
- Blood Disorders Affecting White Blood Cells
- Blood Disorders Affecting Platelets
- Blood Disorders Affecting Blood Plasma

Blood Disorders Affecting Red Blood Cells

- Anemia
 - Iron-deficiency anemia
 - Anemia of chronic disease
 - Pernicious anemia (B12 deficiency)
 - Aplastic anemia
 - Autoimmune hemolytic anemia
 - Thalassemia
 - Sickle cell anemia
- Polycythemia
- Malaria

Blood Disorders Affecting White Blood Cells

- Lymphoma
- Leukemia (main types)
 - Acute myeloid leukemia (AML)
 - Chronic myeloid leukemia (CML)
 - Acute lymphocytic leukemia (ALL)
 - Chronic lymphocytic leukemia (CLL)
- Multiple myeloma
- Myelodysplastic syndrome

Blood Disorders Affecting Platelets

- Thrombocytopenia
 - Idiopathic thrombocytopenic purpura
 - Heparin -induced thrombocytopenia
- Essential thrombocytosis (primary thrombocythemia)

Blood Disorders Affecting Blood Plasma

- Sepsis
- Hemophilia
- von Willebrand disease
- Hypercoaguable state (hypercoagulable state)
- Deep venous thrombosis
- Disseminated intravascular coagulation (DIC)

Methods of Examination

Complete Blood Count (CBC)

- red blood cells
- white blood cells
 - Differential white blood cells count
- platelets



Methods of Examination

Red Blood Cells

| Red blood cells (RBCs) count | 4.2 to 5.9 million cells per microliter |
|-----------------------------------|--|
| Hematocrit (Hct) | Men: 42 to 50%; Women: 36 to 45% |
| Hemoglobin (Hb) | Men: 12.7 to 13.7 grams per deciliter Women: 11.5 to 12.2 grams per deciliter |
| Red cell distribution width (RDW) | Less than 14.5% |

Other

- Mean volume of red blood cells (MCV – mean corpuscular/cell volume) 80 – 100 femtoliters ($1 \text{ fL} = 10^{-15} \text{ L}$)
- Mean cellular hemoglobin (MCH)
- Mean cellular hemoglobin concentration (MCHC)

Methods of Examination

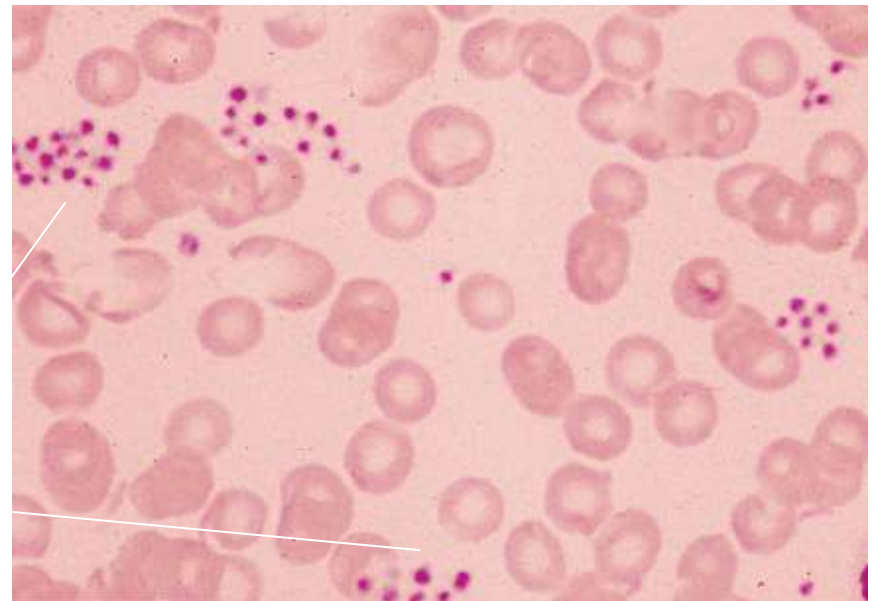
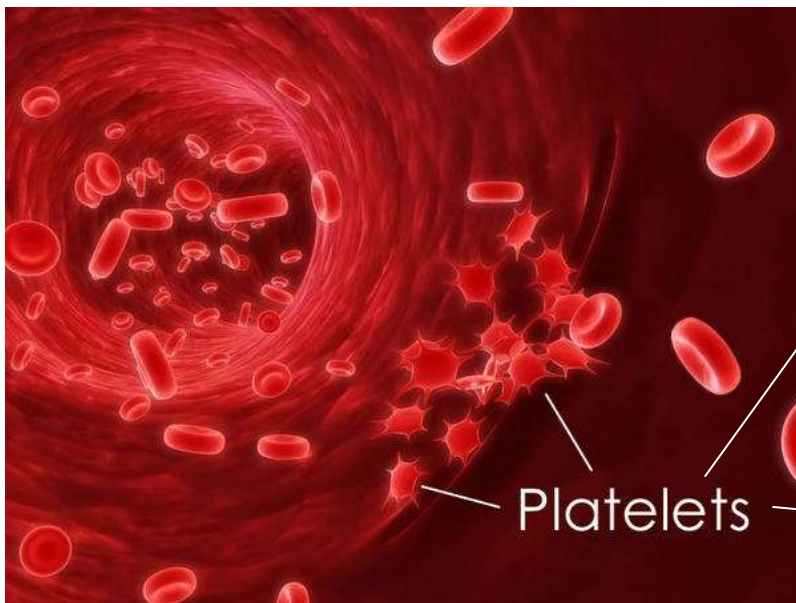
White blood cells count

| | |
|--------------------------------------|---|
| White blood cells count | 4,500 to 10,500 per microliter |
| Differential white blood cells count | <p>Segmented neutrophils: 34 to 75% (1800 to 7800 1/mL)</p> <p>Band neutrophils (immature segmented neutrophils): 0 to 8% (0 to 1/mL)</p> <p>Lymphocytes: 12 to 50% (1000 to 4800 1/mL)</p> <p>Monocytes: 2 to 9% (0 to 800 1/mL)</p> <p>Eosinophils: 0 to 5% (0 to 450 1/mL)</p> <p>Basophils: 0 to 3% (0 to 200 1/mL)</p> |

Methods of Examination

Platelet count

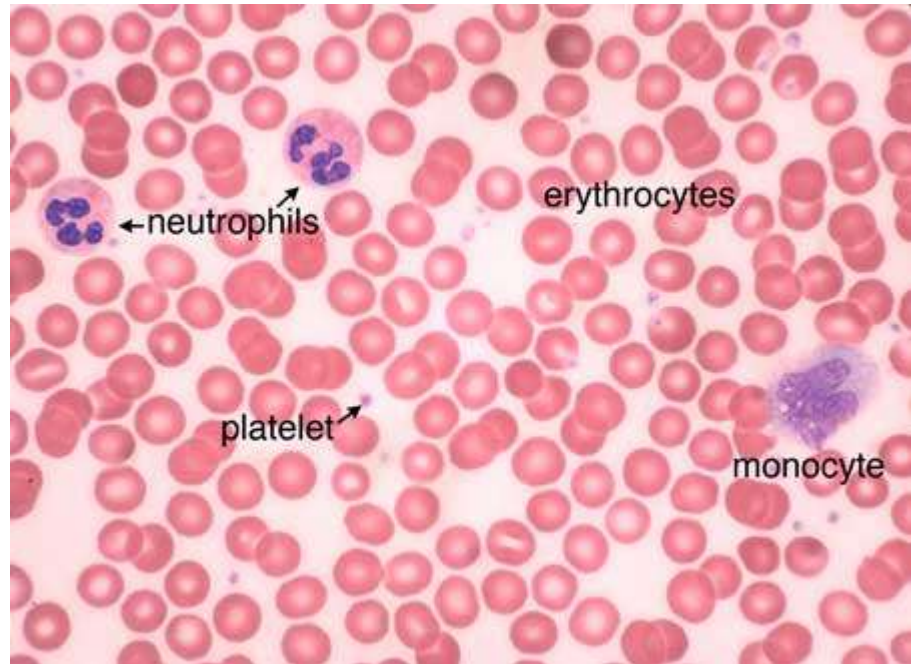
140,000 to 450,000 p



Methods of Examination

Blood Smear:

A follow-up test to abnormal results on a complete blood count (CBC) to evaluate the different types of blood cells



Methods of Examination

Shape and Size of a Red Blood Cell

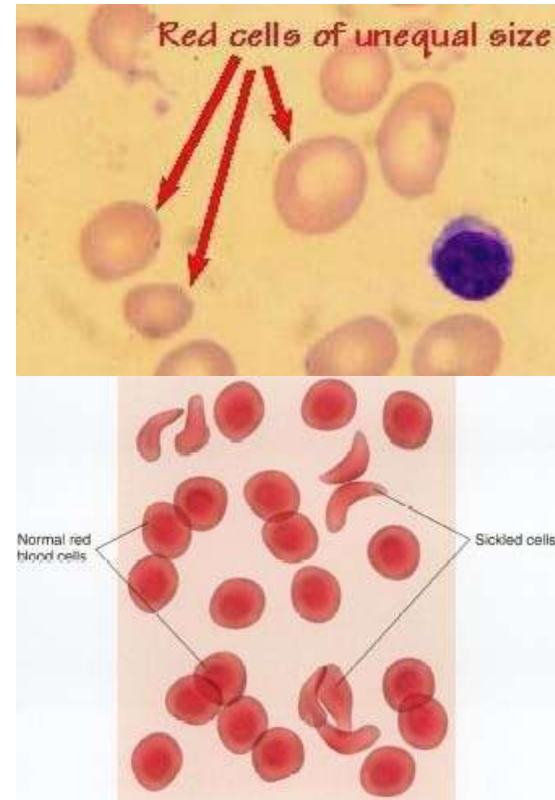
- A red blood cell is a biconcave disc. Simply it is a round ball that is squeezed from two opposite ends to appear, widest at the sides and narrowest in the middle
- A red blood cell measures about 6 to 8 micrometers in diameter (average = 7.8 μm) with an average thickness of 2 micrometers (2.5 μm at the thickest point and less than 1 μm at the center). Although a red blood cell is wider than some capillaries, its flexibility allows it to become distorted as it squeezes through narrow passages and then restores to its original shape

Methods of Examination

Variation and Irregularity of Red Blood Cells:

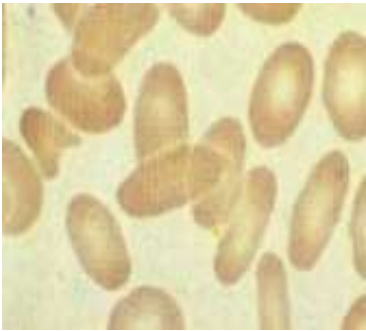
anisocytosis (aniso = unequal) - various sizes

poikilocytosis (poikilo = various) - various shapes

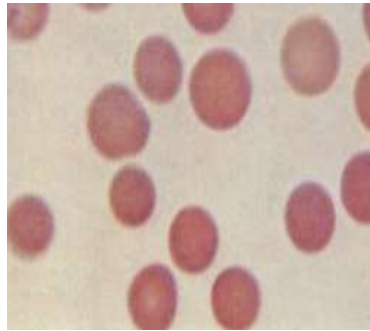


Methods of Examination

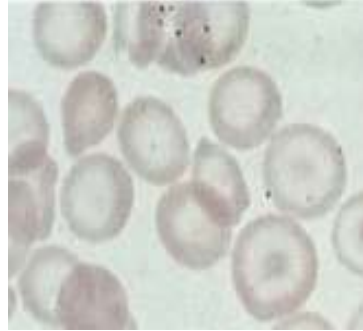
Variation and Irregularity of Red Blood Cells



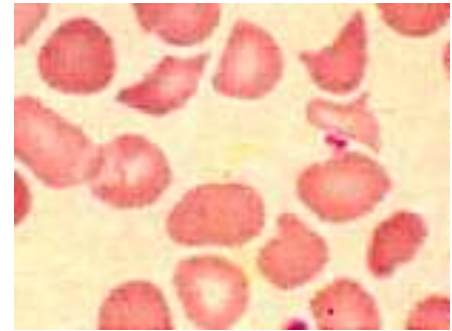
Elliptocytes



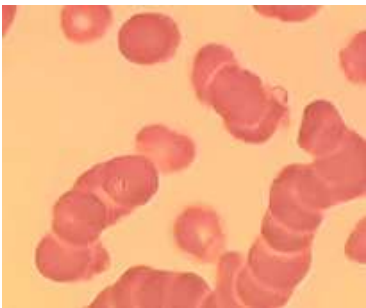
Spherocytes



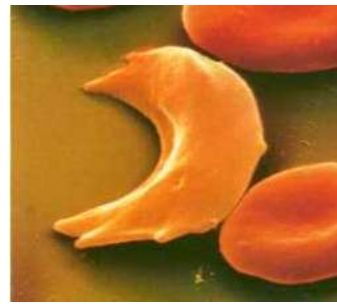
Leptocytes



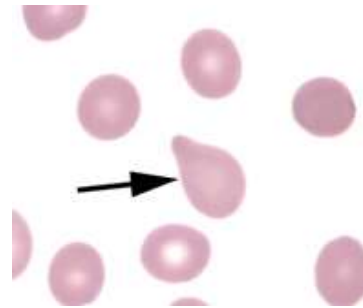
Schistocytes



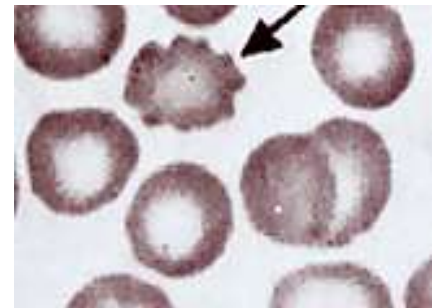
Rouleaux



Sickle cells



Dacrocytes



Echinocytes

Methods of Examination

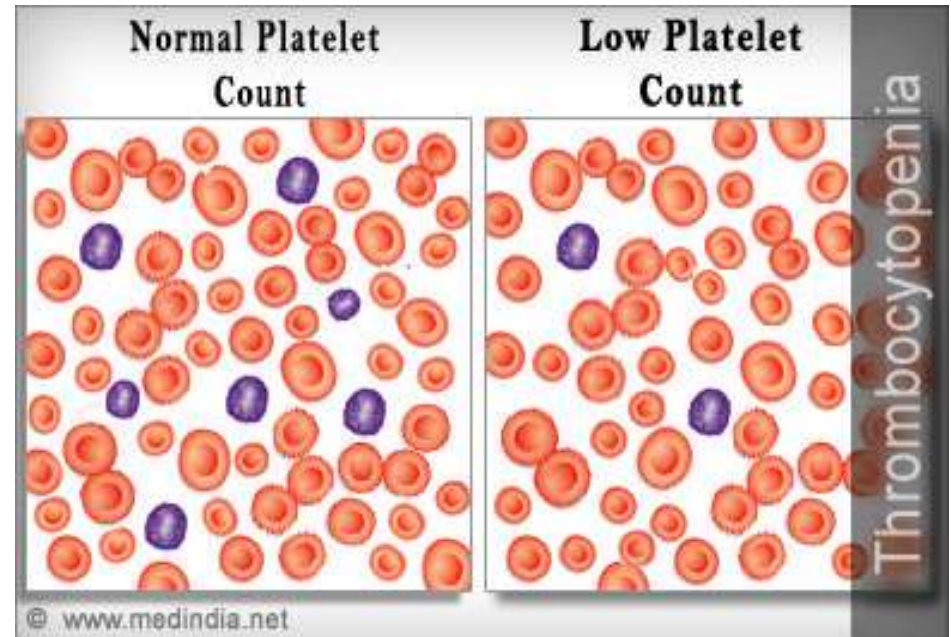
Diagnosis

- The platelet count
- The platelet function (bleeding time, platelet aggregation studies, von Willebrand Factor studies, specialized tests)
- A coagulation screen (clotting factor deficiencies)
- If the patient is on warfarin, INR (International Normalized Ratio)
- Autoantibody screen for connective tissue disorders

Methods of Examination

Platelets

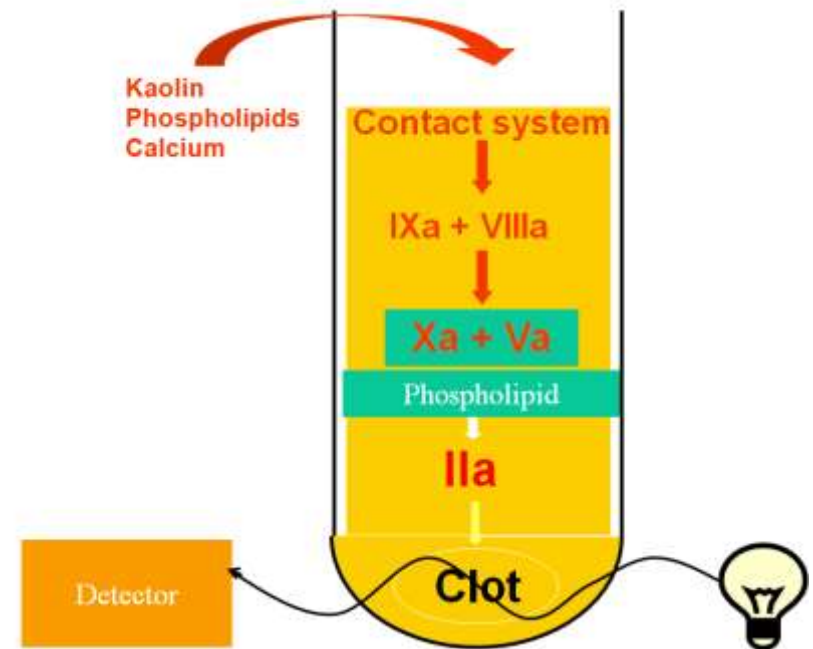
- The platelet count
- The platelet function:
 - bleeding time
 - platelet aggregation studies
 - von Willebrand Factor studies
 - specialized tests



Methods of Examination

Coagulation screen

- Prothrombin ratio
- Activated Partial Thromboplastin time
- Thrombin clotting time
- Fibrinogen



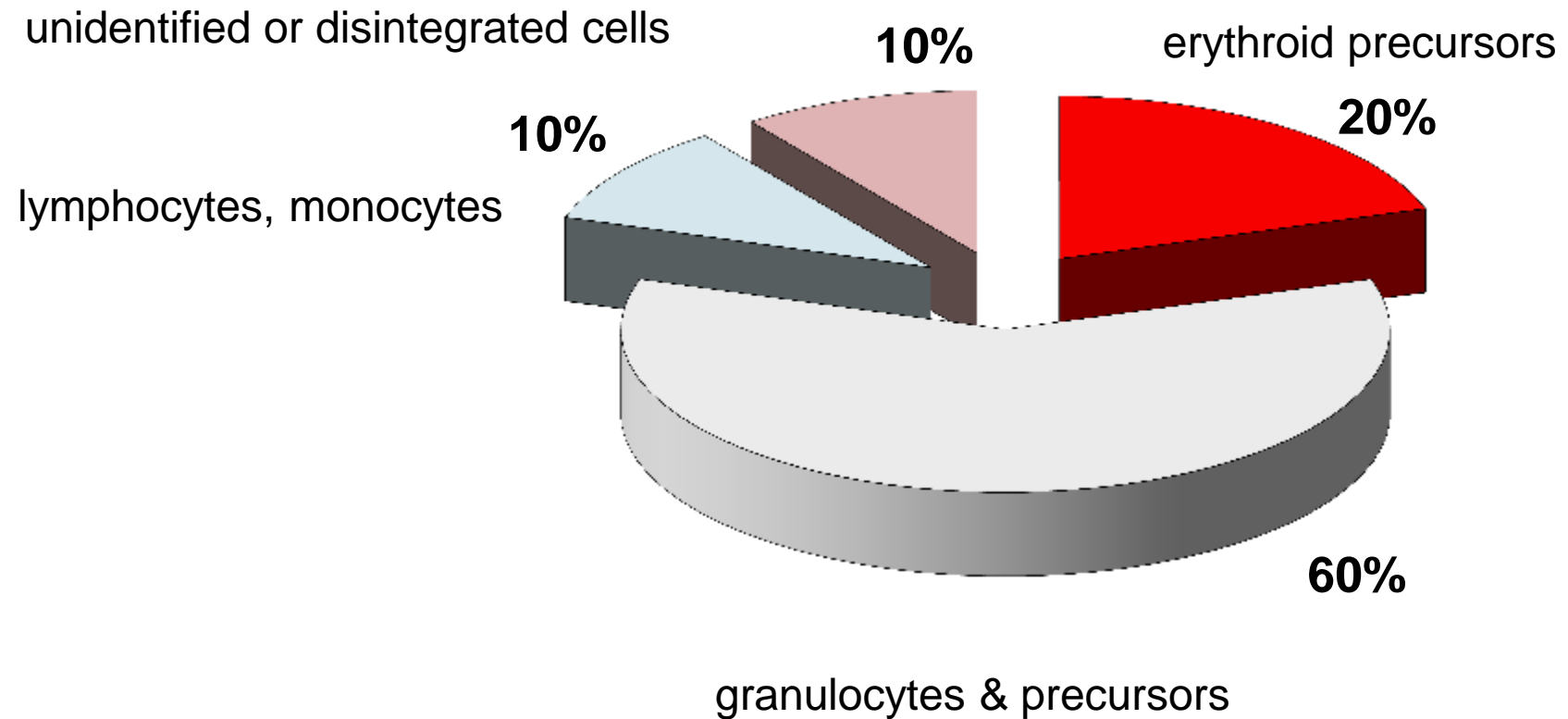
Methods of Examination

Bone Marrow Examination (usually from the iliac crest or from the sternum)

- Bone marrow aspirate
 - what cells, normal and abnormal, are present in the bone marrow
- Bone marrow core biopsy
 - how full the bone marrow is with cells and where the cells are located within the marrow

Methods of Examination

Normal Marrow Composition



Methods of Examination

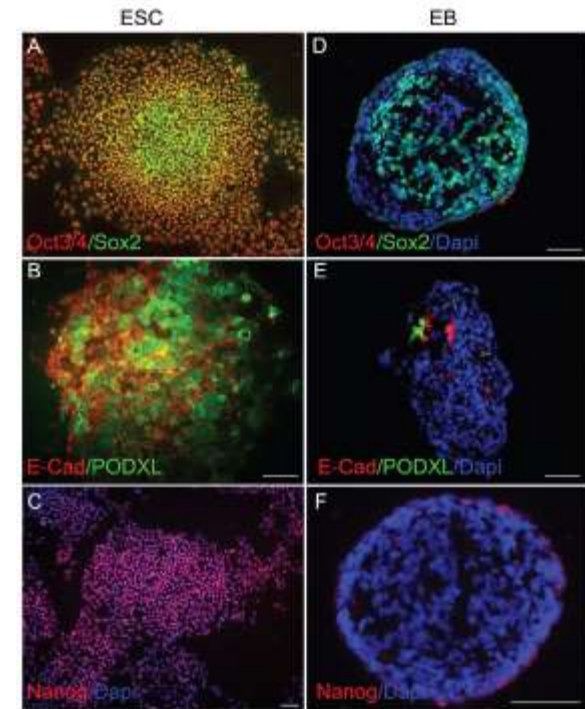
Markers

Stem cell: CD34, c-kit
rhodamine, Hoechst
dyes (pale)

B-cell: CD19, CD20, (CD22),
CD79a

T-cell: CD3, CD2, CD5,
CD4/CD8

NK-cell: CD16, CD57, CD56



Anemia

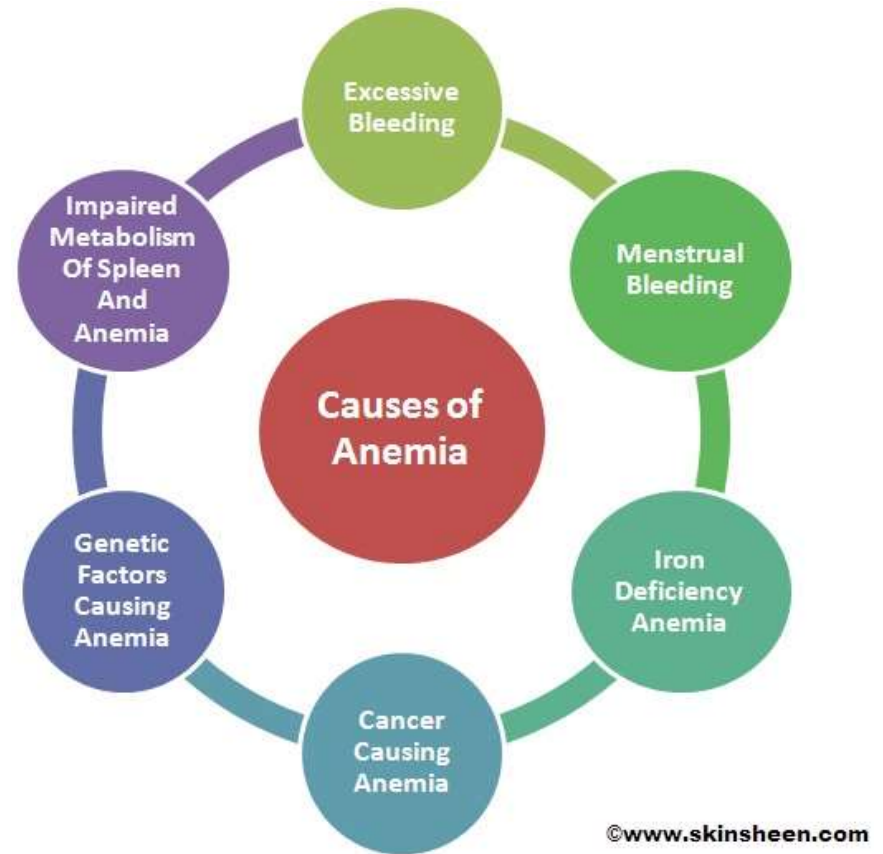
Definition

Anemia (anaemia) is a decrease in the amount of RBCs or hemoglobin in the blood or a lowered ability of the blood to carry oxygen

Anemia

Causes

- Impaired RBC production
- Increased RBC destruction
- Blood loss
- Fluid overload



Anemia

Causes: Impaired production

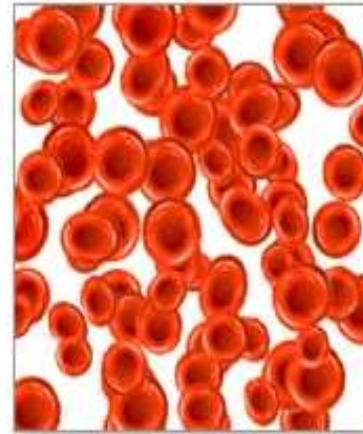
- Disturbance of proliferation and differentiation of stem cells (Pure red cell aplasia, Aplastic anemia, Anemia of renal failure, Anemia of endocrine disorders)
- Disturbance of proliferation and maturation of erythroblasts (Pernicious anemia, Anemia of folic acid deficiency, Megaloblastic anemia, Anemia of prematurity, Iron deficiency anemia, Thalassemias, Congenital dyserythropoietic anemias, etc.)
- Other mechanisms of impaired RBCs production (Myelophthisic anemia, Myelodysplastic syndrome, Anemia of chronic inflammation)

Anemia

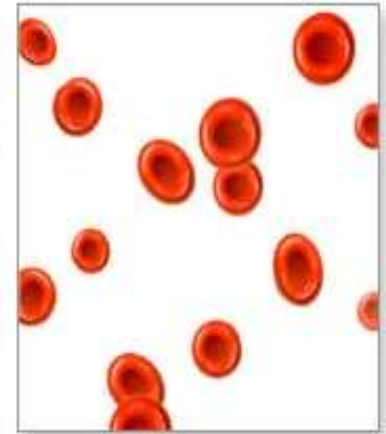
Causes: Increased RBCs destruction (hemolytic anemias)

- Intrinsic (intracorpuseular) abnormalities cause premature destruction (except paroxysmal nocturnal hemoglobinuria, are hereditary genetic disorders)
- Extrinsic (extracorpuseular) abnormalities (antibody-mediated, mechanical trauma to red cells)

Normal amount of red blood cells



Anemic amount of red blood cells



Anemia

Causes: Blood loss

- Anemia of prematurity
- Trauma or surgery, causing acute blood loss
- Gastrointestinal tract lesions (acute bleeds: peptic ulcers, chronic blood loss (angiodysplasia))
- Gynecologic disturbances (chronic blood loss)
- Menstruation, among young women or older women with fibroids
- Infection by intestinal nematodes feeding on blood

Anemia

Hydremia

Causes: Fluid overload (hypervolemia with hemodilution, normal total amount of Hb and RBCs in the body)

- Excessive sodium or fluid intake, sodium or water retention and fluid shift into the intravascular space
- Anemia of pregnancy (induced by blood volume expansion experienced in pregnancy)



Anemia

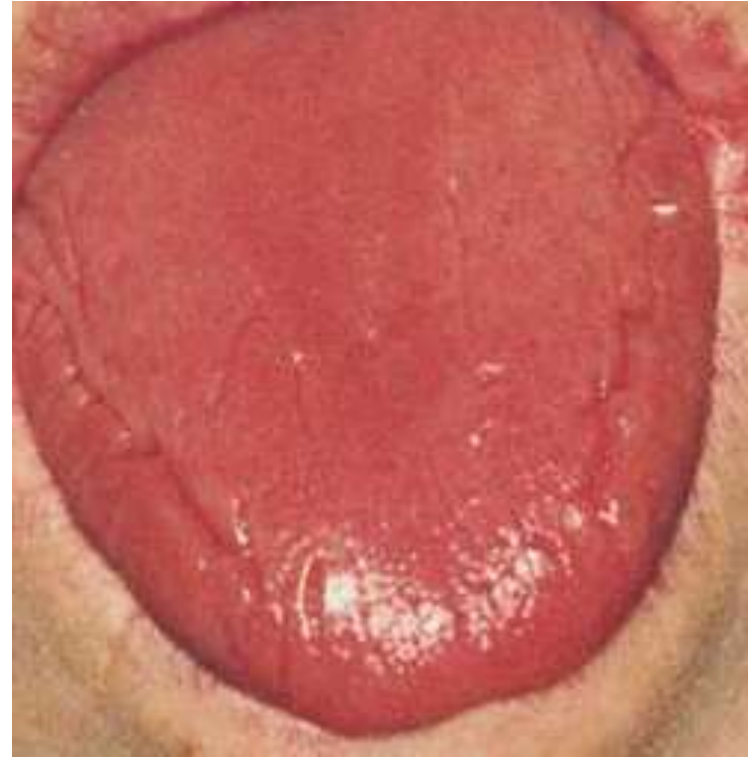
Diagnostic steps

- Clinical manifestations
- Hematological syndromes (blood tests abnormalities)
- Blood biochemistry abnormalities
- Bone marrow abnormalities

Anemia

Signs and symptoms

- weakness, fatigue, general malaise, poor concentration
- dyspnea (shortness of breath) on exertion
- increasing cardiac output, palpitations, angina (if pre-existing heart disease is present), heart failure
- intermittent claudication
- pallor (pale skin, lining mucosa, conjunctiva and nail beds)



Anemia

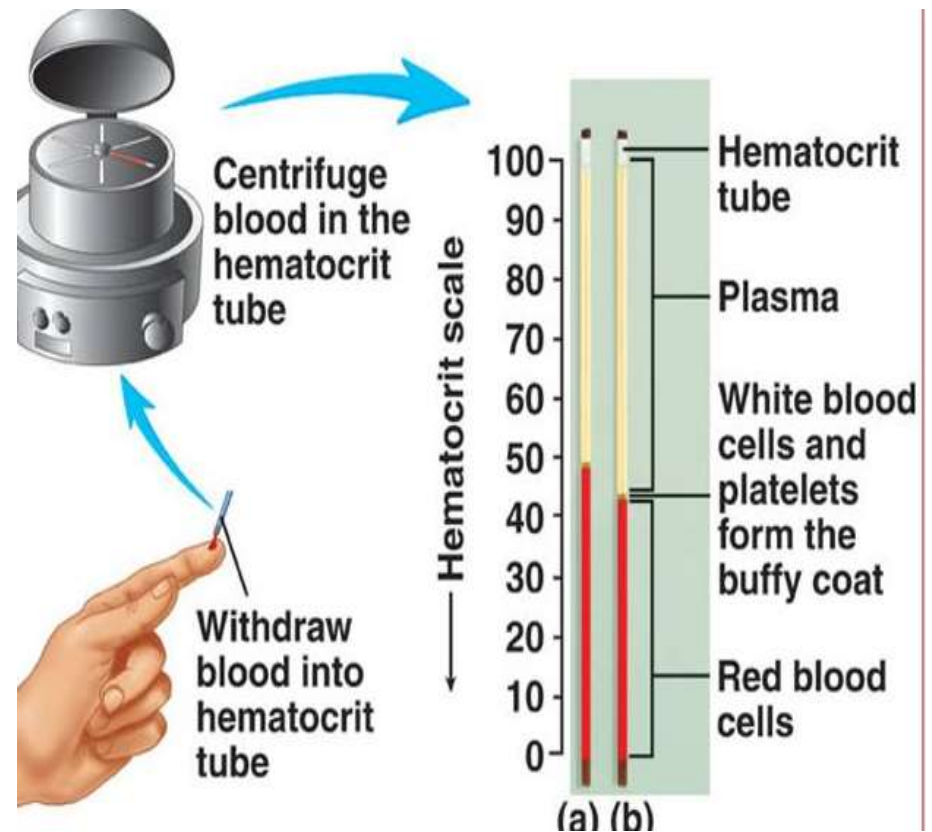
Additional signs of severe anemia

- hyper dynamic circulation
(tachycardia, bounding pulse, flow murmurs, cardiac ventricular hypertrophy)
- heart failure
- pica
- restless legs syndrome (iron-deficiency anemia)

Anemia

Diagnosis

- Complete blood count
- Blood smear
- Hemoglobin
- Hematocrit
- Red blood cell size
- Reticulocyte count
- Reticulocyte production index



Anemia

WHO's Hemoglobin Thresholds used to define Anemia

| Age, Gender | Hb threshold (g/dl) | Hb threshold (mmol/l) |
|------------------------------|------------------------|--------------------------|
| Children (0.5–5.0 yrs) | 11.0 | 6.8 |
| Children (5–12 yrs) | 11.5 | 7.1 |
| Teens (12–15 yrs) | 12.0 | 7.4 |
| Women, non-pregnant (>15yrs) | 12.0 | 7.4 |
| Women, pregnant | 11.0 | 6.8 |
| Men (>15yrs) | 13.0 | 8.1 |

Anemia

Color index

- Hypochromic ($<0,85$) – e. g chronic posthemorrhagic, Fe-deficient
- Normochromic ($0,85 - 1,05$) – e. g acute posthemorrhagic , hemolytic
- Hyperchromic ($>1,05$) – e.g. B12-deficient, folate-deficient, aplastic

Anemia

Types of red blood cells size

- The cells are small - microcytic anemia (MCV < 80 fL) - e.g Fe deficient anemia
- The cells are large - macrocytic anemia (MCV > 100 fL) – e.g B12-folate deficient anemia
- The cells are normal - normocytic anemia - e.g anemia if chronic diseases



Anemia

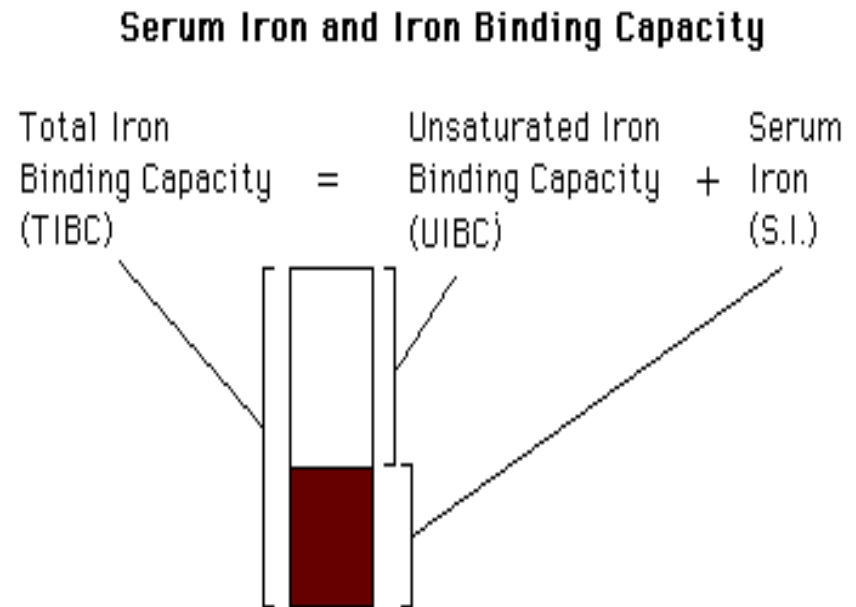
Regenerative abilities of bone marrow-
reticulocytes, $\%$

- Normoregenerative (6 – 12) – anemias due to deficiency (Fe, B12-folate, etc)
- Hyperregenerative (> 12) – hemolytic,
acute posthemorrhagic
- Hyporegenerative (< 6) – aplastic

Anemia

Blood biochemistry

- Ferritin (↓ in Fe deficiency)
- Serum iron (↓ in Fe deficiency)
- Transferrin saturation (↓ in Fe deficiency)
- RBC folate level
- Serum vitamin B₁₂
- Serum methylmalonic acid and homocysteine (in B₁₂ def.)
- Renal and liver function tests
- Erythropoietin level



Polycythemia

Definition

Polycythemia is a myeloproliferative condition that results in an increased level of circulating red blood cells in the bloodstream with increase in hematocrit, hemoglobin, or red blood cell count above the normal limits

Polycythemia

Synonyms

Erythremia

Osler-Vaquez disease

Polycythemia rubra vera

Primary polycythemia

Splenomegalic polycythemia

Vaquez-Osler disease

Polyglobulia

Polycythemia

Risk factors:

- Hypoxia from long standing (chronic) lung disease and smoking
- Chronic carbon monoxide (CO) exposure
- People living at high altitudes due to low environmental oxygen levels
- People with genetic mutations and familial types of polycythemia and certain hemoglobin abnormalities

Polycythemia

Causes

- Primary (a slow-growing type of blood cancer)
 - Polycythemia Vera
 - Primary familial and congenital polycythemia
- Secondary
 - Physiologically appropriate (adaptation to living at high altitudes, iatrogenic, etc.)
 - Chronic hypoxia (COPD, hypoventilation syndrome, chronic heart diseases, sleep_apnea, pulmonary_hypertension)
 - Erythropoietin secreting tumors (hepatocellular carcinoma, renal cell carcinoma, adenocarcinomas, uterine tumors)
 - Relative polycythemia (the underlying cause is reduced blood plasma)

Polycythemia

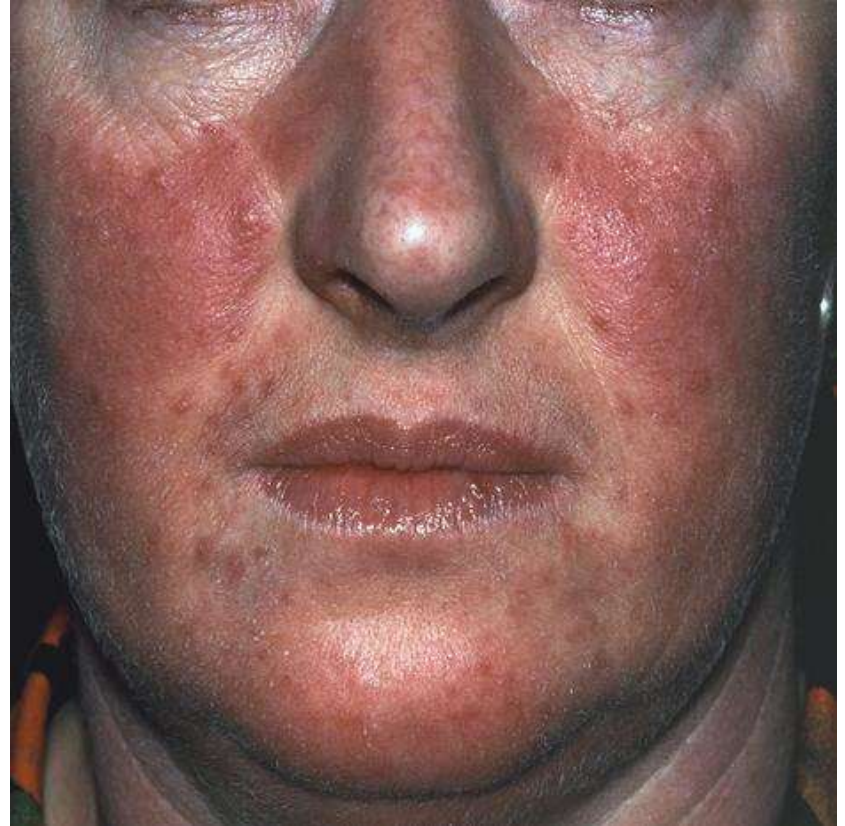
Signs and symptoms Polycythemia Vera

- Trouble breathing when lying down
- Dizziness
- Excess bleeding
- Full feeling in the left upper abdomen (enlarged spleen)
- Headache
- Itchiness, especially after a warm bath
- Red skin coloring, especially of the face
- Shortness of breath
- Phlebitis

Polycythemia

Other symptoms that may occur with Polycythemia Vera

- Bluish skin color
- Fatigue
- Red skin spots
- Vision problems



Polycythemia

Diagnosis

- Bone marrow biopsy
- Complete blood count with differential
- Comprehensive metabolic panel
- Erythropoietin level
- Genetic test for the JAK2V617F mutation
- Oxygen saturation of the blood
- Red blood cell mass
- Vitamin B12 level



Polycythemia

Diagnosis (WHO criteria):

- Major criteria
 - Hemoglobin > 18.5 g/dL in men and > 16.5 g/dL in women, or other evidence of increased red blood cell volume
 - Presence of JAK2617V F or other functionally similar mutation, such as *JAK2* exon 12 mutation
- Minor criteria
 - Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
 - Serum erythropoietin level below the reference range for normal
 - Endogenous erythroid colony formation in vitro

Polycythemia

Diagnosis (The Polycythemia Vera Study Group criteria : the diagnosis is established if all three category A criteria are present, or if criteria A1 plus A2 plus any two criteria from category B are present):

- Category A criteria
 - Total red blood cell mass ≥ 36 mL/kg in males or ≥ 32 mL/kg in females
 - Arterial oxygen saturation $\geq 92\%$
 - Splenomegaly
- Category B criteria
 - Thrombocytosis, with platelet count $> 400,000/\mu\text{L}$
 - Leukocytosis, with a white blood cell count $> 12,000/\mu\text{L}$
 - Increased leukocyte alkaline phosphatase (ALP) > 100 U/L
 - Serum vitamin B-12 concentration > 900 pg/mL or binding capacity > 2200 pg/mL

Leukopenia

Definition

Leukopenia or leucopenia or leukocytopenia is a decrement in the white blood cells (WBC) or leukocytes present in the blood that places individuals at greater infection risks

Leukopenia

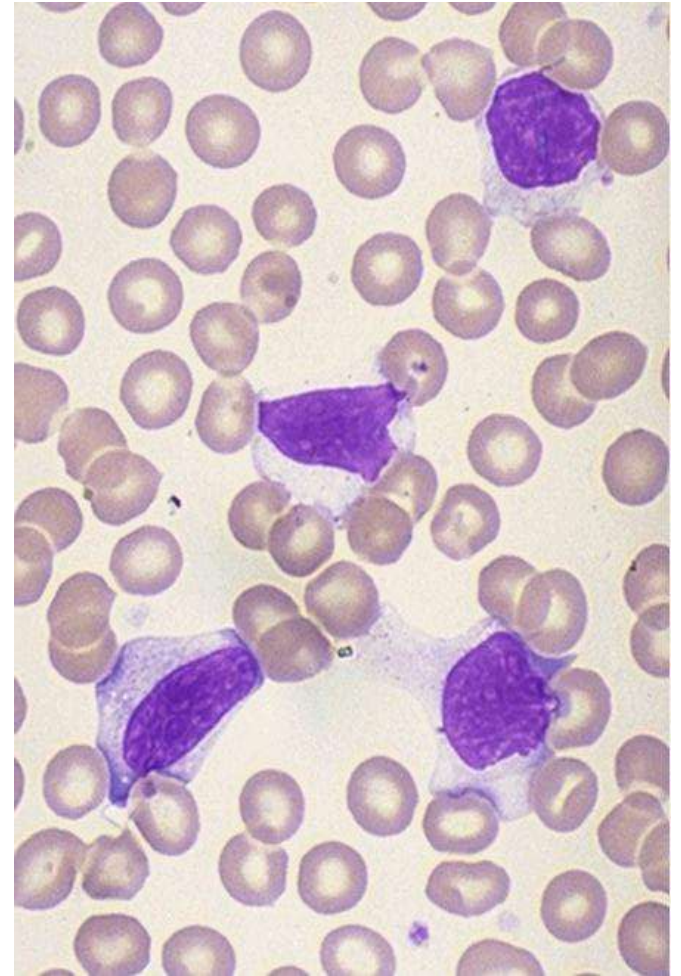
Causes

- Viral infections (cold/flu, HIV/AIDS, etc.)
- Microbial infections (sepsis, psittacosis, rickettsial infections, tuberculosis, malaria, dengue, etc.)
- Autoimmune connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, etc.)
- Cancer or other diseases that damage bone marrow (leukemia, myelofibrosis, Hodgkin's lymphoma)
Congenital disorders (Kostmann's syndrome, Myelokathexis)
- Vitamin deficiencies (folate deficiency, etc.)
- Deficiency of minerals (zinc, copper, etc.)
- Medications and radiation therapy (diuretics , antibiotics, antipsychotics, antidepressants, etc.)

Leukopenia

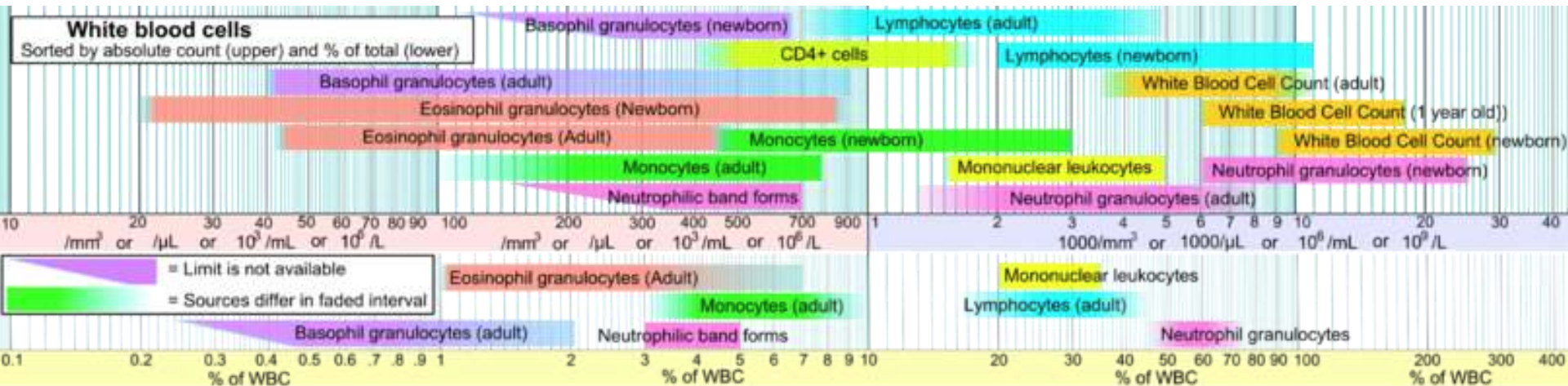
Signs and symptoms

- Anemia
- Thrombocytopenia
- Pneumonia
- Stomatitis, oral ulcer and various infections
- Liver abscesses
- Metrorrhagia, menorrhagia
- Neurasthenia
- Fatigue and hot flashes
- Strong desire to consume hot drinks



Leukopenia

Diagnosis: leukopenia can be identified with a complete blood count



Leukocytosis

Definition

A white blood cell (the leukocyte) count above the normal range ($<50 \times 10^9/\text{L}$) in the blood

Leukocytosis

Five principal types and Causes

| | |
|---|---|
| Neutrophilic leukocytosis (neutrophilia) | Bacterial infections, Tissue necrosis |
| Eosinophilic leukocytosis (eosinophilia) | Allergic disorders, Parasitic infections, Malignancy, Systemic autoimmune diseases, etc.), Acute stress |
| Basophilic leukocytosis (basophilia) | Myeloproliferative disease |
| Monocytosis | Chronic infections (Tuberculosis, Systemic autoimmune diseases, etc.) |
| Lymphocytosis | Chronic infections (Tuberculosis, Brucellosis, Viral infections, Pertussis, Malignancy |

Leukocytosis

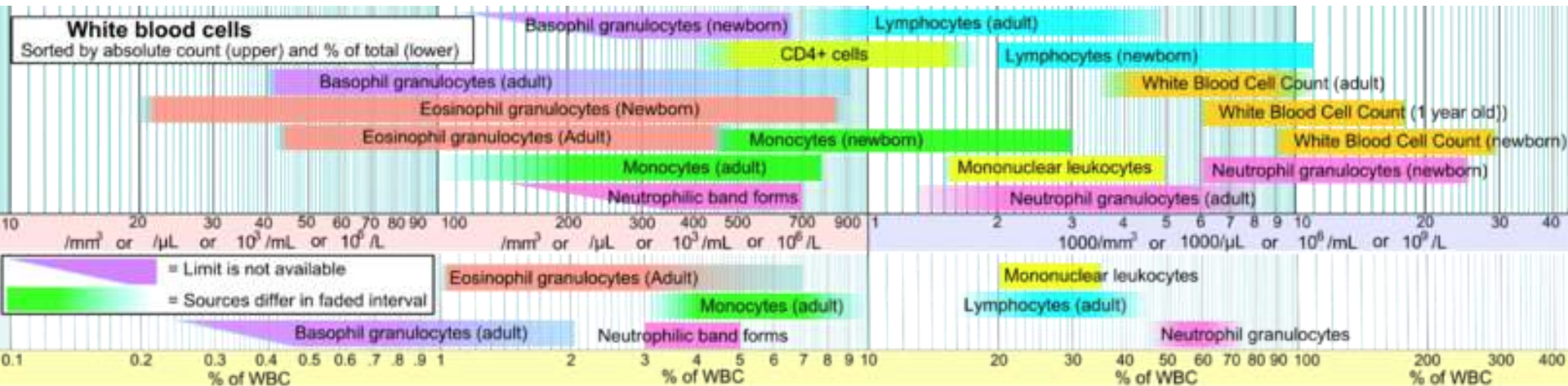
Signs and symptoms

- Fever
- Bleeding or bruising
- Feeling weak, tired, or sick
- Feeling dizzy, faint, or sweaty
- Pain or tingling in arms, legs, or abdomen
- Trouble breathing, thinking, or seeing
- Losing weight without trying, or a poor appetite



Leukocytosis

Diagnosis: leukocytosis can be identified with a complete blood count



Leukocytosis

Comment

- Excessive numbers of white blood cells are most often due to the response of normal bone marrow to infection or inflammation
- In some instances, leukocytosis is a sign of more serious primary bone marrow disease (leukemia or myeloproliferative disorders)

Hemorrhagic Syndrome

Definition

The extravasation of red blood cells from the vasculature into the skin and/or subcutaneous tissue in form of petechiae, purpura, and ecchymoses (collectively referred to as purpura) with purpuric rashes formation

Hemorrhagic Syndrome

Appendix for Definition

The extravasation occur internally, where red blood cells leaks from blood vessels inside the body

Hemorrhagic Syndrome

Purpura forms

- Petechiae - pinpoint red lesions less than 2 mm in size
- Purpura - pinpoint red lesions from 2 mm to 10 mm in size
- Ecchymoses pinpoint red lesions more than 10 mm in size



Hemorrhagic Syndrome

Principal types and Causes

| | |
|------------------|--|
| Thrombocytopathy | Any of blood disorders characterized by dysfunctional platelets (thrombocytes) with either normal platelet counts (non-thrombocytopenic purpuras) or decreased platelet counts (thrombocytopenic purpuras), which result in prolonged bleeding time, defective clot formation, and a tendency to hemorrhage (Henoch-Schönlein Purpura, von Willebrand disease, thrombasthenia, platelet aggregation, etc.) |
| Hemophilia | A group of hereditary genetic disorders that impair the body's ability to control blood clotting, which is used to stop bleeding when a blood vessel is broken (Hemophilia A - clotting factor VIII deficiency (the most common form of the disorder) and Hemophilia B - factor IX deficiency (occurs in around 1 in about 20,000–34,000 male births) |
| Telangiectasia | A small dilated blood vessels near the surface of the skin or mucous membranes, measuring between 0.5 and 1 millimeter in diameter |

Hemorrhagic Syndrome

Signs and symptoms

- Purpura, sometimes mucosal bleeding (localisation, distribution)
- Arthritis and Arthralgia
- Central Nervous, Gastrointestinal, Cardiovascular, Urethral Systems involvement
- Prolonged, heavy menstrual periods (menorrhagia)
- Unexplained nosebleeds
- Extended bleeding after minor cuts, blood draws or vaccinations, minor surgery or dental procedures
- Bleeding after aspirin

Hemorrhagic Syndrome

WHO' grading scale to measure the severity of bleeding

| | |
|----------------|---|
| Grade 0 | no bleeding |
| Grade 1 | petechial bleeding |
| Grade 2 | mild blood loss (clinically significant) |
| Grade 3 | gross blood loss, requires transfusion (severe) |
| Grade 4 | debilitating blood loss, retinal or cerebral associated with fatality |

Hemorrhagic Syndrome

Diagnosis

- The platelet count
- The platelet function (bleeding time, platelet aggregation studies, von Willebrand Factor studies, specialized tests)
- A coagulation screen (clotting factor deficiencies)
- If the patient is on warfarin, INR (International Normalized Ratio)
- Autoantibody screen for connective tissue disorders

Leukemia

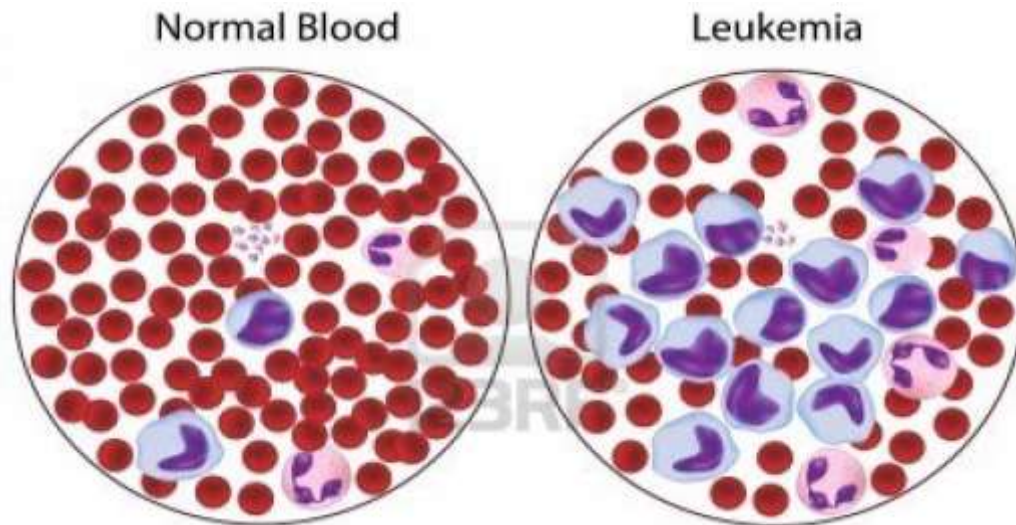
Definition

Abnormal proliferation of the blood-forming tissues that usually begins in the bone marrow and results in high numbers of abnormal white blood cells

Leukemia

Causes

- Mutations in the DNA as a result of exposure to radiation or carcinogenic substance
- A genetic predisposition



Leukemia

Classification

| Cell type | Acute | Chronic |
|--------------------------------------|------------------------------------|------------------------------------|
| Lymphocytic (lymphoblastic) leukemia | Acute lymphoblastic leukemia (ALL) | Chronic lymphocytic leukemia (CLL) |
| Myelogenous (myeloid) leukemia | Acute myeloblastic leukemia (AML) | Chronic myelogenous leukemia (CML) |

Leukemia

Signs and symptoms

- Fever or chills
- Persistent fatigue, weakness
- Frequent or severe infections
- Losing weight without trying
- Swollen lymph nodes, enlarged liver or spleen
- Easy bleeding or bruising
- Recurrent nosebleeds
- Tiny red spots in skin (petechiae)
- Excessive sweating, especially at night
- Bone pain or tenderness

Leukemia

Acute leukemia

is characterized by a rapid increase in the number of immature blood cells (blasts) crowding due to such cells makes the bone marrow unable to produce healthy blood cells immediate treatment is required in acute leukemia due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body

Leukemia

Chronic leukemia

is characterized by the excessive buildup of relatively mature, but still abnormal, white blood cells

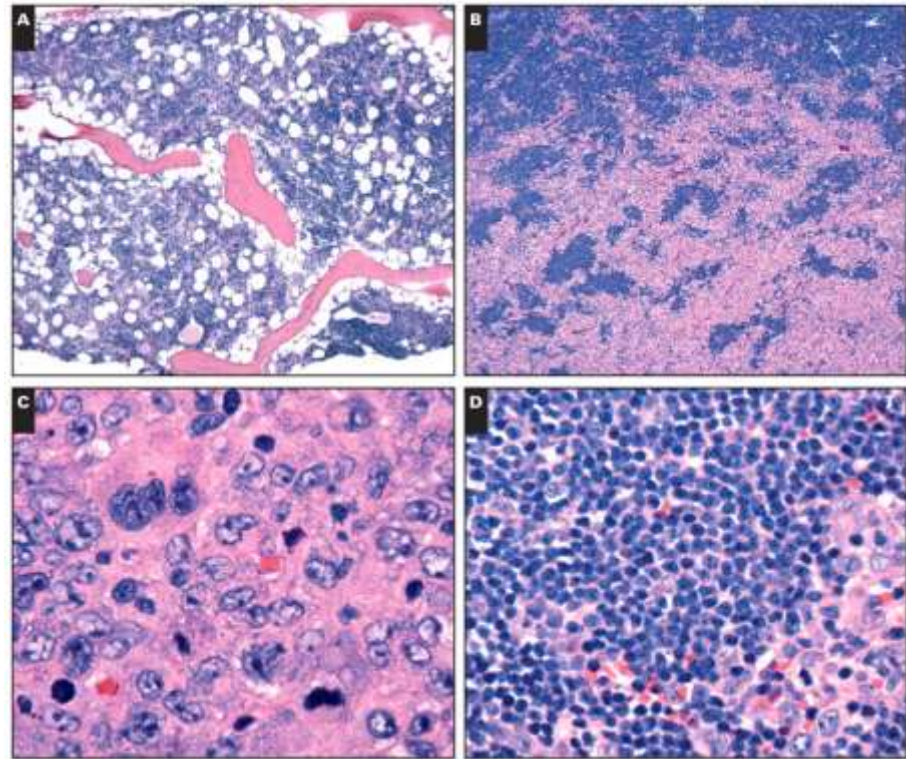
typically taking months or years to progress, the cells are produced at a much higher rate than normal, resulting in many abnormal white blood cells

mostly occurs in older people, but can theoretically occur in any age group

Leukemia

Diagnosis

- Repeated complete blood counts and blood films
- Philadelphia chromosome in CML
- Bone marrow examination
- A lymph node biopsy (in lymphoma)
- X-ray, MRI, or ultrasound



Glossary of blood disorders pathology' terms

GLOSSARY of BLOOD RELATED TERMS
BLOOD AND HEMATOLOGY DICTIONARY
BLOODBOK.COM